CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	21372/S019
Priority or Standard	Priority (Response to Written Request)
Submit Date(s)	November 28, 2013
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Division / Office	DGIEP/ODE3
Reviewer Name(s)	Farrokh Sohrabi, M.D.
Review Completion Date	May 5, 2014
Established Name	Palonosetron hydrochloride
(Proposed) Trade Name	ALOXI
Therapeutic Class	5-HT_3 receptor antagonist
Applicant	Helsinn Healthcare SA
Formulation(s)	Intravenous (I.V.) injection
Dosing Regimen	A single 20 mcg/kg (maximum 1.5 mg) dose given as a 15 minute I.V. infusion beginning approximately 30 minutes before the start of chemotherapy
Indication(s)	Prevention of acute chemotherapy-induced nausea/vomiting
Intended Population(s)	Pediatric patients aged ≥1 month with cancer scheduled to receive chemotherapy

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of palonosetron hydrochloride intravenous injection for the indication of prevention of acute nausea and vomiting with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy, in pediatric patients aged ≥1 month. For the above indication, this reviewer recommends approval of a 20 mcg/kg (maximum 1.5 mg) dose administered as a 15 minute intravenous infusion. The infusion should start approximately 30 minutes before the start of emetogenic cancer chemotherapy. The information in this submission provides substantial evidence to support the above indication, and there are data to provide adequate directions for use.

(b) (4)

This reviewer's recommendation is contingent upon the findings of other reviewers that include the clinical pharmacology and pharmacometrics reviewers from the Office of Clinical Pharmacology (OCP) and the statistics reviewer from the Office of Biostatistics (OB).

1.2 Risk Benefit Assessment

Palonosetron hydrochloride intravenous (I.V.) injection has been prescribed in the United States since 2003 for the prevention of chemotherapy-induced nausea and vomiting (CINV) in adults. The data in this submission demonstrate the efficacy of I.V. palonosetron for the prevention of acute nausea and vomiting with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy, in pediatric patients aged ≥1 month when administered intravenously as a single 20 mcg/kg (maximum 1.5 mg) dose approximately 30 minutes before the start of emetogenic cancer chemotherapy.

Efficacy of the 20 mcg/kg dose of palonosetron for the aforementioned indication was established by non-inferiority analysis of the Complete Response (CR) rate in the acute phase of the first cycle of chemotherapy. CR in the acute phase was defined as no vomiting, no retching, and no rescue medication in the first 24 hours after starting chemotherapy. Efficacy was based on demonstrating non-inferiority of I.V. palonosetron compared to I.V. ondansetron. Non-inferiority criteria were met if the lower bound of the 97.5% confidence interval for the difference between CR rates of I.V. palonosetron

minus I.V. ondansetron was larger than -15%. I.V. palonosetron 20 mcg/kg (maximum 1.5 mg) demonstrated non-inferiority to the active comparator (ondansetron administered at a dose of 0.15 mg/kg x 3 with a maximum total dose of 32 mg) during the 0 to 24 hour time interval. The reader is referred to section 6 Review of Efficacy for detailed discussion of efficacy findings. No safety signals emerged from the clinical data in this submission. The reader is referred to section 7 Review of Safety for detailed discussion of safety findings. Therefore, given the evidence of efficacy and the acceptable safety profile in the clinical data submitted to sNDA 21372 (S019), the use of I.V. palonosetron as a single 20 mcg/kg (maximum 1.5 mg) dose in pediatric patients aged ≥1 month for the prevention of acute nausea and vomiting with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy, is warranted.

The efficacy results indicated that a10 mcg/kg dose of palonosetron did not demonstrate non-inferiority to the comparator (ondansetron administered at a dose of 0.15 mg/kg x 3 with a maximum total dose of 32 mg) for the prevention of acute chemotherapy-induced nausea and vomiting. Therefore, the use of I.V. palonosetron as a single 10 mcg/kg dose in pediatric patients aged ≥1 month for the prevention of acute nausea and vomiting with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy, is not adequately supported.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended for this sNDA.

1.4 Recommendations for Postmarket Requirements and Commitments

This medical officer recommends no postmarket requirements or commitments for this sNDA. In this reviewer's assessment, this sNDA represents a complete response to Pediatric Research Equity Act (PREA) postmarket requirements (described below).

Before the initial approval date of I.V. palonosetron for prevention of CINV in adults (July 25, 2003), the Sponsor had already submitted a Proposed Pediatric Study Request (PPSR) to FDA. Given that the July 2003 approval date for I.V. palonosetron for prevention of CINV in adults pre-dated PREA, the July 25, 2003 Approval Letter acknowledged the Sponsor's PPSR, but did not stipulate any required pediatric studies. PREA, signed into law on December 3, 2003, codified FDA's Pediatric Rule. Under PREA, the Sponsor was required to include assessments of safety and efficacy for all relevant pediatric populations for all relevant indications, including the CINV indication.

On August 3, 2005, FDA waived the CINV pediatric assessment for birth to <1 month of age (the reason given was that palonosetron is not likely to be used by a substantial

number of pediatric patients in this age group for CINV) and deferred the pediatric assessment for acute and delayed CINV for ages 1 month to 17 years. The PREA postmarket requirements (PMRs) issued on August 3, 2005 were the following:

- 806-1: Deferred pediatric study under PREA for the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy (CINV) in pediatric patients 1 month to 17 years of age
- 806-2: Deferred pediatric study under PREA for the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV) in pediatric patients 1 month to 17 years of age

On July 21, 2010, FDA issued a Written Request (WR) for pediatric studies of I.V. palonosetron, and this WR included two studies for the CINV indication (the reader is referred to section 2.5 Summary of Presubmission Regulatory Activity Related to Submission for details). WR Study 2 (PALO-99-07) evaluated I.V. palonosetron for prevention of acute CINV during a single course of chemotherapy. Inclusion criteria were to enroll subjects 1 month to <17 years of age, although the youngest subject in the study (open label safety cohort) was 3 months old and the oldest subject was 17 years old. WR Study 4 (PALO-10-20) assessed I.V. palonosetron for the prevention of CINV in both the acute and delayed phases of initial and repeat courses of chemotherapy. Inclusion criteria were to enroll subjects from full term neonates to <17 years, although the youngest subject enrolled was 64 days old at the time of randomization.

Regarding Study 4 (i.e., PALO-10-20) the WR indicated the following:

> "A PK and Tolerability Sub-study should be conducted in pediatric patients 0 to 1 month old to assess exposure and tolerability in this age group. You must justify the dose for this sub-study based on available data on known developmental differences in neonates that may affect disposition of palonosetron. You should seek to enroll at least 3 patients in this initial PK and Tolerability Sub-study. If there is adequate justification based on the sub-study data, additional neonates may be enrolled to an appropriate dose level."

Because the Sponsor was unable to enroll any neonates into study PALO-10-20, the PK and Tolerability Sub-study was not conducted.

The Pediatric Review Committee (PeRC) PREA subcommittee meeting was held on April 23, 2014. At this meeting, DGIEP reviewed the pediatric assessment of I.V. palonosetron with the PeRC.

2 Introduction and Regulatory Background

2.1 Product Information

ALOXI (palonosetron hydrochloride) is a selective 5-HT_3 antagonist available as a parenteral antiemetic agent. The product used in the CINV pediatric WR clinical trials is the currently available FDA-approved commercial product ALOXI Injection (palonosetron HCl, 0.05 mg/mL, 5 mL vial). ALOXI has been marketed at dose of 0.25 mg I.V. for use in the prevention of CINV in adults since September 2003.

In adults, palonosetron is metabolized by both renal and hepatic mechanisms. Approximately 40% of palonosetron is eliminated via renal clearance. According to the Sponsor, renal clearance of palonosetron may be close to adult levels after 1 year of age. In adults, about 50% of palonosetron is eliminated via hepatic metabolism. Hepatic metabolism is dependent on cytochrome P450 2D6 (CYP2D6) with minimal additional contributions from CYP3A4 and CYP1A2. CYP2D6 does not reach adult capacity until between 1 and 5 years of age. The two major metabolites of palonosetron are N-oxide-palonosetron and 6-S-hydroxy-palonosetron, each of which has <1% of the 5-HT_3 receptor antagonist activity of palonosetron.

2.2 Tables of Currently Available Treatments for Proposed Indications

Ondansetron and granisetron, both 5-HT_3 antagonists with approved I.V. formulations, are approved for the prevention of CINV. Ondansetron I.V. is approved for use in prevention of CINV in patients aged ≥6 months and granisetron is approved for use in prevention of CINV in patients aged ≥2 years. Dolasetron, another 5-HT_3 antagonist, is also available in an I.V. formulation, but the I.V. formulation is not approved for the prevention of CINV. An oral tablet formulation of dolasetron, however, is approved for the prevention of CINV in patients aged ≥2 years. Table 1 summarizes the labeled pediatric CINV indications and pediatric dosage/administration for ondansetron, granisetron, and dolasetron.

Table 1. 5-HT$_3$ Antagonists Currently Approved For Prevention of CINV in Pediatric Patients

Drug Formulation	Labeled CINV Indication	Dosage and Administration in Pediatric Patients
Ondansetron HCl I.V.	Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin	Patients aged ≥6 months: 3 x 0.15 mg/kg doses up to a maximum of 16 mg per dose. First dose is infused beginning 30 minutes before the start of chemotherapy
Ondansetron HCl Oral (tablet, disintegrating tablet, solution)	1. Prevention of nausea and vomiting associated with HEC, including cisplatin ≥50 mg/m^2 2. Prevention of nausea and vomiting associated with initial and repeat courses of MEC	Patients aged 4 through 11 years: 4 mg given 3 times a day. First dose should be given 30 minutes before the start of chemotherapy, with subsequent doses 4 and 8 hours after the first dose. 4 mg orally every 8 hours may be continued for 1 to 2 days after chemotherapy is complete. Pediatric patients aged ≥12 years: 8 mg given 2 times a day. First dose should be given 30 minutes before the start of chemotherapy, with subsequent dose 8 hours after the first dose. 8 mg orally every 12 hours may be continued for 1 to 2 days after chemotherapy is complete.
Granisetron HCl I.V.	Prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin	Pediatric patients aged ≥2 years: 10 mcg/kg given within 30 minutes before initiation of chemotherapy
Dolasetron mesylate Oral tablet	Prevention of nausea and vomiting associated with MEC, including initial and repeat courses	Pediatric patients aged ≥2 years: 1.8 mg/kg given within 1 hour before initiation of chemotherapy, up to a maximum of 100 mg

Abbreviations: HCl, hydrochloride; I.V., intravenous; HEC, highly emetogenic cancer chemotherapy; MEC, moderately emetogenic cancer chemotherapy
Source: Reviewer's table, with information obtained from current ondansetron, granisetron, and dolasetron labeling.

There are currently no 5-HT$_3$ antagonists approved for use in prevention of CINV in pediatric patients aged <6 months.

2.3 Availability of Proposed Active Ingredient in the United States

NDA 21372 ALOXI (palonosetron HCl) I.V. was first approved for marketing on July 25, 2003. Currently ALOXI I.V. is approved for the following indications:

- Prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (7/25/03)
- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (7/25/03)
- Prevention of postoperative nausea and vomiting for up to 24 hours following surgery (S-008; 2/29/08).

Additionally, NDA 22233 ALOXI (palonosetron HCl) capsules was approved on August 22, 2008 for the following indication:

- Prevention of acute nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

However, the Sponsor never marketed ALOXI capsules in the United States. On July 19, 2012, the Agency determined that ALOXI capsules, NDA 22233, was not withdrawn or withheld from sale for reasons of safety or effectiveness.

Currently approved dosing regimens in adults
Chemotherapy-Induced Nausea and Vomiting (CINV)

- A single 0.25 mg I.V. dose administered over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy.
- One 0.5 mg capsule administered approximately one hour prior to the start of chemotherapy (not currently available).

Postoperative Nausea and Vomiting (PONV)

- A single 0.075 mg I.V. dose administered over 10 seconds immediately before the induction of anesthesia.

Constipation and headache are among the most common adverse drug reactions with ALOXI in adults and are included in current product labeling.

2.4 Important Safety Issues With Consideration to Related Drugs

Other 5-HT_3 antagonists that are currently approved for prevention of CINV include ondansetron, dolasetron, and granisetron. Important safety issues with consideration to these related drugs are discussed below.

QT prolongation
Ondansetron prolongs the QT interval in a dose-dependent manner. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. The Warnings section of product labeling indicates that ondansetron should be avoided in patients with congenital long QT syndrome. Moreover, ondansetron labeling recommends ECG monitoring in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation.

Regarding granisetron, although an adequate QT assessment has not been conducted, QT prolongation has been reported. The Warnings section of granisetron hydrochloride labeling indicates that granisetron should be used with caution in patients with pre-existing arrhythmias or cardiac conduction disorders. Patients with cardiac disease, on cardio-toxic chemotherapy, with concomitant electrolyte abnormalities and/or on concomitant medications that prolong the QT interval are particularly at risk.

Dolasetron, approved as an oral formulation for the prevention of CINV associated with MEC in patients aged 2 years and older, also prolongs the QT interval, PR interval, and QRS interval in a dose-dependent fashion. Product labeling includes warnings advising avoidance of dolasetron in patients with congenital long QT syndrome, hypomagnesemia, hypokalemia, and patients with complete heart block or at risk for complete heart block, unless they have an implanted pacemaker.

The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in adult CINV clinical trials. In nonclinical studies palonosetron demonstrated the ability to block ion channels involved in ventricular de- and re polarization and to prolong action potential duration.

The effect of palonosetron on QTc interval was evaluated in a double blind, randomized, parallel, placebo and positive (moxifloxacin) controlled trial in adult men and women. The objective was to evaluate the ECG effects of I.V. administered palonosetron at single doses of 0.25, 0.75 or 2.25 mg in 221 healthy patients. The study demonstrated no significant effect on any ECG interval including QTc duration (cardiac repolarization) at doses up to 2.25 mg.

Reviewer comments: *Of the 5-HT_3 antagonists currently available, palonosetron appears to have the best safety profile with regard to risk of cardiac arrhythmias.*

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The regulatory activity related to the current submission is extensive and collectively spans more than 13 years. Below is a summary of the key pre-submission regulatory activity and Agency interactions with the Sponsor. The summary below pertains to the CINV indication for palonosetron.

- 24 Apr 2000: The Sponsor submitted the initial Proposal for Pediatric Studies Request (PPSR) to IND 39,797 requesting a Written Request (WR) based on plans to perform study PALO-99-07. Shortly thereafter, on 14 Aug 2000, the Sponsor submitted the protocol for PALO-99-07. Over the next few years, FDA cited several safety concerns that are summarized below:
    - 2001 through 2003: The Agency cited concerns about ocular safety data in juvenile animal studies. These concerns were addressed by data from a repeat juvenile rat toxicology study. On 26 Jun 2003, the Sponsor submitted a second PPSR based on revisions to the PALO-99-07 protocol and based on prior discussions with FDA.
    - 2003 through 2006: The Agency cited concerns about potential QTc effects of palonosetron and requested an adult thorough QT study. These concerns were addressed ultimately by data from the adult thorough QT study.

- 3 Aug 2005: In response to the Sponsor's request for deferral of PREA pediatric studies for the CINV indication, FDA waived pediatric assessment for birth to <1 month of age because palonosetron is not likely to be used by a substantial number of pediatric patients in this age group for the approved CINV indications. Based on the Sponsor's proposed development plan and timeframe for study completion, the Agency set the pediatric assessment deferral date for the CINV indication for the 1 month to 17 year pediatric age group to 31 Jul 2008.
- 9 Nov 2006: Telephone conference between FDA and Sponsor to discuss status of overall pediatric program. At that meeting, FDA indicated that the Sponsor could submit a PPSR for CINV studies based on PALO-99-07, following which the Agency would review the PPSR and develop a WR based on PALO-99-07. At this meeting, FDA indicated that no additional CINV studies would be included in the WR. Moreover, FDA asked that when the Sponsor submits their sNDA in response to the WR, they should include an integrated summary of safety of palonosetron in pediatric patients based on analysis of all safety data collected from ongoing and completed studies.
- 14 Feb 2007: The Sponsor submitted a third PPSR in accordance with the Agency's recommendation at the 9 Nov 2006 meeting.
- 22 Feb 2007: The Sponsor submitted the clinical study report for PALO-99-07, an uncontrolled, randomized, double-blind study comparing two doses of palonosetron (3 mcg/kg and 10 mcg/kg) for the prevention of acute CINV in approximately 70 pediatric cancer subjects.
- 16 Nov 2009: Telephone conference between Sponsor and FDA to discuss FDA's WR outline in response to PPSR. At this meeting, the Sponsor indicated that they planned to use data from the completed study PALO-99-07 as a pilot study to inform selection of appropriate pediatric doses for a larger phase 3 study (i.e., PALO-10-20).
- 23 July 2010: Written Request issued by FDA. The WR was amended three times, on 30 Sep 2010, 22 Oct 2012, and 15 Feb 2013 (discussed below). For the CINV indication, the WR required an adequate, well-controlled, randomized parallel-group trial (i.e., study PALO-10-20) of more than one dose level of palonosetron administered intravenously. The WR required the study to include a palonosetron dose greater than 10 mcg/kg. The WR also indicated that the active comparator administered to pediatric patients, including patients <6 months old, must be consistent with the standard of care for CINV prevention (e.g., ondansetron).
- 30 Sep 2010: WR amendment #1 issued by FDA. The original WR contained requirements for previously completed studies (e.g., PALO-99-07) that were not included in these studies. The amendment altered the original WR to be consistent with provisions for the previously completed studies. There were no changes to requirements for PALO-10-20 in the WR amendment.
- 30 Nov 2010: The Sponsor submitted the initial protocol and initial statistical analysis plan (SAP) for PALO-10-20. In the initial protocol, the Sponsor proposed

to study two doses of palonosetron, 10 mcg/kg and [redacted]. Moreover, the initial SAP pre-specified a noninferiority margin of -15%. The Sponsor provided the following rationale for proposing study of the [redacted] dose in PALO-10-20:

[redacted]

For the comparator, the Sponsor proposed ondansetron, which was to be administered intravenously in three doses of [redacted] for all subjects, up to a maximum total dose of [redacted]

- 3 Feb 2011: FDA sent an Advice Letter (AL) regarding the protocol and SAP for PALO-10-20. Key comments/recommendations included:
  - FDA recommended that the Sponsor change palonosetron dose from [redacted] to 20 mcg/kg, in order to increase the chances of detecting a dose/exposure-response relationship for efficacy, if one existed. The AL did not comment specifically on the proposed dosing of the active comparator (ondansetron), but the FDA clinical review team indicated in their review of the protocol that the dosing was acceptable (see clinical review by Dr. John Troiani under IND 39,797 in DARRTS, dated 6 Jan 2011).
  - For the primary endpoint analysis, the Sponsor planned to employ a Cochran-Mantel-Haenszel (CMH) test with stratum weights to compare the treatment effect using age class as strata. FDA recommended that instead, for each non-inferiority null hypothesis stated in the SAP, the Sponsor apply a stratum-adjusted Mantel-Haenszel method (described in the AL) to calculate the two-sided 97.5% confidence interval of the difference in proportions. In addition, in order to show the robustness of the primary endpoint analysis, FDA recommended the Sponsor also apply the Miettinen and Nurminen method using a two-sided significance level of 0.025.
  - In the event that a subject is randomized to one treatment but receives the alternative treatment, FDA indicated that the primary endpoint analysis should be repeated using the actual treatment that a subject receives. In order to demonstrate substantial evidence to support the proposed indication, FDA noted that this sensitivity analysis and the primary analysis comparing as randomized treatment groups should show positive results in favor of palonosetron.

  - Regarding methods for handling missing data for the primary and secondary binary endpoints, FDA indicated that missing data should be treated as "failure/no-CR." In addition, FDA noted that missing time-to-event data should be classified as "failure" at the time missing or "failure" at time of study drug administration (T_0) + 24 hours (acute phase) or T_0 + 120 hours (overall/delayed phase) if no observed time is available.
- 26 Apr 2011: FDA sent Sponsor a letter stating that the protocol for PALO-10-20 and the pooled population PK analysis protocol PALO-10-35 were acceptable.
- 29 Sep 2011, 14 Dec 2011, 14 Mar 2012, 30 May 2012, 1 Aug 2012, and 26 Oct 2012: Sponsor submitted enrollment status updates (six in total) to FDA regarding PALO-10-20 and asked for FDA guidance. Enrollment updates included descriptions of challenges, despite ongoing efforts, in enrolling across all age groups (especially the <2 years age group) and races/ethnicities as required by the WR.
- 21 Jun 2012: FDA sent an AL regarding the Sponsor's revised SAP (submitted on 29 Mar 2012). The comments and recommendations were as follows:
  - "...in order to show that your proposed indication for each of the two studies is supported by substantial evidence, the results from the following four analyses should be positive in favor of the study drug:
    a. Stratum adjusted Mantel-Haenszel based on the Full Analysis Set (FAS)
    b. Stratum adjusted Mantel- Haenszel based on the "as-treated" population
    c. Miettinen and Nurminen method taking into account the stratification on the FAS
    d. Miettinen and Nurminen method taking into account the stratification on the "as-treated" population"
  - In subsection 13.2.1 of the SAP, CR in the delayed phase (from 24 to 120 hours after chemo start on day one) is defined as the key secondary endpoint. CR delayed will be analyzed by the Mantel-Haenszel method and the Miettinen and Nurminen method on the FAS population and the "as-treated" population. However, since at the protocol stage, the non-inferiority margin of 15% for this key secondary endpoint was not pre-specified with the support of historical well-controlled placebo studies following ICH E-10 guidance, the non-inferiority analyses for the key secondary endpoint will be considered an informal comparison... Accordingly, those results may not be able to support a clinical benefit claim in the labeling package."
- 22 Oct 2012: WR amendment #2 issued by FDA. Given the Sponsor's difficulties in meeting protocol-specified thresholds for enrollment of subjects into each age group for the PK sub-study of PALO-10-20, the amendment cited specific sample size numbers for each age group and added a requirement that these data be combined with such data from other relevant studies (e.g., PALO-99-07) to provide descriptive statistics for each age group.

- 4 Dec 2012: Pediatric pre-sNDA meeting convened. Key clinical discussions included:
    - Because the WR required pediatric age groups for PALO-99-07 which differed from those in the original PALO-99-07 study report, the Sponsor proposed to reanalyze the data in accordance with the pediatric age groups stipulated in the WR and submit this reanalysis as an addendum to the original study report. FDA accepted this proposal.
    - FDA agreed with the Sponsor's planned content/format of the Summary of Clinical Efficacy, Summary of Clinical Safety, and the safety database.
    - For PALO-10-20, FDA re-iterated their correspondence with the Sponsor from 21 Jun 2012, in which FDA had commented on the Sponsor's SAP.
- 16 Jan 2013: Type C Meeting Written Responses. In follow up to the pre-sNDA meeting, FDA conveyed the following additional comments/recommendations:
    - The Sponsor proposed that if the pediatric adverse event (AE) profiles are similar to those in adults, a statement that the AE profiles are similar to those observed in adults would be included in labeling in lieu of AE tables. Moreover, the Sponsor proposed a cutoff for including common AEs in a table of ≥2%, which is the same cutoff for the adult AE tables presently in I.V. ALOXI labeling. FDA responded that pediatric AE tables should be submitted, even if the pediatric AE profiles are similar to adults. The proposed ≥2% cutoff was deemed acceptable.
    - Because the sNDA would be submitted in response to a WR, Priority Review would be granted.
- 15 Feb 2013: WR amendment #3 issued by FDA. This amendment reflected minor changes relating to CMC and the PK analysis.
- 27 Nov 2013: Sponsor submitted the sNDA that is the subject of this review.

2.6 Other Relevant Background Information

Palonosetron I.V. for the prevention of CINV in pediatric patients was developed under IND 39,797.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Methods used to evaluate data quality and integrity included:

- Review of possible bias based on financial ties
- Seeking source documentation for efficacy and safety analyses
- Review of Sponsor's compliance with Good Clinical Practices

The Sponsor submitted the application in electronic modular format. The application was generally well organized and navigable.

3.2 Compliance with Good Clinical Practices

According to the Sponsor, all of the trials were conducted in accordance with U.S. Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), and the obligations of clinical investigators (21 CFR 312). Per the Sponsor, the two trials submitted for this NDA were conducted in accordance with U.S. Title 21 CFR on Good Clinical Practices (GCPs), which is consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonisation, and the FDA.

A request for Office of Scientific Investigations (OSI) audit was placed for this sNDA. Of the 59 sites that enrolled subjects for PALO-10-20, the 2 sites (listed below) with highest subject enrollment were selected for inspection:

1. Site #622 (Hungary, Principal Investigator Gabor Kovacs) enrolled 38 subjects.
2. Site #581 (Czech Republic, Principal Investigator Edita Kabickova) enrolled 34 subjects.

Together, the two aforementioned sites enrolled 72 subjects out of the 493 total subjects (15%) in the full analysis set (FAS) population (i.e., the population used in the primary efficacy analysis). There were insufficient domestic data to warrant inspection of U.S. sites (i.e., of the 11 U.S. sites in the study, none enrolled more than 6 subjects and the U.S. sites collectively enrolled only 27 subjects).

For details of the Clinical Inspection Summary, the reader is referred to the review by Dr. Susan Leibenhaut dated April 28, 2014. Briefly, for site #622, the reviewer noted no significant regulatory violations. For site #581, the reviewer noted two instances of failure to follow the protocol. The first involved use of the wrong treatment kit in one subject (subject 5423). This deviation was reported appropriately in the line listings in the sNDA as a protocol violation (see Table 7). The second violation involved administration of chemotherapy more than 35 minutes following study drug (the protocol had specified that study drug be administered 30 (±5) minutes prior to chemotherapy). The reviewer noted that this violation was minor and should not affect study outcome. Dr. Leibenhaut concluded that the study appears to have been conducted adequately at both inspected sites, and that the data generated by both sites appear acceptable in support of the sNDA.

3.3 Financial Disclosures

The Sponsor provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangements with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). The Sponsor also certified that each clinical investigator had no proprietary interest in this product or significant equity in the Sponsor as defined

by 21 CFR 54.2(b). As defined by 21 CFR 54.2(f), the Sponsor certified that no clinical investigator received any significant payments of any sorts. The above certification applied to study PALO-99-07 and study PALO-10-20. See Appendix 6: Clinical Investigator Financial Disclosure for additional details.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Sponsor indicated that because the FDA-approved I.V. ALOXI 0.05 mg/mL, 5 mL vial is proposed for commercial pediatric use, no new CMC information would be included in this sNDA. At the 4 Dec 2012 pre-sNDA meeting FDA accepted the Sponsor's proposal to include no CMC information in the sNDA.

4.2 Clinical Microbiology

This section is not applicable to this submission.

4.3 Preclinical Pharmacology/Toxicology

Based on review of the available nonclinical data, the WR did not require any additional nonclinical studies to be performed to support the pediatric clinical program described in this application. The pharmacology/toxicology review focused on the revision of the pregnancy subsection of the label (in conjunction with the Maternal Health Team), to comply with the Proposed Pregnancy and Lactation Labeling Rule (PLLR) format. For details, please see review by Dr. Ke Zhang, dated April 22, 2014.

4.4 Clinical Pharmacology

The WR indicated that in Study 2 (i.e., PALO-99-07), for each of the 4 outlined age groups (i.e., <2 , 2 to <6, 6 to <12, and 12 to <18 years), PK endpoints must include C_{max}, T_{max}, AUC, $T_{1/2}$, clearance, and Vd.

For Study 4 (i.e., PALO-10-20), the WR indicated that for the PK component, there must be a minimum of 24 patients per age group for PK sampling for the 2 to <6, 6 to <12, and 12 to 17 year old groups and a minimum of 15 patients for PK sampling for the 0 to <2 year old group. The PK endpoints were to include C_T (concentration at end of infusion for I.V. formulation), C_{max}, T_{max}, AUC, $T_{1/2}$, clearance, and Vd. Moreover, the WR indicated that the PK data from this study must be combined with data from other relevant studies to provide descriptive statistics for each age group. The WR noted that a population PK approach may be used.

Regarding Study 4 (i.e., PALO-10-20), the WR also indicated the following:

> "The PK data may be collected in a subset of patients to obtain data for the palonosetron dose(s) and age groups for which data are not available from previously conducted pediatric CINV studies. The PK data from this study and previously conducted palonosetron pediatric CINV studies may be pooled to assess the PK parameters for 3 palonosetron doses in the full range of pediatric ages. The C_{max} values following either the 15 minute infusion or 30 second bolus may be reported using a population PK analysis as appropriate."

The PK of palonosetron (and its metabolite M9), administered by I.V. bolus over 30 seconds, were characterized in pediatric CINV subjects receiving HEC or MEC in the first clinical study PALO-99-07. These PK parameters were then evaluated using a population PK approach and the relevant data used for a PK/PD analysis (PALO-07-06 and PALO-07-34, respectively) to evaluate concentration-response and a pediatric dosing rule justification. These studies were performed prior to the WR issuance. After discussions with the Agency, additional PK and PD analyses were performed. Data from the original pediatric CINV study PALO-99-07 were re-analyzed by WR-specified age groups. PK objectives of study PALO-10-20 included the evaluation of palonosetron concentration at the end of the 15-minute infusion (C_T) in all subjects, and a PK sub-study in a subset of subjects who underwent PK sampling at multiple time points.

Palonosetron plasma concentrations from PALO-10-20 were pooled with those from PALO-99-07 to provide a population PK analysis (PALO-10-35) across all pediatric CINV subjects. Lastly, a population PK/PD analysis (PALO-11-20) to evaluate exposure/response with data deriving only from PALO-10-20 was also conducted.

For detailed clinical pharmacology review, please see review by the Office of Clinical Pharmacology (OCP).

4.4.1 Mechanism of Action

Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no known affinity for other receptors.

Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex.

4.4.2 Pharmacodynamics

PK/PD analyses were performed in two studies:

- PALO-07-34, titled “Population PK and PD modeling and simulation of palonosetron in pediatric patients”; this study used PALO-99-07 data (n=71 subjects) with reference data from adult CINV study 2330 to describe the relationship between palonosetron PK and PD in pediatric patients and to define a pediatric dosing rule.
- PALO-11-20, titled “PK/PD analysis of palonosetron in pediatric patients”; this study used PALO-10-20 palonosetron PK/PD data (n=279 subjects) to evaluate palonosetron exposure response in pediatric cancer patients.

For details of the assessment of these studies, please see review by the Office of Clinical Pharmacology (OCP).

4.4.3 Pharmacokinetics

The Sponsor conducted PK assessments in the two clinical studies (PALO-99-07 and PALO-10-20) and the following two population PK analyses:

- PALO-07-06, titled “Population PK modeling of palonosetron in pediatric patients”; this study used PALO-99-07 data (n=71 subjects) to characterize I.V. palonosetron PK in pediatric patients and to evaluate the effect of demographic factors (including weight) on palonosetron PK.
- PALO-10-35, titled “Population PK modeling of palonosetron in pediatric patients”; this was a pooled population PK analysis of I.V. palonosetron data from PALO-99-07 (n=71 subjects) and PALO-10-20 (n=63 subjects).

Regarding PALO-99-07, the Sponsor concluded that exposure was generally proportional or slightly less than dose proportional for the 3 to 10 mcg/kg dose levels, across all 4 age groups. The Sponsor noted no relevant differences in any of the PK parameters when gender, race/ethnicity, and emetogenicity were considered. Regarding PALO-10-20, the Sponsor concluded that the analyses do not indicate that the PK of palonosetron is strictly dependent on patient age. The Sponsor noted that no further adjustment of dosing, beyond dosing palonosetron on an individual patient weight basis, is required for pediatric patients based on PK evidence.

Regarding PALO-07-06, the Sponsor concluded that variability in CL was primarily affected by weight and that the results supported an I.V. palonosetron dosing regimen in pediatric patients that is scaled by body weight. Regarding PALO-10-35, the Sponsor concluded that the PK of palonosetron are not dependent on patient age and that no further adjustment of dosing, beyond dosing palonosetron on an individual patient weight basis, is required for pediatric patients.

For details of the assessment of these studies, please see review by the Office of Clinical Pharmacology (OCP).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical data utilized in this review were based on the sponsor's electronic submission, and the Agency's amended Written Request was used as a reference. For the prevention of CINV indication, included in the sponsor's electronic submission are two clinical trials: PALO-10-20, a randomized, active-controlled, double-blind, double-dummy, parallel (3 group), safety and efficacy study in cancer subjects full term neonates to <17 years of age receiving MEC or HEC; and PALO-99-07, a randomized, double-blind, parallel (2 group), uncontrolled proof-of-concept study in cancer subjects >28 days up to and including 17 years of age receiving MEC or HEC. Table 2 summarizes key aspects of the two clinical trials.

Table 2: Clinical Trials Submitted to Support NDA 21372, S-019

Study Number Study Dates Study Sites	Objective Study Design Study Population	No. Treated (ITT, FAS) Gender M/F Mean Age (SD) Treatment[a];	Primary Efficacy Endpoint Other Efficacy Endpoints
PALO-99-07 December 2002 – August 2005 7 sites in the US and 1 in Mexico	Safety and Tolerability, and Pharmacokinetics and Efficacy Randomized, balanced, double-blind, parallel (2 group), stratified by age and emetogenicity (moderate and high). Open-label cohort: patients aged >28 days to 23 months. Pediatric cancer patients >28 days up to and including 17 years of age receiving moderately or highly emetogenic chemotherapy.	72 treated 44M/28F Palonosetron 3 mcg/kg: 9.1 (5.5) y Palonosetron 10 mcg/kg: 8.8 (5.4) y **Palonosetron IV:** Randomized cohort: 3 mcg/kg (max 0.25 mg) single dose given by 30 sec IV bolus, or 10 mcg/kg (max 0.75 mg) single dose given by 30 sec IV bolus. Open label cohort: first 3 µg/kg IV, then 10 µg/kg IV in two sequential single rising dose cohorts groups of n=6 each.	Complete Response 0-24h (no emetic episodes, no rescue medication) after starting chemotherapy. Complete control[b] 0-24h (patients aged ≥ 6 y); Number of emetic episodes 0-24h; Need for rescue therapy 0-24h; Severity of nausea[c] 0-24h (patients aged ≥ 6 y); Time to first emetic episode, time of administration rescue therapy and time to treatment failure.
PALO-10-20 September 2011 – October 2012 71 sites in Argentina, Austria, Bulgaria, Chile, Czech Republic, Estonia, France, Germany, Hungary, Peru, Poland, Romania, Russia, Serbia, Ukraine, and United States	Efficacy, Safety, Tolerability and Pharmacokinetics Randomized, active-controlled, double-blind, double-dummy, parallel group (3 group), noninferiority active-control, stratified by age and emetogenicity, repeat cycle. Open-label sub-study: neonates aged <28d full term, repeat cycle. Pediatric cancer patients full term neonates to <17 years of age receiving moderately or highly emetogenic chemotherapy.	493 treated 262M/231F Palonosetron 10 mcg/kg: 8.1 (4.8) y Palonosetron 20 mcg/kg: 8.4 (4.9) y Ondansetron 3x0.15 mg/kg 8.2 (5.2) y **Palonosetron IV:** 10mcg/kg (max 0.75 mg) single dose 20mcg/kg (max 1.5 mg) single dose **Ondansetron IV**: 0.15 mg/kg x 3 single doses (max 32 mg) with 2nd and 3rd doses given 4 and 8 hours after 1st dose. Open-label sub-study in neonates: 3, 10 or 20 µg/kg Palonosetron IV in sequential rising dose cohorts of n=3 each (as enrollable).	Complete Response 0-24h (no vomiting, no retching, no use of antiemetic rescue medication) after starting chemotherapy during the first chemotherapy cycle. Cycle 1 Complete Response > 24 to 120 h (key end-point); Complete Response 0-120h; No vomiting, no emetic episodes, no nausea (patients aged ≥ 6 years), no use of rescue medication: 0-24h, > 24-120h and 0-120h; Time to first vomiting, time to first emetic episode, time to first administration of antiemetic rescue medication and time to treatment failure; Cycles 2 to 4 (0-24h, > 24-120h and 0-120 h): CR, no vomiting, no emetic episode, no nausea (patients aged ≥ 6 years), no use of antiemetic rescue medication.

[a] In PALO-99-07, palonosetron was given as a single I.V. push administered 30 minutes before the start of MEC or HEC. In PALO-10-20, palonosetron and ondansetron were given as a 15 minute I.V. infusion, 30 minutes prior to start of MEC or HEC and ondansetron was re-administered 4 hours and 8 hours after the first study drug administration.
[b] Complete Control defined as Complete Response and no more than mild nausea.
[c] Assessed at the end of the first 24 hours after the start of chemotherapy.
Source: Sponsor's Table 1-1, page 11, Summary of Clinical Efficacy.

5.2 Review Strategy

The Sponsor conducted two clinical studies, PALO-99-07 and PALO-10-20, to investigate the efficacy and safety of palonosetron I.V. in the prevention of CINV in pediatric cancer patients. PALO-99-07 was an early trial that completed prior to FDA issuance of the WR. As noted by the Agency in the WR after PALO-99-07 was completed, the objective of PALO-99-07 was to determine pharmacokinetic parameters of I.V. palonosetron and provide proof of concept for a single dose to prevent acute CINV in pediatric patients receiving both MEC and HEC. The WR indicated that PALO-99-07 was to be a multicenter, double-blind, randomized study in pediatric subjects 2 to <18 years of age, with an open-label cohort of subjects 1 month to <2 years of age.

Based on results from the pilot study PALO-99-07, the WR-specified larger study PALO-10-20 was subsequently conducted. Therefore, PALO-10-20 is considered the key phase 3 study that provides substantial evidence for the efficacy and safety of palonosetron I.V. in the prevention of acute CINV in pediatric cancer patients aged ≥1 month. The efficacy findings from PALO-10-20 are reviewed in detail in section 6 Review of Efficacy. Efficacy findings from the supportive, proof-of-concept study,

PALO-99-07 are discussed in Appendix 2: Discussion of Individual Trials: PALO-99-07. The safety data from both studies will be reviewed in section 7 Review of Safety.

5.3 Discussion of Individual Studies/Clinical Trials

The Sponsor conducted two clinical studies, PALO-99-07 and PALO-10-20, to investigate the efficacy and safety of palonosetron I.V. in the prevention of CINV in pediatric cancer patients.

Study PALO-99-07
PALO-99-07 was a randomized, double-blind, parallel, uncontrolled study in cancer subjects 3 months to <18 years of age receiving MEC or HEC. Subjects were randomized to receive either a single I.V. dose of 3 mcg/kg (up to a maximum of 0.25 mg) of palonosetron or a single I.V. dose of 10 mcg/kg (up to a maximum dose of 0.75 mg) of palonosetron 30 minutes before the start of chemotherapy. There was no comparator in PALO-99-07. Eligible subjects were those with histologically and/or cytologically (or imaging in the case of brain tumors) confirmed malignant disease who were scheduled to receive a single dose of ≥1 MEC or HEC agent specified in the protocol (the reader is referred to Appendix 3: Emetogenic Classification of Chemotherapy Agents for emetogenicity classification in PALO-99-07).

Subjects who received any drug with potential antiemetic effect or had experienced any vomiting, retching, or nausea within 24 hours prior to study drug administration, or were suffering from ongoing vomiting from any organic etiology were excluded. Subjects with a clinically unstable seizure disorder or with seizure activity requiring anticonvulsant medication, serum creatinine values above normal limits for the subject's age, or who were to be treated with chemotherapy that required corticosteroids on Study Day 1 were also excluded from the study.

A total of 72 subjects received study drug, at least MEC, and were included in the intent-to-treat (ITT) population for analysis. Of the 72 subjects, 60 subjects were included in the double blind portion: 29 subjects received 3 mcg/kg palonosetron and 31 subjects received 10 mcg/kg palonosetron. All of the subjects in each treatment group completed the study. Of the 12 subjects enrolled in the open-label portion of the study, 6 subjects received 3 mcg/kg palonosetron, 6 subjects received 10 mcg/kg palonosetron, and all 12 subjects completed the study.

The efficacy parameters (vomiting, retching) were collected at cycle 1 through subject diary. Study rescue medication and nausea parameters were collected in the diary. The reader is referred to Appendix 5: Definition of Efficacy Parameters Analyzed in PALO-99-07 and PALO-10-20 for additional details on the definition of efficacy parameters analyzed in PALO-99-07. A primary efficacy endpoint was not defined. The efficacy endpoint of major interest was the proportion of subjects with Complete Response (CR),

defined as no emetic episode and no rescue medication, during the first 24 hours after administration of chemotherapy.

PALO-99-07 completed enrollment in August 2005, and the PALO-99-07 clinical study report (CSR) was submitted to IND 39,797 in February 2007. Subsequent to the IND submission of the original CSR data, the FDA issued a WR to the Sponsor to perform limited re-analysis of PALO-99-07 study data using the following age groups: (a) <2 years; (b) 2 to <6 years; (c) 6 to <12 years; and (d) 12 to <18 years. Because the WR age groups differed from those evaluated in the original PALO-99-07 CSR (i.e., >28 days to 23 months, 2 to 11 years, and 12 to 17 years), the PALO-99-07 study data were re-analyzed according to the WR age groups. The re-analysis by age group also included new analyses by gender and race/ethnicity and analyses of emetogenicity for all subjects who received chemotherapy. The WR also required the analysis of the PALO-99-07 study data to include the endpoint of CR (defined as no vomiting, no retching, and no use of rescue medication) from 0 to 24 hours after the first chemotherapy dose was administered.

Because PALO-99-07 was an uncontrolled study (i.e., no active comparator arm) and because the study was designated as a proof-of-concept study for the CINV indication in pediatric cancer patients, a detailed efficacy review of PALO-99-07 will not be provided in section 6 of this review. The reader is referred to Appendix 2: Discussion of Individual Trials: PALO-99-07 for details of efficacy findings in PALO-99-07.

Study PALO-10-20
PALO-10-20 was a multicenter, double-blind, double-dummy, randomized, parallel group, phase 3 study of pediatric cancer subjects 2 months to <17 years of age involving 3 study groups receiving palonosetron in two different doses or ondansetron standard therapy (according to labeled dosage and administration instructions) for prevention of CINV. The study enrolled subjects at 59 sites distributed in the United States, Latin America, Western Europe, Russia, and Eastern European countries. For neonates, an open-label sub-study was planned starting with a palonosetron dose of 3 mcg/kg. Because the investigators were unable to enroll neonates, however, the open-label sub-study was not carried out.

Eligibility criteria
Key inclusion criteria included: (1) in- or out-patients from neonates (full term) to <17 years with histologically and/or cytologically (or imaging in the case of brain tumors) confirmed malignant disease; (2) weight at least 3.2 kg; (3) scheduled and eligible to receive at least one of the moderately or highly emetogenic chemotherapeutic agents; and (4) Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤2 for subjects aged ≥10 years to <17 years.

Key exclusion criteria included: (1) receipt of total body irradiation, upper abdomen radiotherapy, radiotherapy of the cranium, craniospinal regions or the pelvis within 1

week prior to study entry or scheduled to receive such treatment up to 24 hours after study drug administration; (2) marked baseline prolongation of QTc interval [QTcB or QTcF >460 msec] in any of the ECG assessments at screening; (3) any vomiting, retching, or nausea within 24 hours prior to the administration of the study drug; and (4) receipt of any drug with potential antiemetic effect within 24 hours prior to administration of study treatment.

First cycle
At the beginning of the screening period (completed no more than 14 days prior to administration of study drug for subjects ≥2 years old and no more than 7 days prior to administration of study drug for subjects <2 years old), instructions were provided on how to complete the paper subject diary.

The treatment period began with the first dose of study drug [randomization visit (Day 1)]. Eligible subjects (i.e., subjects meeting all eligibility criteria and who had not had vomiting, retching, or nausea within 24 hours prior to administration of study drug) were randomly assigned in a 1:1:1 ratio to blinded dosing of palonosetron 10 mcg/kg (up to a maximum total dose of 0.75 mg), palonosetron 20 mcg/kg (up to a maximum total dose of 1.5 mg), or ondansetron. Ondansetron was administered in three doses of 0.15 mg/kg for all subjects, up to a maximum total dose of 32 mg.

Reviewer comments: *The maximum total dose of ondansetron permitted in study PALO-10-20 was 32 mg, which is in accordance with the DOSAGE AND ADMINISTRATION section of labeling for I.V. ondansetron for the prevention of CINV indication during the time period in which study PALO-10-20 was conducted (first subject was enrolled September 12, 2011 and the last subject's last visit was October 26, 2012). Specifically, during the conduct of PALO-10-20, I.V. ondansetron dosage for prevention of CINV was labeled as follows (sourced from PI approved on September 14, 2011):*

> *"Adults: The recommended adult intravenous dosage of ZOFRAN is a single 32-mg dose or three 0.15-mg/kg doses. A single 32-mg dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. Efficacy of the 32-mg single dose beyond 24 hours has not been established. The recommended infusion rate should not be exceeded...With the three-dose (0.15-mg/kg) regimen, the first dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. Subsequent doses (0.15 mg/kg) are administered 4 and 8 hours after the first dose of ZOFRAN.*
>
> *Pediatrics: For pediatric patients 6 months through 18 years of age, the intravenous dosage of ZOFRAN is three 0.15-mg/kg doses...The first dose is to be administered 30 minutes before the start of moderately to highly emetogenic chemotherapy. Subsequent doses (0.15 mg/kg) are administered 4 and 8 hours after the first dose of ZOFRAN. The drug should be infused intravenously over 15 minutes."*

Although the labeled pediatric dosage regimen did not explicitly restrict maximum total dose to 32 mg, in this medical officer's assessment, the ceiling of 32 mg employed in PALO-10-20 is reasonable given the potential adverse effects of ondansetron on cardiac conduction (e.g., QT prolongation). Moreover, 32 mg was the maximum total dose of I.V. ondansetron permitted in the studies used to support approval in 2003 of I.V. palonosetron for use in adults receiving MEC or HEC.

On November 14, 2012, after the completion of study PALO-10-20, FDA approved a labeling supplement to I.V. ondansetron, in which the DOSAGE AND ADMINISTRATION section for the prevention of CINV indication was revised to the following:

> *"Adults: The recommended adult intravenous dosage of ZOFRAN is three 0.15-mg/kg doses up to a maximum of 16 mg per dose...The first dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. Subsequent doses (0.15 mg/kg up to a maximum of 16 mg per dose) are administered 4 and 8 hours after the first dose of ZOFRAN.*
>
> *Pediatrics: For pediatric patients 6 months through 18 years of age, the intravenous dosage of ZOFRAN is three 0.15-mg/kg doses up to a maximum of 16 mg per dose...The first dose is to be administered 30 minutes before the start of moderately to highly emetogenic chemotherapy. Subsequent doses (0.15 mg/kg up to a maximum of 16 mg per dose) are administered 4 and 8 hours after the first dose of ZOFRAN. The drug should be infused intravenously over 15 minutes."*

This dosing regimen implies a maximum total dose of 48 mg (16 mg x 3) in adult and pediatric patients. By the date of approval of this labeling supplement, however, study PALO-10-20 had already been completed. Therefore, in this medical officer's assessment, the Sponsor administered the comparator (ondansetron) as standard of care therapy in a manner congruent with the labeled dosage recommendations in effect during the study.

As the placebo for palonosetron, a solution with the same excipients but without palonosetron and disodium edetate (EDTA) was used, while an isotonic saline solution served as the placebo for ondansetron.

Subjects eligible for the study were assigned randomly to one of the three treatment groups:

- Group 1: palonosetron 10 mcg/kg– active palonosetron and placebo to ondansetron
- Group 2: palonosetron 20 mcg/kg – active palonosetron and placebo to ondansetron

- Group 3: ondansetron – active ondansetron and placebo to palonosetron

The first dose of study drug was administered 30 minutes (± 5) prior to initiating MEC or HEC, while subsequent ondansetron/matching placebo doses were administered 4 hours (± 30 minutes) and 8 hours (± 30 minutes) after the first dose (i.e., 3.5 and 7.5 hours after start of chemotherapy). All study drug doses were administered as a 15 minute infusion.

Subjects could also receive corticosteroids (e.g., dexamethasone) as a co-medication (at the discretion of the investigator), except if this was contraindicated or if corticosteroids were already included in the chemotherapy regimen (the reader is referred to section 6.1.10 Additional Efficacy Issues/Analyses for additional discussion).

Subsequent to the time of administration of study drug (T_0) on Day 1, subjects had 5 assessments (on Day 2, Day 3, Day 4, Day 6, and Day 7 to Day 10). During these visits, PK sampling was performed in a subset of subjects. A final follow-up assessment occurred on Day 15 to Day 18.

Subsequent cycles
Subjects could undergo study treatment for up to 4 cycles if they were scheduled to receive at least one of the moderately or highly emetogenic chemotherapeutic agents (the most emetogenic agent) on Day 1 of these subsequent cycles.

During cycles 2 to 4 the subjects were administered the same treatment as in the first cycle. The dose administered was calculated based on the actual body weight. During cycles 2 to 4 the same study procedures as during the first cycle were performed, except that the subject diary was not used during the subsequent cycles. The interval between two consecutive study drug administrations (i.e., the time interval between two consecutive 'Study Day 1' in chemotherapy cycles) was to be at least fourteen days. Study drug administration for the fourth cycle was to be performed within 12 weeks after administration of the first cycle.

Prior and concurrent therapy
Information on prior and concomitant medications was collected beginning 14 days prior to administration of the first cycle up to the follow-up visit (Day 15 to Day 18) of the last cycle. Medication for the prevention of nausea and vomiting or any other medication with potential antiemetic properties within the 24 hours prior to the start of chemotherapy (T_0) or during the 120 hours after T_0 were prohibited. For subjects receiving HEC or MEC during Day 2 to Day 6, the use of antiemetic medication for the prevention of CINV was allowed starting from 24 hours after start of chemotherapy on Day 1 (T_0). Prohibited medications are listed in Appendix 1: Discussion of Individual Trials: PALO-10-20. Systemic corticosteroid therapy at any dose within 24 hours prior to Day 1 was permitted only if part of the chemotherapy, to reduce intracranial pressure, or

in case of topical and inhaled corticosteroids with dose of ≤10 mg of prednisone daily or its equivalent.

Rescue medication could be administered to alleviate established, refractory or persistent nausea or vomiting and was permitted on an as-needed basis, not as prevention or to increase the expected antiemetic effects of the study medication. Rescue medication was defined as any drug taken for nausea or vomiting symptoms at any time during the 120-hour time interval after chemotherapy administration. Antiemetics considered as rescue medication are listed in Appendix 1: Discussion of Individual Trials: PALO-10-20. Use of metoclopramide as rescue medication was not permitted.

Study populations
The subject populations used for efficacy and safety analyses [as defined in the statistical analysis plan (SAP)] were:

- Randomized population: All randomized subjects.
- Full analysis set (FAS) population: All randomized subjects receiving the active study drug and HEC or MEC. Following the intent-to-treat principle, subjects were assigned to the study treatment group according to the randomized treatment. The FAS population was the main population for the efficacy analyses.
- Per-protocol (PP) population: The PP was a subset of the FAS. After data cleaning, a blind data review was conducted in order to define the violations leading to exclusion from the PP. For the purpose of the analysis the PP was defined only for the first cycle. The reader is referred to section 6.1.3 Subject Disposition for additional details.
- As-treated population: All randomized subjects receiving the active study drug and HEC or MEC (evaluable subjects), each subject being assigned to the treatment actually received. If all subjects received the treatment as randomized, then the as-treated population was equal to the FAS.
- Safety population (SAF): All randomized subjects receiving at least one study treatment and having at least one post-treatment safety assessment. Subjects were assigned to study treatment groups according to the actual treatment received. For subsequent cycles, the SAF population at each cycle was defined as all subjects receiving the actual study drug during the cycle.

Stratification
As pre-specified in the SAP, subjects were stratified by emetogenicity (HEC/MEC) and by the following age groups:

- <2 years
- 2 years up to <6 years
- 6 years up to <12 years
- 12 years up to <17 years.

Within each stratum, subjects were randomized prior to study drug administration to receive one of the three treatments (i.e., ondansetron, palonosetron 10 mcg/kg, palonosetron 20 mcg/kg). As pre-specified in the SAP, center was not included as a stratification factor in the randomization or as a factor in the analysis because it was "expected that some centers will enroll only few subjects."

The Sponsor noted that for the purpose of statistical analysis, the emetogenicity as entered by the investigators at randomization was revised, based on the effectively administered chemotherapy. According to the Sponsor, this reassessment was completed at the time of the blind data review meeting (before unblinding of the data) for a variety of reasons. The reader is referred to section 6.1.10 Additional Efficacy Issues/Analyses for detailed discussion. A total of 22 subjects had their corresponding emetogenicity corrected at the time of the blind data review meeting. Consequently when looking at the single age strata, minor changes could be observed across all three treatment arms (see Table 31 in section 6.1.10 Additional Efficacy Issues/Analyses). To ensure that such reassessment had not impacted the results, the outcomes of the original assessments and the reassigned assessments were compared for the primary efficacy endpoint (see Table 32). This comparison showed similar results. When not stated differently, in all tables and listings the revised assignment to HEC or MEC is used throughout this review.

Efficacy measures and the primary endpoint
The efficacy parameters (vomiting, retching) were collected at cycle 1 through subject diary. Study rescue medication was collected through the diary and the electronic case report form (eCRF), and nausea collected with the eCRF. All efficacy parameters for cycles 2 to 4 were collected directly in the eCRF. In particular, vomiting and retching were collected with a "yes/no" question. The reader is referred to Appendix 5: Definition of Efficacy Parameters Analyzed in PALO-99-07 and PALO-10-20 for additional details on the definition of efficacy parameters analyzed in PALO-10-20.

Regarding the populations for the efficacy analyses, the SAP indicated the following:

- The main population for the efficacy analyses would be the FAS population.
- The primary efficacy endpoint would also be analyzed on the PP and the "as-treated" population.
- Analyses of other efficacy endpoints would be performed on the FAS only.

The pre-specified primary efficacy endpoint was to demonstrate the non-inferiority of palonosetron compared to ondansetron in terms of the proportion of subjects reporting Complete Response (CR), defined as no emetic episode (no retching, no vomiting) and no use of antiemetic rescue medication, in the time interval 0-24 hours (acute phase) after the start of chemotherapy (T_0) during the first cycle.

Secondary endpoints
For the first cycle, the key secondary efficacy endpoint pre-specified in the final SAP for PALO-10-20 was the CR from >24 to 120 hours (delayed) after T_0.

Non-key secondary efficacy endpoints for the first cycle pre-specified in the final SAP for PALO-10-20 included the following:

- The CR from 0 to 120 hours after T_0 (overall) of the first cycle of chemotherapy
- Proportion of subjects without vomiting
- Proportion of subjects without emetic episodes
- Proportion of subjects without antiemetic rescue medication
- Proportion of subjects without nausea (subjects aged ≥ 6 years)
- Time to first vomiting
- Time to first emetic episode
- Time to first administration of rescue medication
- Time to treatment failure (time to first emetic episode or time to first administration of rescue medication, whichever comes first)

With the exception of the first non-key secondary efficacy endpoint (i.e., the CR from 0 to 120 hours after T_0 (overall) of cycle 1), all of the non-key secondary efficacy endpoints were determined for each period (acute, delayed, and overall) of cycle 1.

For subsequent cycles (cycles 2, 3, and 4), the Sponsor pre-specified the following secondary endpoints for each period (acute, delayed, and overall):

- Proportion of subjects showing CR
- Proportion of subjects without vomiting
- Proportion of subjects without emetic episodes
- Proportion of subjects without antiemetic rescue medication
- Proportion of subjects without nausea (subjects aged ≥ 6 years)

Handling of missing data is discussed in the efficacy sections 6.1.4 Analysis of Primary Endpoint(s) and 6.1.5 Analysis of Secondary Endpoints(s), and in Appendix 1: Discussion of Individual Trials: PALO-10-20.

Detailed discussion of efficacy data for PALO-10-20 is the focus of section 6 below.

6 Review of Efficacy

Efficacy Summary

In this medical officer's assessment, the efficacy data from study PALO-10-20, reviewed in detail in this section, provide substantial evidence of efficacy for I.V. palonosetron 20

mcg/kg for the prevention of acute CINV in pediatric cancer patients aged ≥1 month. For the primary efficacy endpoint of Complete Response (CR), defined as no emetic episode (no retching, no vomiting) and no use of antiemetic rescue medication, in the time interval 0-24 hours (acute phase) after the start of administration of MEC/HEC during cycle 1, the proportion of palonosetron 20 mcg/kg subjects that showed CR was 59.4%, as compared with 58.6% of subjects that received the active comparator (ondansetron). The lower bound of the 97.5% Confidence Interval (CI) of the difference between treatments (palonosetron 20 mcg/kg – ondansetron) was -11.7%, which is strictly superior to the pre-specified non-inferiority margin of -15%. This primary efficacy analysis was supported by three other pre-specified co-primary analyses, together demonstrating that palonosetron 20 mcg/kg is non-inferior to ondansetron for the prevention of acute CINV in pediatric cancer patients aged ≥1 month.

6.1 Indication

The Sponsor is seeking approval to market palonosetron hydrochloride intravenous injection for prevention of chemotherapy-induced nausea and vomiting in pediatric cancer patients aged >1 month. The proposed indication statement is:

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

The proposed dose is a single 20 mcg/kg (maximum 1.5 mg) dose administered as a 15 minute I.V. infusion to start approximately 30 minutes before the start of chemotherapy.

Reviewer comments: *The Sponsor's proposed indication statement for palonosetron in the prevention of pediatric CINV is nearly identical to the labeled indication statement for palonosetron in the prevention of adult CINV, which states the following:*

> ALOXI is indicated for:
> - Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
> - Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses

The above indication statement is based on adequate and well-controlled studies conducted in adult cancer patients (i.e., study PALO-99-03, which compared palonosetron 0.25 mg I.V. to ondansetron 32 mg I.V. in adult cancer patients receiving MEC, and study PALO-99-05, which compared palonosetron 0.25 mg I.V. to ondansetron 32 mg I.V. in adult cancer patients receiving HEC). In study PALO-99-03, the lower bound of the 97.5% CI for the difference of CR rates was greater than 0 for both the acute phase and delayed phase, supporting a superiority claim for

palonosetron 0.25 mg I.V. for the acute and delayed phases in adults receiving MEC as compared with ondansetron.

In study PALO-99-05, the lower bound of the 97.5% CI for the difference of CR rates was greater than the pre-specified NI margin of -15%, but less than 0, for both the acute phase and delayed phase. Therefore, the statistical analysis in study PALO-99-05 demonstrated non-inferiority of palonosetron 0.25 mg I.V. to ondansetron for the acute phase in adults receiving HEC. However, ondansetron does not have a labeled indication for the delayed phase. Therefore, in order to demonstrate efficacy in the delayed phase, palonosetron would need to show superiority to ondansetron in the delayed phase. Because the lower bound of the 97.5% CI for the difference of CR rates was less than 0, study PALO-99-05 did not support a superiority claim for palonosetron for the delayed phase in adults receiving HEC. For detailed discussion, the reader is referred to reviews by the statistical reviewer (Stella Grosser) for NDA 21372 in DARRTS, dated July 3, 2003 and by the medical officer (Dr. Narayan Nair) for NDA 21372 in DARRTS, dated July 8, 2003.

The above background on the labeled indication statement for palonosetron I.V. in the prevention of CINV in adults serves as an important consideration in labeling palonosetron I.V. for the prevention of CINV in pediatric patients. See section 6.1.5 Analysis of Secondary Endpoints(s) and section 9.2 Labeling Recommendations for additional discussion.

6.1.1 Methods

The Sponsor submitted data from two double-blind clinical trials (PALO 99-07 and PALO-10-20) in this sNDA. Evidence for efficacy of I.V. palonosetron comes principally from PALO-10-20, which was a multicenter, double-blind, randomized, parallel group, phase 3 study of pediatric cancer subjects aged <17 years involving 3 study groups receiving HEC or MEC and receiving palonosetron in two different doses or ondansetron for prevention of CINV. The design, eligibility criteria, and efficacy endpoints of PALO-10-20 were summarized in section 5.3 Discussion of Individual Studies/Clinical Trials and are described in additional detail in Appendix 1: Discussion of Individual Trials: PALO-10-20. The primary endpoint was the proportion of subjects showing Complete Response (CR), defined as no emetic episode (no retching, no vomiting) and no use of antiemetic rescue medication, from 0 to 24 hours after T_0 (acute phase) during the first cycle. Efficacy findings are discussed in detail in the subsections that follow.

Supportive evidence for efficacy of I.V. palonosetron is suggested by PALO-99-07, a proof-of-concept, double-blind, randomized, parallel group, phase 3 study of pediatric cancer subjects aged <18 years involving 2 study groups receiving HEC or MEC and receiving palonosetron in two different doses (i.e., 3 mcg/kg and 10 mcg/kg). Efficacy

findings for PALO-99-07 are discussed in Appendix 2: Discussion of Individual Trials: PALO-99-07.

The remainder of Section 6 focuses on efficacy findings from PALO-10-20.

6.1.2 Demographics

Table 3 presents key baseline demographic characteristics data for study PALO-10-20.

Table 3. Demographic Characteristics at Baseline – Study PALO-10-20 (FAS Population)

Variable	Palonosetron 10 (N=166)	Palonosetron 20 (N=165)	Ondansetron (N=162)
Age (Years)			
Mean ± Standard Deviation	8.1 ± 4.8	8.4 ± 4.9	8.2 ± 5.2
Median (Minimum, Maximum)	7.1 (0.2, 16.9)	7.9 (0.2, 16.9)	6.6 (0.2, 16.9)
Age Group, n (%)			
<2 Years	15 (9.0)	15 (9.1)	15 (9.3)
2 to <6 years	54 (32.5)	54 (32.7)	54 (33.3)
6 to <12 years	46 (27.7)	46 (27.9)	44 (27.2)
12 to <17 years	51 (30.7)	50 (30.3)	49 (30.2)
Sex, n (%)			
Female	78 (47.0)	89 (53.9)	64 (39.5)
Male	88 (53.0)	76 (46.1)	98 (60.5)
Race, n (%)			
White	156 (94.0)	154 (93.3)	159 (98.1)
Mixed: White and Native Indian	5 (3.0)	11 (6.7)	3 (1.9)
Asian	2 (1.2)	0	0
Black or African American	2 (1.2)	0	0
Latino	1 (0.6)	0	0
Ethnicity, n (%)			
Not Hispanic/Latino	140 (84.3)	139 (84.2)	150 (92.6)
Hispanic/Latino	26 (15.7)	26 (15.8)	12 (7.4)
Geographic Region, n (%)			
United States	11 (6.6)	8 (4.8)	8 (4.9)
Russia and Ukraine	25 (15.1)	26 (15.8)	26 (16.0)
Europe	112 (67.5)	108 (65.5)	117 (72.2)
Latin America	18 (10.8)	23 (13.9)	11 (6.8)

Source: Reviewer's table, adapted from Sponsor's Table 16, page 110; and Table 17, page 112, CSR of PALO-10-20.

Reviewer comments: *The three study arms were generally well matched with regard to age, age group, race, ethnicity, and geographic region. The proportion of males was somewhat lower in the palonosetron arms than in the ondansetron arm. Overall, the demographic subsets of subjects were limited by the inadequate percentage of subjects in the youngest age group (i.e., <2 years) and ethnic/racial minorities. For detailed*

discussion of the Sponsor's efforts to recruit into these demographic subsets, see section 6.1.7 Subpopulations.

Table 4 summarizes the classes of chemotherapy agents administered in PALO-10-20.

Table 4. Characteristics of Concomitant Chemotherapy Administered – Study PALO-10-20 (FAS Population)

Variable	Palonosetron 10 (N=166)	Palonosetron 20 (N=165)	Ondansetron (N=162)
Antineoplastic and Immunomodulating Agents, n (%)[1]			
Vinca alkaloids and analogues	105 (63.3)	107 (64.8)	111 (68.5)
Nitrogen mustard analogues	96 (57.8)	104 (63.0)	106 (65.4)
Anthracyclines and related substances	84 (50.6)	83 (50.3)	79 (48.8)
Podophyllotoxin derivatives	67 (40.4)	60 (36.4)	44 (27.2)
Platinum compounds	52 (31.3)	53 (32.1)	48 (29.6)
Pyrimidine analogues	47 (28.3)	40 (24.2)	38 (23.5)
Folic acid analogues	46 (27.7)	38 (23.0)	32 (19.8)
Other antineoplastic agents	26 (15.7)	25 (15.2)	33 (20.4)
Purine analogues	24 (14.5)	25 (15.2)	35 (21.6)
Actinomycines	29 (17.5)	19 (11.5)	24 (14.8)
Other alkylating agents	10 (6.0)	14 (8.5)	11 (6.8)
Other cytotoxic antibiotics	7 (4.2)	12 (7.3)	8 (4.9)
Nitrosoureas	3 (1.8)	6 (3.6)	6 (3.7)
Monoclonal antibodies	4 (2.4)	5 (3.0)	3 (1.9)
Methylhydrazines	2 (1.2)	7 (4.2)	0
Protein kinase inhibitors	1 (0.6)	2 (1.2)	0
Taxanes	1 (0.6)	1 (0.6)	1 (0.6)
Alkyl sulfonates	1 (0.6)	0	0
Emetogenicity of Chemotherapy, n (%)			
Highly emetogenic chemotherapy (HEC)	54 (32.5)	49 (29.7)	51 (31.5)
Moderately emetogenic chemotherapy (MEC)	112 (67.5)	116 (70.3)	111 (68.5)

[1] n (%) = total number (percentage) of subjects with at least one concomitant chemotherapy for each Anatomical Therapeutic Chemical (ATC) level 1 and 4.
Source: Reviewer's table, adapted from Sponsor's Table 23, page 121; and Table 16, page 110, CSR of PALO-10-20.

The most frequently administered chemotherapies classified as MEC or HEC were nitrogen mustard analogues such as cyclophosphamide and ifosfamide (62% of subjects), anthracyclines such as doxorubicin and daunorubicin (50% of subjects), podophyllotoxin derivatives such as etoposide (35% of subjects), and platinum compounds such as cisplatin and carboplatin (31% of subjects). For emetogenicity classifications used in study PALO-10-20, the reader is referred to Appendix 3: Emetogenic Classification of Chemotherapy Agents. In PALO-10-20, cyclophosphamide at doses ≥1500 mg/m^2 was considered HEC, whereas cyclophosphamide at doses

<1500 mg/m^2 was categorized as MEC. Anthracyclines (i.e., daunorubicin, doxorubicin, epirubicin, idarubicin, and mitoxantrone >12 mg/m^2) were categorized as MEC.

Combined anthracycline and cyclophosphamide (AC) regimens were re-classified from MEC to HEC in 2011 by the American Society of Clinical Oncology (ASCO) based on the high emetogenic potential of the agents when used together.[1] This topic is discussed further in section 6.1.10 Additional Efficacy Issues/Analyses.

Reviewer comments: *The three study arms were generally well matched with regard to the emetogenicity of chemotherapy administered and the classes of chemotherapy agents administered. Platinum compounds, including high-dose cisplatin, were also frequently administered, with ≥30% of subjects receiving platinum compounds during the overall study period.*

The labeled indication statement for palonosetron in adult cancer patients distinguishes between MEC and HEC. However, this distinction for adults is supported by separate adequate and well-controlled studies, one of which studied adults receiving MEC and another which studied adults receiving HEC. The pediatric clinical program, however, combined subjects receiving HEC and/or MEC into a single study (i.e., PALO-10-20). Moreover, it is not clear to this reviewer that a distinction between MEC and HEC is useful to prescribers for the purposes of product labeling (e.g., the indication statement) in pediatric cancer patients. See section 9.2 Labeling Recommendations for additional discussion.

Table 5 shows the primary cancer diagnosis for each system organ class (SOC) and for preferred terms (PTs) reported by ≥2% of subjects in the FAS.

[1] Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2011;29(31):4189-4198.

Table 5. Disease Characteristics at Baseline – Study PALO-10-20 (FAS Population)

Primary Cancer Summarized by SOC and PTs Reported for ≥2% of Subjects in Any Treatment Group	Palonosetron 10 (N=166) n (%)	Palonosetron 20 (N=165) n (%)	Ondansetron (N=162) n (%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**165 (99.4)**	**162 (98.2)**	**160 (98.8)**
Acute lymphoblastic leukemia	18 (10.8)	21 (12.7)	23 (14.2)
Nephroblastoma	17 (10.2)	15 (9.1)	7 (4.3)
Rhabdomyosarcoma	17 (10.2)	8 (4.8)	13 (8.0)
Neuroblastoma	13 (7.8)	10 (6.1)	11 (6.8)
Medulloblastoma	14 (8.4)	10 (6.1)	9 (5.6)
B precursor type acute leukemia	11 (6.6)	8 (4.8)	12 (7.4)
Ewing's sarcoma	5 (3.0)	11 (6.7)	9 (5.6)
Hodgkin's disease	8 (4.8)	10 (6.1)	6 (3.7)
Bone sarcoma	8 (4.8)	11 (6.7)	3 (1.9)
Non-Hodgkin's lymphoma	2 (1.2)	6 (3.6)	7 (4.3)
Hodgkin's disease nodular sclerosis stage unspecified	1 (0.6)	8 (4.8)	2 (1.2)
Primitive neuroectodermal tumor	4 (2.4)	2 (1.2)	5 (3.1)
Hodgkin's disease mixed cellularity stage unspecified	4 (2.4)	2 (1.2)	3 (1.9)
Acute myeloid leukemia	5 (3.0)	2 (1.2)	0
Ependymoma malignant	0	2 (1.2)	5 (3.1)
Optic tract glioma	1 (0.6)	5 (3.0)	1 (0.6)
T-cell type acute leukemia	0	2 (1.2)	5 (3.1)
Congenital, familial and genetic disorders	**1 (0.6)**	**3 (1.8)**	**2 (1.2)**

Abbreviations: PT, preferred term; SOC, system organ class.
Source: Reviewer's table, adapted from Sponsor's Table 19, page 115, CSR of PALO-10-20.

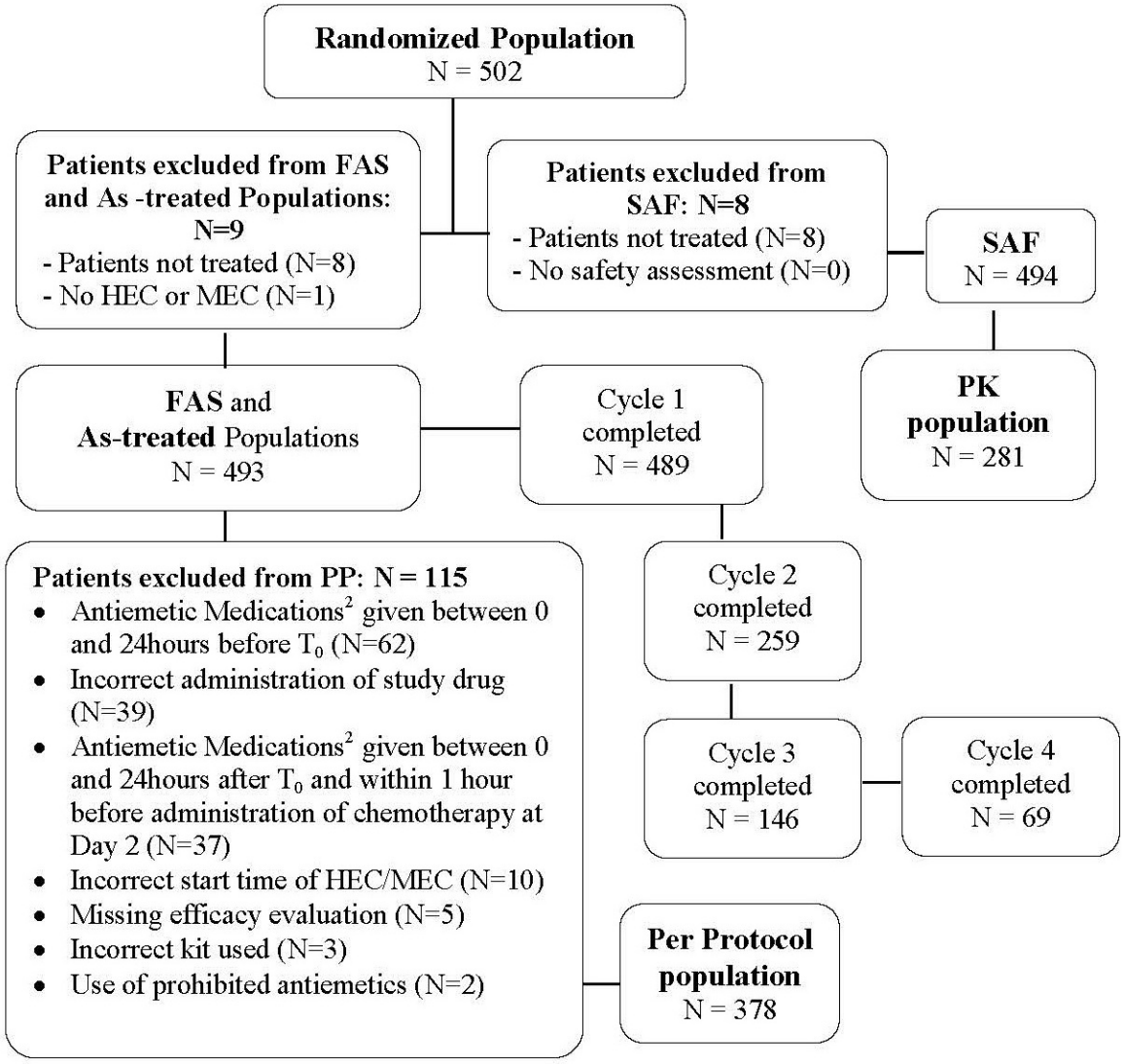
Reviewer comments: *The most frequent diagnoses were acute lymphocytic leukemia (13%), nephroblastoma (8%), rhabdomyosarcoma (8%), neuroblastoma (7%), and medulloblastoma (7%). Although all the individual diagnoses were not evenly distributed across the three treatment groups, the three treatment groups represent adequately the intended population of pediatric cancer patients.*

6.1.3 Subject Disposition

In study PALO-10-20, a total of 502 subjects were enrolled and randomly assigned to treatment at 59 sites. Study drug was not administered to 8 (1.6%) randomized subjects due to vomiting (4 subjects), chemotherapy not administered (2 subjects), central line infection (1 subjects), or an incorrect body weight (1 subject). Of the 494 subjects that received study drug (i.e., treated subjects), 167 were included in the palonosetron 10 mcg/kg group, 165 in the palonosetron 20 mcg/kg group and 162 in the ondansetron group. A subject was considered to have completed the study if he/she completed Visit 8 of the last initiated cycle. A total of 485 subjects completed all initiated study cycles,

while 17 subjects terminated the study during one of the cycles. Figure 1 summarizes subject flow in study PALO-10-20.

Figure 1. Population Flow Chart of Study PALO-10-20



Source: Sponsor's Figure 2, page 109, CSR of PALO-10-20.

Table 6 provides a more detailed summary of subject disposition and subject populations by study treatment arm. See section 5.3 Discussion of Individual Studies/Clinical Trials for definitions of the various subject populations in PALO-10-20.

Table 6. Subject Disposition – Study PALO-10-20 (Randomized Subjects)

Disposition	Palonosetron 10 (N=169)	Palonosetron 20 (N=169)	Ondansetron (N=164)
Randomized subjects[1], n (%)	169 (100.0)	169 (100.0)	164 (100.0)
Treated subjects[2], n (%)	167 (98.8)	165 (97.6)	162 (98.8)
Safety population (SAF)[3], n (%)	167 (98.8)	163 (96.4)	164 (100.0)
Full analysis set (FAS)[4], n (%)	166 (98.2)	165 (97.6)	162 (98.8)
As-treated population[5], n (%)	166 (98.2)	163 (96.4)	164 (100.0)
Per-protocol population[6], n (%)	130 (76.9)	124 (73.4)	124 (75.6)
Subjects completing the study[7], n (%)	166 (98.2)	160 (94.7)	159 (97.0)
Subjects completing cycle 1, n (%)	166 (98.2)	163 (96.4)	160 (97.6)
Subjects completing cycle 2, n (%)	84 (49.7)	89 (52.7)	86 (52.4)
Subjects completing cycle 3, n (%)	43 (25.4)	59 (34.9)	44 (26.8)
Subjects completing cycle 4, n (%)	19 (11.2)	31 (18.3)	19 (11.6)
Subjects prematurely terminating study[8], n (%)	3 (1.8)	9 (5.3)	5 (3.0)
Reason for Terminating from Study, n (%)			
Adverse event[9]	0	3 (1.8)	2 (1.2)
Death[10]	0	1 (0.6)	1 (0.6)
Withdrawal of consent	0	0	1 (0.6)
Other[11]	3 (1.8)	5 (3.0)	1 (0.6)

[1] Subjects who did not receive study treatment as randomized were included with the randomized treatment in the FAS and with the actual treatment for the SAF and the as-treated population.
[2] Study drug was not administered to 8 (1.6%) randomized subjects. Reasons included vomiting in 4 subjects (1 subject each in the palonosetron 10 mcg/kg arm and 20 mcg/kg arms, and 2 subjects in the ondansetron arm), chemotherapy not administered in 2 subjects (both in the palonosetron 20 mcg/kg arm), central line infection in 1 subject (palonosetron 20 mcg/kg arm), and incorrect body weight in 1 subject (palonosetron 10 mg/kg arm).
[3] Subjects were assigned to study treatment groups according to the actual treatment received.
[4] The FAS population was identical to the treated subjects population, except that one subject in the palonosetron 10 mcg/kg arm was excluded from the FAS population due to not receiving HEC or MEC (subject 623-5311 received study drug, but was treated with low emetogenic chemotherapy).
[5] The as-treated population included all randomized subjects receiving the active study drug and HEC or MEC (evaluable subjects), each subject being assigned to the treatment actually received. Because not all subjects received the treatment as randomized (see Table 7), the as-treated population was not equal to the FAS.
[6] Major protocol violators were excluded from the per-protocol analyses. Major protocol violations were defined as deviations affecting the primary efficacy endpoint and were therefore defined only for the first cycle. See Table 7 for listing of major violations.
[7] A subject was considered to have completed the study if he/she completed Visit 8 of the last initiated cycle. A total of 485 subjects completed all initiated study cycles, while 17 subjects terminated the study during one of the cycles.
[8] Subjects prematurely terminating the study include not treated subjects.
[9] In the palonosetron 20 mcg/kg arm: (1) Subject 515-5032, a 6-year-old male, had TEAE of febrile neutropenia (see narrative in section 7.3.2 Nonfatal Serious Adverse Events); (2) Subject 562-5430, a 2-year-old female, had AE of central line infection (and was therefore not treated); and (3) Subject 672-5358, a 9-year-old male with neuroleukemia, had TEAE of hemorrhagic stroke (following 3rd cycle of chemotherapy; see narrative in section 7.3.1 Deaths). In the ondansetron arm: (1) Subject 505-5161, a 2-year-old male, had TEAE of febrile neutropenia; and (2) Subject 623-5022, a 7-year-old male, had AE of vomiting (and was therefore not treated).
[10] In the palonosetron 20 mcg/kg arm, subject 652-5156, an 11-year-old male with acute lymphoblastic leukemia, died of acute respiratory distress syndrome and cardiac arrest. In the ondansetron arm, subject 515-5320, a 15-year-old female with osteosarcoma, died of sepsis leading to multi-organ failure. For detailed death summaries, see section 7.3.1 Deaths.
[11] Six subjects were randomized but not treated for cycle 1 (3 subjects vomited before treatment, 2 subjects could not receive chemotherapy due to decreased leukocytes and missing urine test, and 1 subject had incorrect weight entered). Three subjects (one in the palonosetron 10 mcg/kg group and 2 subjects in the palonosetron 20 mcg/kg group) were screened for a subsequent cycle but were excluded due to exclusion criteria.
Source: Reviewer's table, adapted from Table 2-15, page 40, Summary of Clinical Efficacy; Table 9, page 99 and Table 10, page 100, CSR of Study PALO-10-20.

Reviewer comments: *Premature study termination rates were somewhat greater in the palonosetron 20 mcg/kg arm (5% of subjects) than in the palonosetron 10 mcg/kg arm*

(2% of subjects) or the ondansetron arm (3% of subjects), but overall study termination rates were low. Of the subjects whose premature study termination was attributed to adverse events, none of the adverse events was, in this medical officer's assessment, related to the study drug.

Determination of per-protocol population

Major protocol violators were excluded from the per-protocol analyses. Major protocol violations were defined as deviations affecting the primary efficacy endpoint and were therefore defined only for the first cycle. Subjects having more than one deviation were counted once under each category of deviation. Major protocol violations included:

1. Antiemetic medications given between 0 and 24 hours before T_0
2. Incorrect administration of study drug
3. Antiemetic medications given between 0 and 24 hours after T_0 and within 1 hour before administration of chemotherapy at Day 2
4. Incorrect start time of HEC/MEC
5. Missing efficacy evaluation
6. Incorrect kit used
7. Use of prohibited antiemetics

In the palonosetron 10 mcg/kg arm, 39 (23%) subjects had at least one major protocol violation, as compared with 45 (27%) subjects in the palonosetron 20 mcg/kg arm, and 40 (24%) subjects in the ondansetron arm. Table 7 lists the major protocol violations.

Table 7. Summary of Major Protocol Violations in Study PALO-10-20 (Randomized Population)

Major Protocol Violation[1]	Palonosetron 10 (N=169)	Palonosetron 20 (N=169)	Ondansetron (N=164)
Antiemetic medications[2] given between 0 and 24 hours before T_0	20 (11.8)	23 (13.6)	19 (11.6)
Incorrect administration of study drug[3]	14 (8.3)	8 (4.7)	17 (10.4)
Antiemetic medications[2] given between 0 and 24 hours after T_0 and within 1 hour before administration of chemotherapy at Day 2	14 (8.3)	16 (9.5)	7 (4.3)
Incorrect start time of HEC/MEC	1 (0.6)	4 (2.4)	5 (3.0)
Missing efficacy evaluation	2 (1.2)	0	3 (1.8)
Incorrect kit used[4]	1 (0.6)	2 (1.2)	0
Use of prohibited antiemetics	0	1 (0.6)	1 (0.6)
Number of subjects with at least one major violation	39 (23.1)	45 (26.6)	40 (24.4)

[1] A major protocol violation was defined as a deviation affecting the primary endpoint and was therefore defined only for the first cycle. A subject might have multiple protocol violations. Subjects who met multiple violations were counted once in each category.
[2] Any medication with an antiemetic effect given after T_0 was considered as a rescue medication.
[3] Incorrect administration of study drug was mostly due to incorrect duration of infusion (<12 minutes or > 18 minutes) or to incorrect timing of administration with respect to start of chemotherapy.
[4] Three subjects did not receive study treatment as randomized during cycle 1 and were thus considered as major deviations. Subject 551-5277 was randomized to palonosetron 10 mcg/kg and received ondansetron. Subject 581-5423 was randomized to palonosetron 20 mcg/kg and received palonosetron 10 mcg/kg. Subject 623-5026 was randomized to palonosetron 20 mcg/kg and received ondansetron.
Source: Reviewer's table, adapted from Sponsor's Table 14, page 107, CSR of PALO-10-20.

Reviewer comments: *Overall, most major protocol violations were generally balanced across the treatment arms. More subjects in the palonosetron arms received antiemetic rescue medications after T_0 (8% in the palonosetron 10 mcg/kg arm and 10% in the palonosetron 20 mcg/kg arm) than subjects in the ondansetron arm (4%). However, because the use of antiemetic rescue medications in a subject precluded the possibility of that subject demonstrating CR, this imbalance in antiemetic rescue medication use would not be expected to favor the palonosetron arms in terms of efficacy. Incorrect administration of study drug occurred in fewer subjects in the palonosetron 20 mcg/kg arm as compared with the other 2 study arms, but this minor imbalance would not be expected to affect substantially the efficacy results. The analysis of the primary efficacy endpoint in the per-protocol population was consistent with the pre-specified primary efficacy analysis results in the FAS population (the reader is referred to the end of section 6.1.4 Analysis of Primary Endpoint(s) for additional discussion).*

6.1.4 Analysis of Primary Endpoint(s)

Stratification and handling of dropouts or missing data
As pre-specified in the SAP, subjects in PALO-10-20 were stratified by emetogenicity (HEC/MEC) and by the following age groups:

- <2 years
- 2 years up to <6 years
- 6 years up to <12 years
- 12 years up to <17 years.

These factors (i.e., age and emetogenicity) were taken into consideration for randomization and for the analyses. Within each stratum, subjects were randomized prior to study drug administration to receive one of the three treatments (ondansetron, palonosetron low or high dose). As pre-specified in the SAP, centers were not included either as a stratification factor in the randomization or as a factor in the analyses because the Sponsor expected that some centers would enroll only a few subjects, leading to empty strata. The SAP indicated that the main population for the efficacy analyses would be the FAS population. The SAP noted that in addition, the primary efficacy endpoint would be analyzed on the PP and the “as-treated” population.

Reviewer comments: *In fact, many centers in PALO-10-20 did enroll only a few subjects. Of the 57 centers that enrolled subjects included in the FAS population, 39 (68%) enrolled ≤10 subjects, and 24 (42%) enrolled ≤5 subjects.*

As pre-specified in the SAP, a conservative approach for handling of dropouts or missing data was employed. For variables with binary outcomes (e.g., presence or absence of retching, vomiting, or nausea) the value defined as lack of efficacy was used to classify the missing values.

Reviewer comments: *The Sponsor's approach to handling missing data appears congruent with recommendations from the FDA statistics review team, who in a 3 Feb 2011 Advice Letter, advised the Sponsor as follows: "For the primary and secondary binary endpoints, we recommend that you treat missing data as 'failure/no-CR.'"*

Primary efficacy endpoint: CR from 0 to 24 hours (acute) after T_0 of cycle 1

The pre-specified primary efficacy endpoint was to demonstrate the non-inferiority of palonosetron compared to ondansetron in terms of the proportion of subjects reporting Complete Response (CR), defined as no emetic episode (no retching, no vomiting) and no use of antiemetic rescue medication, in the time interval 0-24 hours (acute phase) after the start of administration (T_0) of the most emetogenic chemotherapy during the first cycle. Table 8 summarizes the results.

Table 8. Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) During First Cycle (FAS Population)

Variable	Palonosetron 10 mcg/kg (N=166)	Palonosetron 20 mcg/kg (N=165)	Ondansetron 3 x 0.15 mg/kg (N=162)
Subjects with CR, n (%)	90 (54.2)	98 (59.4)	95 (58.6)
95% CI[1] of CR Rate	[46.3, 61.9]	[51.5, 66.9]	[50.6, 66.2]

Abbreviations: CI, confidence interval; CR, complete response
[1]Wilson 95% CI with correction of continuity.
Source: Reviewer's table, adapted from Sponsor's Table 2-17, page 43, Summary of Clinical Efficacy.

The pre-specified statistical analysis of the primary endpoint included primary and co-primary efficacy analyses. As pre-specified in the SAP, in order to provide substantial evidence of efficacy, all the primary and co-primary efficacy analyses had to demonstrate positive results in favor of palonosetron.

Reviewer comments: *In this medical officer's assessment, the pre-specified primary and co-primary efficacy analyses appear congruent with recommendations from the FDA statistics review team. The reader is referred to section 2.5 Summary of Presubmission Regulatory Activity Related to Submission for additional discussion.*

The primary and co-primary efficacy analyses are described below.

Primary efficacy analysis

With a preset threshold for non-inferiority of -15%, the null hypothesis of no difference between treatments can be stated as:

$H_{0\ 20\ mcg/kg}$: $CR_{0\text{-}24\ hr\ palonosetron\ 20\ mcg/kg} - CR_{0\text{-}24\ hr\ ondansetron} \leq -15\%$
$H_{0\ 10\ mcg/kg}$: $CR_{0\text{-}24\ hr\ palonosetron\ 10\ mcg/kg} - CR_{0\text{-}24\ hr\ ondansetron} \leq -15\%$

As pre-specified in the SAP, the primary efficacy analysis was based on the stratum adjusted Mantel-Haenszel method to compute the CI for the FAS. Two palonosetron

doses were tested (10 mcg/kg and 20 mcg/kg) and type I error was adjusted for multiplicity. Table 9 summarizes the difference in proportion of subjects with CR.

Table 9. Primary Efficacy Analysis: Difference Between Treatments – Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) During First Cycle (FAS Population)

Variable	Delta Palonosetron 10 mcg/kg Minus Ondansetron (N=328)	Delta Palonosetron 20 mcg/kg Minus Ondansetron (N=327)
Overall – Weighted Sum of Delta CR[1], (%)	-4.41	0.36
97.5% CI[2]	[-16.4, 7.6]	[-11.7, 12.4]
P-value	0.0242	0.0022

Abbreviations: CI, confidence interval; CR, complete response
[1] Delta CR = Difference of rates of subjects showing complete response (CR palonosetron – CR ondansetron).
[2] Computed from the stratum adjusted Mantel-Haenszel method. H_0 is rejected if one of the p-values is <0.0125.
Source: Reviewer's table, adapted from Sponsor's Table 2-18, page 43, Summary of Clinical Efficacy.

The difference between treatments [Mantel-Haenszel 97.5% CI] for palonosetron 10 mcg/kg and ondansetron was -4.4% [-16.4%; 7.6%]. The lower bound of the 97.5% CI is not strictly superior to the non-inferiority margin of -15%. Thus, the null hypothesis for palonosetron 10 mcg/kg (i.e., $H_{0\ 10\ mcg/kg}$) is not rejected.

The difference between treatments [Mantel-Haenszel 97.5% CI] for palonosetron 20 mcg/kg and ondansetron was 0.36% [-11.7%; 12.4%]. The lower bound of the 97.5% CI is strictly superior to the non-inferiority margin of -15%. Thus, the null hypothesis for palonosetron 20 mcg/kg (i.e., $H_{0\ 20\ mcg/kg}$) is rejected.

Reviewer comments: *The above results demonstrate that the palonosetron 20 mcg/kg dose, but not the palonosetron 10 mcg/kg dose, is non-inferior to ondansetron in the prevention of CINV from 0 to 24 hours (acute phase) during the first study cycle.*

Co-primary efficacy analyses
There were three pre-specified co-primary efficacy analyses on the primary endpoint:

1. Stratum adjusted Mantel-Haenszel based on the as-treated population
2. Stratum adjusted Miettinen and Nurminen method on the FAS population
3. Stratum adjusted Miettinen and Nurminen method on the as-treated population

Table 10 summarizes results of the three co-primary efficacy analyses.

Table 10. Co-Primary Efficacy Analyses: Difference Between Treatments – Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) During First Cycle (FAS Population)

Method (Population	Delta Palonosetron 10 mcg/kg Minus Ondansetron	Delta Palonosetron 20 mcg/kg Minus Ondansetron
Stratum Adjusted Mantel-Haenszel (As-Treated Population)		
Overall – Weighted Sum of Delta CR[1], (%)	-3.66	1.92
97.5% CI	[-15.7, 8.4]	[-10.1, 14.0]
P-value[2]	0.0173	0.0008
Stratum Adjusted Miettinen and Nurminen (FAS)		
Overall Chi-2	4.0442	8.3480
Overall p-value[3]	0.0443	0.0039
Stratum Adjusted Miettinen and Nurminen (As-Treated Population)		
Overall Chi-2	4.6395	10.1025
Overall p-value[3]	0.0312	0.0015

Abbreviations: CI, confidence interval; CR, complete response
[1] Delta CR = Difference of rates of subjects showing complete response (CR palonosetron – CR ondansetron).
[2] H_0 is rejected if one of the p-values is <0.0125.
[3] H_0 is rejected if one of the p-values is <0.025.
Source: Reviewer's table, adapted from Sponsor's Table 2-19, page 44, Summary of Clinical Efficacy.

Reviewer comments: *The three co-primary efficacy analyses met pre-specified statistical thresholds and support the conclusion of the primary efficacy analysis. It appears that the pre-specified NI margin of -15% was based on adult CINV of studies of I.V. ALOXI, which also used a NI margin of -15%. The NI margin of -15% for study PALO-10-20 was also specified in the Written Request. Overall, the primary endpoint analyses produce consistent results, are statistically valid, and demonstrate non-inferiority of palonosetron 20 mcg/kg to ondansetron in the prevention of CINV from 0 to 24 hours (acute phase) during the first cycle.*

Supportive sensitivity analyses using the per protocol (PP) population also showed findings consistent with the pre-specified primary efficacy analysis on the FAS population and the co-primary efficacy analyses on the FAS and as-treated populations. In the per-protocol population, 85 of 124 (69%) of subjects that received palonosetron 20 mcg/kg showed CR in the acute phase, as compared with 78 of 130 (60%) of subjects that received palonosetron 10 mcg/kg and 79 of 124 (64%) of subjects that received ondansetron. The lower bound of the stratum-adjusted Mantel-Haenszel 97.5% CI of the difference between treatments (palonosetron 20 mcg/kg – ondansetron) was -9.1%.

6.1.5 Analysis of Secondary Endpoints(s)

The final SAP of PALO-10-20 notes that the statistical analysis would not be powered and would not be adjusted to take into account the multiplicity of the non-primary efficacy analyses. The SAP also notes that ranges of the CIs for the secondary endpoints would be produced for informative purposes only. Moreover, the final SAP of PALO-10-20 states that although statistical analyses would be performed on the key

secondary endpoint (CR from >24 to 120 hours after T_0 of the first cycle of chemotherapy), these computations would not be done in order to support any statistical claims.

Reviewer comments: *Within the SAP, the Sponsor has acknowledged that the secondary efficacy analyses lack statistical validity.*

Stratification and handling of dropouts or missing data
As pre-specified in the SAP, subjects in PALO-10-20 were stratified by emetogenicity (HEC/MEC) and by the following age groups:

- < 2 years
- 2 years up to < 6 years
- 6 years up to <12 years
- 12 years up to <17 years.

These factors (i.e., age and emetogenicity) were taken into consideration for randomization and for the analyses.

As pre-specified in the SAP, a conservative approach for handling of dropouts or missing data was employed. For variables with binary outcomes (e.g., presence or absence of retching, vomiting, or nausea) the value defined as lack of efficacy was used to classify the missing values. For time to event analyses (e.g., time to first vomiting, first emetic episode, first administration of antiemetic rescue medication, and treatment failure) the value defined as lack of efficacy was used to classify the missing value.

Reviewer comments: *The Sponsor's approach to handling missing data appears congruent with recommendations from the FDA statistics review team, who in a 3 Feb 2011 Advice Letter, advised the Sponsor as follows: "For the primary and secondary binary endpoints, we recommend that you treat missing data as 'failure/no-CR.' In addition, we recommend that you classify missing time-to-event data as 'failure' at the time missing or "failure" at T_0 + 24 hours (acute phase) or T_0 + 120 hours (overall/delayed phase) if no observed time is available."*

First cycle
The key secondary efficacy endpoint pre-specified in the final SAP for PALO-10-20 was the CR from >24 to 120 hours (delayed) after T_0 of the first cycle of chemotherapy.

Non-key secondary efficacy endpoints pre-specified in the final SAP for PALO-10-20 included the following:

- The CR from 0 to 120 hours after T_0 (overall) of the first cycle of chemotherapy
- Proportion of subjects without vomiting
- Proportion of subjects without emetic episodes

- Proportion of subjects without antiemetic rescue medication
- Proportion of subjects without nausea (subjects aged ≥ 6 years)
- Time to first vomiting
- Time to first emetic episode
- Time to first administration of rescue medication
- Time to treatment failure (time to first emetic episode or time to first administration of rescue medication, whichever comes first)

With the exception of the first non-key secondary efficacy endpoint (i.e., the CR from 0 to 120 hours after T_0 (overall) of cycle 1), all of the non-key secondary efficacy endpoints were determined for each period (acute, delayed, and overall) of cycle 1.

Subsequent cycles
For subsequent cycles (cycles 2, 3, and 4), the Sponsor pre-specified the following secondary endpoints for each period (acute, delayed, and overall):

- Proportion of subjects showing CR
- Proportion of subjects without vomiting
- Proportion of subjects without emetic episodes
- Proportion of subjects without antiemetic rescue medication
- Proportion of subjects without nausea (subjects aged ≥ 6 years)

Because they pertain to efficacy beyond the first cycle, the analyses of secondary endpoints for subsequent cycles (cycles 2, 3, and 4) are presented in section 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects.

Key secondary efficacy endpoint: CR >24 to 120 hours (delayed) after T_0 cycle 1
As noted by the statistical review team in a 21 Jun 2012 letter to the Sponsor responding to the Sponsor's SAP:

> "Since at the protocol stage, the non-inferiority margin of 15% for this key secondary endpoint was not pre-specified with the support of historical well-controlled placebo studies following ICH E-10 guidance, the noninferiority analysis for the key secondary endpoint will be considered an information comparison...those results may not be able to support a clinical benefit claim in the labeling package."

Table 11 summarizes the proportion of subjects with CR from >24 to 120 hours (delayed) after T_0 of the first cycle of chemotherapy.

Table 11. Proportion of Subjects with Complete Response in the Delayed Phase (>24-120 Hours) During the First Cycle (FAS Population)

Variable	Palonosetron 10 mcg/kg (N=166)	Palonosetron 20 mcg/kg (N=165)	Ondansetron 3 x 0.15 mg/kg (N=162)
Subjects with CR, n (%)	48 (28.9)	64 (38.8)	46 (28.4)
95% CI[1] of CR Rate	[22.3, 36.5]	[31.4, 46.7]	[21.7, 36.1]

Abbreviations: CI, confidence interval; CR, complete response.
[1]Wilson 95% CI with correction of continuity.
Source: Reviewer's table, adapted from Sponsor's Table 2-21, page 46, Summary of Clinical Efficacy.

Reviewer comments: *Numerically, a similar percentage of subjects had $CR_{>\ 24\text{-}120hrs}$ in the palonosetron 10 mcg/kg group compared with ondansetron group (29% vs. 28%) and a numerically greater percentage of subjects reported $CR_{>\ 24\text{-}120hrs}$ in the palonosetron 20 mcg/kg group compared with the ondansetron group (39% vs. 28%).*

Although the beginning of section 13 of the SAP noted that analyses of efficacy endpoints other than the primary endpoint would be performed on the FAS only, section 13.2.1 of the SAP indicated that for the key secondary endpoint, the difference in CR for the delayed period between treatment groups would be analyzed through the Mantel-Haenszel method and the Miettinen and Nurminen method on the FAS population and the "as-treated" population at a type I error of 5% and at a type I error of 2.5% (for informative purposes, in order to look similar with the primary efficacy analysis). The SAP noted that these computations would not be done in order to support any statistical claims. Table 12 summarizes the results for the Mantel-Haenszel method.

Table 12. Difference Between Treatments – Proportion of Subjects with Complete Response in the Delayed Phase (>24-120 Hours) During the First Cycle (FAS and As-Treated Population)

Stratum-Adjusted Mantel Haenszel	Delta Palonosetron 10 mcg/kg Minus Ondansetron	Delta Palonosetron 20 mcg/kg Minus Ondansetron
FAS		
Overall – Weighted Sum of Delta CR[1], (%)	0.42	10.17
95% CI	[-9.4, 10.3]	[-0.1, 20.4]
97.5% CI	[-10.9, 11.7]	[-1.5, 21.9]
As-Treated Population		
Overall – Weighted Sum of Delta CR[1], (%)	0.84	11.02
95% CI	[-9.0, 10.7]	[0.8, 21.2]
97.5% CI	[-10.4, 12.1]	[-0.7, 22.7]

Abbreviations: CI, confidence interval; CR, complete response. **CIs are presented for an information comparison only.**
[1] Delta CR = Difference of rates of subjects showing complete response (CR palonosetron – CR ondansetron).
Source: Reviewer's table, adapted from Sponsor's Table 2-22, page 46, Summary of Clinical Efficacy; Table 14.2.2.1.1, and Table 14.2.2.1.2, pages 749-750, CSR of PALO-10-20.

Reviewer comments: *Aside from the issues raised by the statistical review team regarding the statistical validity of the 15% NI margin used for the key secondary endpoint (discussed at the beginning of this section), this medical officer questions the interpretability of a noninferiority comparison between palonosetron and ondansetron during the delayed phase because ondansetron is not labeled for the delayed phase*

indication. In order to support efficacy of palonosetron for prevention of delayed CINV, the Sponsor would need to show superiority to ondansetron. Even if superiority were demonstrated, however, the robustness of such results would be limited because unlike the adult CINV program, which studied MEC and HEC separately in distinct adequate and well-controlled studies (the reader is referred to the end of section 6.1 Indication for additional discussion), the pediatric CINV program combined MEC and HEC into a single principal efficacy study (i.e., PALO-10-20).

Numerically, the treatment difference favoring palonosetron 20 mcg/kg over ondansetron increased from the acute to delayed phases. The 95% CI of the difference between palonosetron 20 mcg/kg and ondansetron treatments for the FAS population includes 0, but the lower bound of the 95% CI of the difference between palonosetron 20 mcg/kg and ondansetron treatments for the "as-treated" population exceeds 0, a finding which, according to the Sponsor, indicates that "efficacy of palonosetron 20 mcg/kg may be slightly superior to that of ondansetron regarding CR in the delayed phase." This reviewer notes, however, that the FAS population, not the "as-treated" population, was the pre-specified population for the efficacy analyses. Moreover, the 95% CI, unlike the 97.5% CI, does not adjust for multiplicity. The lower bound of the 97.5% CI of the difference in CR rates is less than 0 for both the FAS and "as-treated" populations. Therefore, this medical officer finds that the delayed phase claim in the proposed indication statement is not supported adequately.

Because palonosetron is labeled for use in the delayed phase in adults only for MEC (not for HEC), this medical officer also examined the proportion of subjects with CR in the delayed phase during cycle 1 by emetogenicity. Results are presented in Table 25 of section 6.1.7 Subpopulations. Briefly, the proportion of palonosetron 20 mcg/kg subjects with CR in the delayed phase of cycle 1 was numerically slightly greater than the proportion of ondansetron subjects with CR in the delayed phase of cycle 1 for subjects receiving MEC (36% vs. 32%). However, statistical testing of the difference in CR in the delayed phase for subjects receiving MEC would not be statistically valid and would not support the delayed phase claim in the proposed indication statement.

CR from 0 to 120 hours after T_0 (overall) of cycle 1

Table 13 summarizes analysis results for this non-key secondary endpoint.

Table 13. Proportion of Subjects with Complete Response and Difference Between Treatments in the Overall Phase (0-120 Hours) During First Cycle (FAS Population)

Variable	Palonosetron 10 mcg/kg (N=166)	Palonosetron 20 mcg/kg (N=165)	Ondansetron 3 x 0.15 mg/kg (N=162)
Subjects with CR, n (%)	39 (23.5)	54 (32.7)	39 (24.1)
Wilson 95% CI of CR Rate	[17.4, 30.8]	[25.8, 40.5]	[17.9, 31.5]
Overall – Weighted Sum of Delta CR[1], (%)	-0.60	8.25	
95% CI of the Weighted Sum of Delta CR[2]	[-10.0, 8.8]	[-1.6, 18.1]	

Abbreviations: CI, confidence interval; CR, complete response. **CIs are presented for an information comparison only.**
[1] Delta CR = Difference of rates of subjects showing complete response (CR palonosetron – CR ondansetron).
[2] Computed from the stratum adjusted Mantel-Haenszel method.
Source: Reviewer's table, adapted from Sponsor's Table 2-23 and Table 2-24, page 47, Summary of Clinical Efficacy.

Reviewer comments: *CR in the overall phase was observed in 24% of palonosetron 10 mcg/kg subjects, 33% of palonosetron 20 mcg/kg subjects, and 24% of subjects treated with ondansetron. The CR rates were numerically similar in palonosetron10 mcg/kg and ondansetron treatment groups and greater in subjects treated with palonosetron 20 mcg/kg.*

Proportion of subjects without vomiting during cycle 1

Each single episode of vomiting was to be collected in the subject's diary during cycle 1. Table 14 summarizes analysis results for this non-key secondary endpoint.

Table 14. Proportion of Subjects without Vomiting and Difference Between Treatments During the First Cycle by Phase (FAS Population)

Variable	Palonosetron 10 mcg/kg (N=166)	Palonosetron 20 mcg/kg (N=165)	Ondansetron 3 x 0.15 mg/kg (N=162)
Acute Phase			
Subjects with no vomiting, n (%)	133 (80.1)	138 (83.6)	119 (73.5)
Wilson 95% CI	[73.1, 85.7]	[76.9, 88.8]	[65.8, 79.9]
Overall – Weighted Sum of Delta[1], (%)	6.60	10.03	
95% CI of the Weighted Sum of Delta[2]	[-2.4, 15.7]	[1.2, 18.8]	
Delayed Phase			
Subjects with no vomiting, n (%)	113 (68.1)	122 (73.9)	94 (58.0)
Wilson 95% CI	[60.3, 75.0]	[66.4, 80.3]	[50.0, 65.6]
Overall – Weighted Sum of Delta[1], (%)	10.08	15.84	
95% CI of the Weighted Sum of Delta[2]	[-0.1, 20.3]	[5.7, 26.0]	
Overall Phase			
Subjects with no vomiting, n (%)	98 (59.0)	114 (69.1)	83 (51.2)
Wilson 95% CI	[51.1, 66.5]	[61.4, 75.9]	[43.3, 59.1]
Overall – Weighted Sum of Delta[1], (%)	7.97	17.46	
95% CI of the Weighted Sum of Delta[2]	[-2.6, 18.5]	[7.0, 27.9]	

Abbreviations: CI, confidence interval. **CIs are presented for an information comparison only.**
[1] Delta = Difference of rates of subjects with no vomiting (No vomiting palonosetron – No vomiting ondansetron).
[2] Computed from the stratum adjusted Mantel-Haenszel method.
Source: Reviewer's table, adapted from Sponsor's Table 2-25 and Table 2-26, page 48, Summary of Clinical Efficacy.

Reviewer comments: *Numerically, the proportions of subjects without vomiting during the acute, delayed, and overall phases of the first cycle were greater in the palonosetron 20 mcg/kg study arm than in the palonosetron 10 mcg/kg study arm, which in turn were greater than in the ondansetron study arm. Numerically, the difference between treatments (i.e., palonosetron 20 mcg/kg – ondansetron) appeared to increase from the acute to the delayed phase.*

Proportion of subjects without emetic episodes during cycle 1

An emetic episode was pre-defined as one or more continuous vomits (expulsion of stomach contents through the mouth) or retches (an attempt to vomit that is not productive of stomach contents). Regurgitation (defined as the sudden effortless return of small volumes of gastric contents into the pharynx and mouth, typically after breastfeeding or bottle feeding) was regarded as a physiological event and was not considered as an emetic episode for subjects up to 12 months of age. Table 15 summarizes analysis results for this non-key secondary endpoint.

Table 15. Proportion of Subjects without Emetic Episodes and Difference Between Treatments During the First Cycle by Phase (FAS Population)

Variable	Palonosetron 10 mcg/kg (N=166)	Palonosetron 20 mcg/kg (N=165)	Ondansetron 3 x 0.15 mg/kg (N=162)
Acute Phase			
Subjects without emetic episodes, n (%)	122 (73.5)	132 (80.0)	111 (68.5)
Wilson 95% CI	[66.0, 79.9]	[72.9, 85.7]	[60.7, 75.5]
Overall – Weighted Sum of Delta[1], (%)	5.12	11.25	
95% CI of the Weighted Sum of Delta[2]	[-4.5, 14.7]	[2.0, 20.5]	
Delayed Phase			
Subjects without emetic episodes, n (%)	102 (61.4)	113 (68.5)	86 (53.1)
Wilson 95% CI	[53.6, 68.8]	[60.7, 75.4]	[45.1, 60.9]
Overall – Weighted Sum of Delta[1], (%)	8.46	15.38	
95% CI of the Weighted Sum of Delta[2]	[-1.9, 18.8]	[5.1, 25.7]	
Overall Phase			
Subjects without emetic episodes, n (%)	87 (52.4)	105 (63.6)	74 (45.7)
Wilson 95% CI	[44.5, 60.2]	[55.8, 70.9]	[37.9, 53.7]
Overall – Weighted Sum of Delta[1], (%)	7.00	17.56	
95% CI of the Weighted Sum of Delta[2]	[-3.6, 17.6]	[7.0, 28.1]	

Abbreviations: CI, confidence interval. **CIs are presented for an information comparison only.**
[1] Delta = Difference of rates of subjects with no emetic episodes (No emetic episodes palonosetron – No emetic episodes ondansetron).
[2] Computed from the stratum adjusted Mantel-Haenszel method.
Source: Reviewer's table, adapted from Sponsor's Table 2-27 and Table 2-28, pages 49-50, Summary of Clinical Efficacy.

Reviewer comments: *As with the secondary endpoint evaluating the proportion of subjects without vomiting during the first cycle, numerically, the difference between treatments (i.e., palonosetron 20 mcg/kg – ondansetron) appeared to increase from the acute to the delayed phase.*

Proportion of subjects without antiemetic rescue medication during cycle 1

Table 16 summarizes analysis results for this non-key secondary endpoint.

Table 16. Proportion of Subjects without Antiemetic Rescue Medication and Difference Between Treatments During the First Cycle by Phase (FAS Population)

Variable	Palonosetron 10 mcg/kg (N=166)	Palonosetron 20 mcg/kg (N=165)	Ondansetron 3 x 0.15 mg/kg (N=162)
Acute Phase			
Subjects without antiemetic rescue med, n (%)	115 (69.3)	124 (75.2)	123 (75.9)
Wilson 95% CI	[61.6, 76.1]	[67.7, 81.4]	[68.5, 82.1]
Overall – Weighted Sum of Delta[1], (%)	-6.83	-1.23	
95% CI of the Weighted Sum of Delta[2]	[-16.4, 2.8]	[-10.8, 8.3]	
Delayed Phase			
Subjects without antiemetic rescue med, n (%)	64 (38.6)	75 (45.5)	57 (35.2)
Wilson 95% CI	[31.2, 46.4]	[37.8, 53.4]	[28.0, 43.1]
Overall – Weighted Sum of Delta[1], (%)	3.21	9.97	
95% CI of the Weighted Sum of Delta[2]	[-7.3, 13.7]	[-0.6, 20.6]	
Overall Phase			
Subjects without antiemetic rescue med, n (%)	60 (36.1)	69 (41.8)	54 (33.3)
Wilson 95% CI	[28.9, 44.0]	[34.3, 49.8]	[26.2, 41.2]
Overall – Weighted Sum of Delta[1], (%)	2.63	8.04	
95% CI of the Weighted Sum of Delta[2]	[-7.8, 13.0]	[-2.5, 18.5]	

Abbreviations: CI, confidence interval. **CIs are presented for an information comparison only.**
[1] Delta = Difference of rates of subjects without antiemetic rescue medications (No antiemetic rescue medications palonosetron – No antiemetic rescue medications ondansetron).
[2] Computed from the stratum adjusted Mantel-Haenszel method.
Source: Reviewer's table, adapted from Sponsor's Table 2-29 and Table 2-30, page 51, Summary of Clinical Efficacy.

Reviewer comments: *Numerically, the proportion of subjects without antiemetic rescue medication was similar in the palonosetron 20 mcg/kg arm and the ondansetron arm during the acute phase of cycle 1. During the delayed phase, the proportion of subjects without antiemetic rescue medication was greater in the palonosetron 20 mcg/kg arm than in the ondansetron arm, again qualitatively suggesting an increase from the acute to the delayed phase in the antiemetic effects of palonosetron 20 mcg/kg.*

Proportion of subjects without nausea (subjects aged ≥ 6 years) during cycle 1

Nausea was assessed in the eCRF as a yes/no question (in subjects aged ≥6 years). Table 17 summarizes analysis results for this non-key secondary endpoint.

Table 17. Proportion of Subjects without Nausea and Difference Between Treatments During the First Cycle by Phase (FAS Population)

Variable	Palonosetron 10 mcg/kg (N=97)	Palonosetron 20 mcg/kg (N=96)	Ondansetron 3 x 0.15 mg/kg (N=93)
Acute Phase			
Subjects with no nausea, n (%)	63 (64.9)	69 (71.9)	62 (66.7)
Wilson 95% CI	[54.5, 74.2]	[61.6, 80.3]	[56.0, 75.9]
Overall – Weighted Sum of Delta[1], (%)	-2.02	4.97	
95% CI of the Weighted Sum of Delta[2]	[-14.7, 10.7]	[-7.7, 17.7]	
Delayed Phase			
Subjects with no nausea, n (%)	55 (56.7)	63 (65.6)	47 (50.5)
Wilson 95% CI	[46.3, 66.6]	[55.2, 74.8]	[40.0, 61.0]
Overall – Weighted Sum of Delta[1], (%)	5.86	14.79	
95% CI of the Weighted Sum of Delta[2]	[-7.7, 19.5]	[1.5, 28.1]	
Overall Phase			
Subjects with no nausea, n (%)	46 (47.4)	56 (58.3)	40 (43.0)
Wilson 95% CI	[37.3, 57.8]	[47.8, 68.2]	[32.9, 53.7]
Overall – Weighted Sum of Delta[1], (%)	4.21	15.00	
95% CI of the Weighted Sum of Delta[2]	[-9.3, 17.7]	[1.4, 28.6]	

Abbreviations: CI, confidence interval. **CIs are presented for an information comparison only.**
[1] Delta = Difference of rates of subjects with no nausea (No nausea palonosetron – No nausea ondansetron).
[2] Computed from the stratum adjusted Mantel-Haenszel method.
Source: Reviewer's table, adapted from Sponsor's Table 2-31 and Table 2-32, pages 52 to 53, Summary of Clinical Efficacy.

Reviewer comments: *Analysis of the difference between treatments with respect to the proportion of subjects without nausea during the first cycle is again internally consistent with the numerical trend toward increased effect of palonosetron 20 mcg/kg from the acute to delayed phases in comparison to ondansetron. Although this numerical trend in the non-key secondary endpoints qualitatively suggests that palonosetron 20 mcg/kg may have benefit in preventing delayed CINV (i.e., beyond 24 hours), the data do not adequately support efficacy in the delayed phase for the purpose of product labeling.*

Time to first vomiting during cycle 1

The Cox Hazard Ratios (95% CI), stratified by age group and emetogenicity, for the time to first vomiting are summarized by phase for the FAS in Table 18.

Table 18. Time to First Vomiting (Hours) During the First Cycle by Phase (FAS Population)

Variable	Delta Palonosetron 10 mcg/kg Minus Ondansetron	Delta Palonosetron 20 mcg/kg Minus Ondansetron
Acute Phase		
Hazard ratio and 95% CI	0.717 [0.454, 1.131]	0.572 [0.352, 0.928]
Delayed Phase		
Hazard ratio and 95% CI	0.676 [0.471, 0.971]	0.564 [0.384, 0.828]
Overall Phase		
Hazard ratio and 95% CI	0.774 [0.558, 1.073]	0.564 [0.396, 0.803]

Abbreviations: CI, confidence interval. **CIs are presented for an information comparison only.**
Source: Reviewer's table, adapted from Sponsor's Table 2-34, page 55, Summary of Clinical Efficacy.

Time to first emetic episode during cycle 1

The Cox Hazard Ratios (95% CI), stratified by age group and emetogenicity, for the time to first emetic episode are summarized by phase for the FAS in Table 19.

Table 19. Time to First Emetic Episode (Hours) During the First Cycle by Phase (FAS Population)

Variable	Delta Palonosetron 10 mcg/kg Minus Ondansetron	Delta Palonosetron 20 mcg/kg Minus Ondansetron
Acute Phase		
Hazard ratio and 95% CI	0.808 [0.539, 1.212]	0.589 [0.379, 0.916]
Delayed Phase		
Hazard ratio and 95% CI	0.734 [0.524, 1.270]	0.574 [0.402, 0.820]
Overall Phase		
Hazard ratio and 95% CI	0.809 [0.595, 1.100]	0.570 [0.409, 0.795]

Abbreviations: CI, confidence interval. **CIs are presented for an information comparison only.**
Source: Reviewer's table, adapted from Sponsor's Table 2-35, page 57, Summary of Clinical Efficacy.

Reviewer comments: *For the palonosetron 20 mcg/kg vs. ondansetron comparison in all three phases of the first cycle, the numerical Cox Hazard Ratios were less than 1, suggesting that the probability of vomiting and that the probability of a first emetic episode was greater in the ondansetron group than in the palonosetron 20 mcg/kg group.*

Time to first antiemetic rescue medication during cycle 1

The Cox Hazard Ratios (95% CI), stratified by age group and emetogenicity, for the time to first antiemetic rescue medication are summarized by phase for the FAS in Table 20.

Table 20. Time to First Antiemetic Rescue Medication (Hours) During the First Cycle by Phase (FAS Population)

Variable	Delta Palonosetron 10 mcg/kg Minus Ondansetron	Delta Palonosetron 20 mcg/kg Minus Ondansetron
Acute Phase		
Hazard ratio and 95% CI	1.362 [0.897, 2.069]	1.025 [0.660, 1.592]
Delayed Phase		
Hazard ratio and 95% CI	0.974 [0.739, 1.282]	0.829 [0.624, 1.101]
Overall Phase		
Hazard ratio and 95% CI	1.032 [0.787, 1.352]	0.867 [0.657, 1.144]

Abbreviations: CI, confidence interval. **CIs are presented for an information comparison only.**
Source: Reviewer's table, adapted from Sponsor's Table 2-36, page 58, Summary of Clinical Efficacy.

Reviewer comments: *For palonosetron 20 mcg/kg vs. ondansetron comparison in all three phases of the first cycle, the numerical Cox Hazard Ratios were either greater than 1 or only slightly less than 1, suggesting that the probability of first antiemetic rescue medication use was similar in the ondansetron group and the palonosetron 20 mcg/kg group.*

Time to treatment failure during cycle 1

The Cox Hazard Ratios (95% CI), stratified by age group and emetogenicity, for the time to treatment failure (time to first emetic episode or time to first administration of rescue medication, whichever occurred first) are summarized by phase for the FAS in Table 21.

Table 21. Time to Treatment Failure (Hours) During the First Cycle by Phase (FAS Population)

Variable	Delta Palonosetron 10 mcg/kg Minus Ondansetron	Delta Palonosetron 20 mcg/kg Minus Ondansetron
Acute Phase		
Hazard ratio and 95% CI	1.099 [0.790, 1.529]	0.929 [0.660, 1.307]
Delayed Phase		
Hazard ratio and 95% CI	1.027 [0.792, 1.333]	0.797 [0.608, 1.044]
Overall Phase		
Hazard ratio and 95% CI	1.037 [0.806, 1.333]	0.823 [0.634, 1.068]

Abbreviations: CI, confidence interval. **CIs are presented for an information comparison only.**
Source: Reviewer's table, adapted from Sponsor's Table 2-33, page 54, Summary of Clinical Efficacy.

Reviewer comments: *As with the secondary endpoint evaluating the time to first antiemetic rescue medication during the first cycle, for the palonosetron 20 mcg/kg vs. ondansetron comparison the numerical Cox Hazard Ratios were only slightly less than 1 in all three phases of the first cycle, suggesting that the probability of treatment failure was similar in the ondansetron group and the palonosetron 20 mcg/kg group.*

6.1.6 Other Endpoints

Sensitivity CR
The Sponsor notes in the final SAP that during the data review process, it became apparent that for an important proportion of subjects, a HEC/MEC regimen was administered on Day 1 of the cycle, but also on Day 2 and/or Day 3, and/or Day 4, and/or Day 5. These multiple days of treatment implied the use of antiemetics including 5-HT_3 antagonists for prophylaxis of the subsequent chemotherapy administration. In the CR analysis, such intake of antiemetic medication is seen as intake of a rescue medication and as such, would be considered a failure in treatment. In order to explore the impact of multi-day chemotherapies and the impact of such antiemetic use, the Sponsor defined a new endpoint called "Sensitivity Complete Response" or Sensitivity CR, which was defined as the CR except that intake of a antiemetic medication during the 60 minutes before intake of a HEC/MEC chemotherapy (i.e., antiemetic likely given as prophylaxis) was not counted as use of a rescue medication. This endpoint was defined only at cycle 1 and only for the delayed phase, because use of prophylactic antiemetics for chemotherapies during Day 2-6 was allowed by the protocol. Table 22 presents the results.

Table 22. Proportion of Subjects with Sensitivity CR and Difference Between Treatments in the Delayed Phase (>24-120 Hours) During First Cycle (FAS Population)

Variable	Palonosetron 10 mcg/kg (N=166)	Palonosetron 20 mcg/kg (N=165)	Ondansetron 3 x 0.15 mg/kg (N=162)
Subjects with Sensitivity CR, n (%)	59 (35.5)	79 (47.9)	51 (31.5)
Wilson 95% CI of Sensitivity CR Rate	[28.4, 43.4]	[40.1, 55.8]	[24.5, 39.3]
Overall – Weighted Sum of Delta Sens CR[1], (%)	4.03	16.30	
95% CI of the Weighted Sum of Delta Sens CR[2]	[-6.2, 14.2]	[5.8, 26.8]	

Abbreviations: CI, confidence interval; CR, complete response; Sens, sensitivity. **CIs are presented for an information comparison only.**
[1] Delta CR = Difference of rates of subjects showing Sensitivity CR (Sensitivity CR palonosetron – Sensitivity CR ondansetron).
[2] Computed from the stratum adjusted Mantel-Haenszel method.
Source: Reviewer's table, adapted from Sponsor's Table 56 and Table 57, page 180, CSR of PALO-10-20.

Reviewer comments: *The sensitivity CR analysis qualitatively suggests, as expected, that when antiemetic use within 60 minutes of HEC/MEC on Days 2-6 of cycle 1 is not counted as a treatment failure, the difference between treatments (palonosetron 20 mcg/kg – ondansetron) favoring palonosetron increases further.*

6.1.7 Subpopulations

Age Group
The FDA WR notes the following requirements for PALO-10-20 to enroll across WR-specified pediatric age groups (<2 years, 2 to <6 years, 6 to <12 years, and 12 to <17 years):

> "Study 4 [PALO-10-20]: CINV – For the PK component, there must be a minimum of 24 subjects per age group for PK sampling for the 2 to <6, 6 to <12, and 12 to <17 year old groups and a minimum of 15 subjects for PK sampling for the 0 to <2 year old group. The PK data from this study must be combined with data from other relevant studies to provide descriptive statistics for each age group."… "The total number of study patients should be distributed approximately evenly among the four age groups to the extent possible. Diligent and reasonable efforts must be made to encourage enrollment across all age groups, including younger children, and these efforts must be documented in the study report."

The Sponsor notes that enrollment by age group was tracked throughout the course of the study with the aim to enroll evenly across all age groups. The Sponsor provided six enrollment status updates to FDA, including information about slow enrollment in some age groups, particularly the youngest age group (0 to <2 years). The Sponsor notes that to encourage enrollment in all age groups, particularly pediatric subjects aged <2 years, they sent newsletters (10 total) to investigators throughout the study emphasizing the need to enroll all age groups proportionally. Moreover, the Sponsor indicates that they directed the CRO to advise investigators during monitoring visits to try to increase enrollment of the youngest pediatric subjects. In their enrollment updates, the Sponsor noted that enrollment of the youngest age groups was challenging in part because parents of the youngest age group were particularly reluctant to sign the informed consent. Moreover, the Sponsor noted that enrollment of pediatric subjects aged <2 years into the PK sub-study was low due to reluctance of parents to allow PK blood samples to be drawn. The Sponsor also noted that despite efforts to enroll as many neonates into the study as feasible, no neonates were enrolled into PALO-10-20.

For the FAS, subject ages ranged from 64 days to 16.9 years. Efforts to enroll all age groups resulted in 45 (9.1%) subjects <2 years being included in the FAS. Subjects in the <2 years age group were enrolled in 12 countries. Enrollment of subjects in this age group was highest in Poland (11 subjects), Hungary (6 subjects), and the Czech Republic and US (5 subjects each).

Reviewer comments: *Theoretically, the <2 years age group would represent approximately 12.5% of subjects enrolled into the study (0-16 years), assuming an equal subject distribution for each year. In this medical officer's assessment, the Sponsor adequately documented diligent and reasonable efforts to encourage enrollment across all age groups.*

As shown in Table 23, the proportion of palonosetron 20 mcg/kg subjects with CR in the acute phase of cycle 1 was greater than the proportion of ondansetron subjects with CR in the acute phase of cycle 1 for subjects aged <2 years (60% vs. 53%) and for subjects aged 2 to <6 years (74% vs. 59%). This trend was reversed for subjects aged 6 to <12

years (50% palonosetron 20 mcg/kg vs. 59% ondansetron) and subjects aged 12 to <17 years (52% palonosetron 20 mcg/kg vs. 59% ondansetron).

Table 23. Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) During First Cycle by Age Group (FAS Population)

Age Group	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3 x 0.15 mg/kg
Age <2 years	N=15	N=15	N=15
Subjects with CR, n (%)	7 (46.7)	9 (60.0)	8 (53.3)
95% CI of CR Rate	[22.2, 72.6]	[32.9, 82.5]	[27.4, 77.7]
Age 2 up to <6 years	N=54	N=54	N=54
Subjects with CR, n (%)	38 (70.4)	40 (74.1)	32 (59.3)
95% CI of CR Rate	[56.2, 81.6]	[60.1, 84.6]	[45.1, 72.1]
Age 6 up to <12 years	N=46	N=46	N=44
Subjects with CR, n (%)	19 (41.3)	23 (50.0)	26 (59.1)
95% CI of CR Rate	[27.3, 56.7]	[35.1, 64.9]	[43.3, 73.3]
Age 12 up to <17 years	N=51	N=50	N=49
Subjects with CR, n (%)	26 (51.0)	26 (52.0)	29 (59.2)
95% CI of CR Rate	[36.8, 65.0]	[37.6, 66.1]	[44.3, 72.7]

Abbreviations: CI, confidence interval; CR, complete response. **CIs are presented for an information comparison only.**
Source: Reviewer's table, adapted from Table 28, page 129, CSR of PALO-10-20.

In PALO-10-20, in the subgroup analysis by age, the proportion of subjects with CR in the acute phase (0-24 hours) was numerically smaller in older pediatrics subjects (i.e., subjects ≥6 years of age) than in younger pediatric subjects (e.g., the 2 to <6 year age group) while there was a trend of increasing systemic exposure with increasing age (the reader is referred to Table 38 and Table 39 for a comparison of exposures by dose arm in PALO-10-20). The pharmacometrics review team's exposure-response analyses using data from the CINV trials also indicated that age and body weight are significant covariates for probability of CR in the acute phase. The pharmacometrics team asked the Sponsor to explore factors (e.g., concomitant medications, type of chemotherapy) that may explain the qualitative differences in efficacy observed by age.

In response, the Sponsor explored factors including age, total dose administered, BMI, laboratory parameters (creatinine clearance, serum ALT, AST, alkaline phosphatase, bilirubin), concomitant treatments according to their action on cytochrome P450 (2D6 inducers, 2D6 inhibitors, 3A4 inducers, 3A4 inhibitors), the type of chemotherapy (HEC/MEC), naivety of patients to chemotherapy, gender, and region (US, Russia and Ukraine, Europe, Latin America) via descriptive statistics and via logistic regression analysis. With these analyses, the Sponsor noted that they did not clearly identify any parameter or set of parameters to explain the differences in CR in the acute phase observed in PALO-10-20 across age groups. The reader is referred to the review by the pharmacometrics reviewer Dr. Jian Wang for additional details.

Reviewer comments: *As noted above, the results of the analysis of CR rates in the acute phase by age group were not consistent across all age groups with the results*

observed in the overall population. However, meaningful conclusions about trends by age group are limited by the relatively small number of subjects in each of the age groups. Given that adult CINV studies of I.V. palonosetron demonstrated efficacy at a lower dose (0.25 mg, which in a 70 kg subject equates to ~3.6 mcg/kg), this medical officer would not expect a trend of reduced efficacy of I.V. palonosetron with increasing age among pediatric subjects.

The Sponsor also performed exploratory analyses of CR rates in the delayed phase by age group and these results were again not consistent across all age groups, but in a different pattern than analyses of the CR rates in the acute phase by age group. The proportion of palonosetron 20 mcg/kg subjects with CR was greater than the proportion of ondansetron subjects with CR for subjects aged <2 years (40% vs. 13%), for subjects aged 2 to <6 years (46% vs. 37%), and for subjects aged 12 to <17 years (40% vs. 16%). This trend was reversed, however for subjects aged 6 to <12 years (28% vs. 36%). As noted previously, however, robust conclusions are precluded by the smaller sample size in each age group.

Emetogenicity

As shown in Table 24, the proportion of palonosetron 20 mcg/kg subjects with CR in the acute phase of cycle 1 was greater than the proportion of ondansetron subjects with CR in the acute phase of cycle 1 for subjects receiving HEC (51% vs. 41%). Among subjects receiving MEC, the proportion of palonosetron 20 mcg/kg subjects with CR in the acute phase of cycle 1 was similar to the proportion of ondansetron subjects with CR in the acute phase of cycle 1 (63% vs. 67%).

Table 24. Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) During First Cycle by Emetogenicity of Chemotherapy (FAS Population)

Emetogenicity	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3 x 0.15 mg/kg
HEC	N=54	N=49	N=51
Subjects with CR, n (%)	23 (42.6)	25 (51.0)	21 (41.2)
95% CI of CR Rate	[29.5, 56.7]	[36.5, 65.4]	[27.9, 55.8]
MEC	N=112	N=116	N=111
Subjects with CR, n (%)	67 (59.8)	73 (62.9)	74 (66.7)
95% CI of CR Rate	[50.1, 68.8]	[53.4, 71.6]	[57.0, 75.2]

Abbreviations: CI, confidence interval; CR, complete response; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy. **CIs are presented for an information comparison only.**
Source: Reviewer's table, adapted from Table 29, page 130, CSR of PALO-10-20.

Reviewer comments: *Numerically, the treatment difference favors palonosetron 20 mcg/kg over ondansetron among subjects that received HEC. In this medical officer's clinical assessment, if a drug is efficacious in prevention of CINV among patients that receive HEC, then it would be expected to be efficacious in prevention of CINV with less emetogenic chemotherapy (i.e., MEC).*

Because palonosetron is labeled in adults for use in the delayed phase only for MEC (not for HEC), this medical officer also examined the proportion of subjects with CR in the delayed phase during cycle 1 by emetogenicity. Table 25 presents the results.

Table 25. Proportion of Subjects with Complete Response in the Delayed Phase (>24-120 Hours) During First Cycle by Emetogenicity of Chemotherapy (FAS Population)

Emetogenicity	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3 x 0.15 mg/kg
HEC	N=54	N=49	N=51
Subjects with CR, n (%)	11 (20.4)	22 (44.9)	10 (19.6)
95% CI of CR Rate	[11.1, 33.9]	[30.9, 59.7]	[10.3, 33.5]
MEC	N=112	N=116	N=111
Subjects with CR, n (%)	37 (33.0)	42 (36.2)	36 (32.4)
95% CI of CR Rate	[24.6, 42.6]	[27.6, 45.7]	[24.0, 42.1]

Abbreviations: CI, confidence interval; CR, complete response; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy. **CIs are presented for an information comparison only.**
Source: Reviewer's table, adapted from Table 14.2.2.1.6, page 772, CSR of PALO-10-20.

The proportion of palonosetron 20 mcg/kg subjects with CR in the delayed phase of cycle 1 was numerically greater than the proportion of ondansetron subjects with CR in the delayed phase of cycle 1 for subjects receiving HEC (45% vs. 20%) and for subjects receiving MEC (36% vs. 32%).

Reviewer comments: *Findings in the delayed phase by emetogenicity are generally consistent with findings in the acute phase by emetogenicity. Namely, the treatment difference favoring palonosetron 20 mcg/kg over ondansetron appears qualitatively more pronounced among subjects receiving HEC than among subjects receiving MEC.*

Age Group and Emetogenicity

As shown in Table 26, the proportion of palonosetron 20 mcg/kg subjects with CR in the acute phase of cycle 1 was numerically greater than the proportion of ondansetron subjects with CR in the acute phase of cycle 1 for all age and emetogenicity subgroups except for subjects aged <2 years that received MEC and subjects 6 years and older that received MEC.

Table 26. Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) During First Cycle by Age Group and Emetogenicity of Chemotherapy (FAS Population)

Age Group – Emetogenicity	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3 x 0.15 mg/kg
<2 years – HEC	N=7	N=7	N=6
Subjects with CR, n (%)	2 (28.6)	4 (57.1)	2 (33.3)
95% CI of CR Rate	[5.1, 69.7]	[20.2, 88.2]	[6.0, 75.9]
2 to <6 years – HEC	N=19	N=14	N=18
Subjects with CR, n (%)	14 (73.7)	8 (57.1)	10 (55.6)
95% CI of CR Rate	[48.6, 89.9]	[29.6, 81.2]	[31.3, 77.6]
6 to <12 years – HEC	N=14	N=13	N=11
Subjects with CR, n (%)	4 (28.6)	8 (61.5)	4 (36.4)
95% CI of CR Rate	[9.6, 58.0]	[32.3, 84.9]	[12.4, 68.4]
12 to <17 years – HEC	N=14	N=15	N=16
Subjects with CR, n (%)	3 (21.4)	5 (33.3)	5 (31.3)
95% CI of CR Rate	[5.7, 51.2]	[13.0, 61.3]	[12.1, 58.5]
<2 years – MEC	N=8	N=8	N=9
Subjects with CR, n (%)	5 (62.5)	5 (62.5)	6 (66.7)
95% CI of CR Rate	[25.9, 89.8]	[25.9, 89.8]	[30.9, 91.0]
2 to <6 years – MEC	N=35	N=40	N=36
Subjects with CR, n (%)	24 (68.6)	32 (80.0)	22 (61.1)
95% CI of CR Rate	[50.6, 82.6]	[63.9, 90.4]	[43.5, 76.4]
6 to <12 years – MEC	N=32	N=33	N=33
Subjects with CR, n (%)	15 (46.9)	15 (45.5)	22 (66.7)
95% CI of CR Rate	[29.5, 65.0]	[28.5, 63.4]	[48.1, 81.4]
12 to <17 years – MEC	N=37	N=35	N=33
Subjects with CR, n (%)	23 (62.2)	21 (60.0)	24 (72.7)
95% CI of CR Rate	[44.8, 77.1]	[42.2, 75.6]	[54.2, 86.1]

Abbreviations: CI, confidence interval; CR, complete response; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy. **CIs are presented for an information comparison only.**
Source: Reviewer's table, adapted from Table 30, page 132, CSR of PALO-10-20.

Reviewer comments: *The number of subjects in each of the age and emetogenicity subgroups was probably too small to draw any meaningful conclusions.*

Gender

As shown Table 27, the CR rates in the acute phase were similar across treatment groups for male subjects, ranging from 54% (ondansetron) to 58% (palonosetron 10 mcg/kg). In female subjects the CR rates were lower in the palonosetron 10 mcg/kg group (50%) than in the palonosetron 20 mcg/kg (63%) and ondansetron (66%) groups.

Table 27. Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) During First Cycle by Gender (FAS Population)

Gender	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3 x 0.15 mg/kg
Female	N=78	N=89	N=64
Subjects with CR, n (%)	39 (50.0)	56 (62.9)	42 (65.6)
95% CI of CR Rate	[38.6, 61.4]	[52.0, 72.7]	[52.6, 76.8]
Male	N=88	N=76	N=98
Subjects with CR, n (%)	51 (58.0)	42 (55.3)	53 (54.1)
95% CI of CR Rate	[47.0, 68.2]	[43.5, 66.5]	[43.7, 64.1]

Abbreviations: CI, confidence interval; CR, complete response. **CIs are presented for an information comparison only.**
Source: Reviewer's table, adapted from Table 31, page 133, CSR of PALO-10-20.

Reviewer comments: *Overall, there appear to be no consistent differences in response rates among male and female subjects.*

Race and Ethnicity

The FDA WR states the following requirements for PALO-10-20 to enroll across WR-specified races/ethnicities:

> "The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful."… "the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement."

The Sponsor's description of their efforts to fulfill the above WR enrollment requirements are described below.

PALO-10-20 was conducted in 17 countries worldwide including USA, Argentina, Chile, Peru, Austria, Bulgaria, Czech Republic, Estonia, France, Germany, Hungary, Poland, Romania, Serbia, Russia, Ukraine and United Kingdom. A total of 71 sites participated in the study. During the course of the study, the Sponsor updated the Agency on the enrollment status and submitted 6 enrollment updates to the FDA. As the study proceeded, the Sponsor indicated that enrollment by race/ethnicity was tracked throughout the trial with the aim to enroll subjects of ethnic and racial minorities.

In addition to the race and ethnicity categories described in the WR, the eCRF included a racial category for "Other, specify" for subjects who could not be included in the WR-

defined categories. Except for 19 (3.9%, all subjects randomized in Peru) subjects described as Mixed (White and Native Indian/Hispanic), categorization of races and ethnicities are in accordance with requirements in the WR.

The Sponsor notes that they selected countries and sites in part based on their capability to enroll minority subjects and diverse races/ethnicities. The Sponsor also indicates that the objective to enroll across all races and ethnicities was regularly emphasized in serial newsletters and during monitoring visits to investigator sites. However, nearly all of those participating sites where minorities are prevalent did not enroll any subjects (regardless of race), and those sites in countries where the vast majority of subjects are white enrolled the majority of subjects in the trial. For example, sites in Hungary, Poland, Czech Republic, Romania, and Russia where nearly all of the population is white were the largest enrolling sites. The Sponsor indicates that this pattern of enrollment explains why few minority subjects such as black and Asian subjects were enrolled in PALO-10-20.

Reviewer comments: *In this medical officer's assessment, the Sponsor adequately documented their efforts to represent pediatric subjects of ethnic and racial minorities and the reasons why their efforts were unsuccessful.*

As shown in Table 28, the proportion of palonosetron 20 mcg/kg subjects with CR in the acute phase of cycle 1 was similar to the proportion of ondansetron subjects with CR in the acute phase of cycle 1 for White subjects (60% vs. 58%). The opposite numerical trend was observed for Hispanic subjects (46% palonosetron 20 mcg/kg vs. 58% ondansetron).

Table 28. Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) During First Cycle by Race and Ethnicity (FAS Population)

Race and Ethnicity	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3 x 0.15 mg/kg
White	N=156	N=154	N=159
Subjects with CR, n (%)	87 (55.8)	92 (59.7)	92 (57.9)
95% CI of CR Rate	[47.6, 63.6]	[51.5, 67.5]	[49.8, 65.6]
Hispanic	N=26	N=26	N=12
Subjects with CR, n (%)	9 (34.6)	12 (46.2)	7 (58.3)
95% CI of CR Rate	[17.9, 55.6]	[27.1, 66.3]	[28.6, 83.5]

Abbreviations: CI, confidence interval; CR, complete response. **CIs are presented for an information comparison only.**
Source: Reviewer's table, adapted from Table 32, page 134, CSR of PALO-10-20.

Reviewer comments: *Because the majority of subjects in Study PALO-10-20 were White, the Sponsor simplified the race/ethnicity subgroup analysis by comparing results for white and Hispanic subjects. In this medical officer's assessment, this is a reasonable approach. Although White subjects appear to have greater response rates than Hispanic subjects, the percentage of Hispanic subjects was too small to allow for any meaningful conclusions.*

The percentage of Black and Asian subjects was too small to allow for any meaningful assessment of CR rates. Given the mechanism of action of palonosetron, this medical officer would not expect any differences in response rates across various races or ethnicities.

Geographic Region

As shown in Table 29, in the Russia and Ukraine region, the percentage of subjects with CR in the acute phase was numerically greater in the palonosetron 20 mcg/kg arm (69%) than the ondansetron arm (58%). In contrast, in the in the United States, the percentage of subjects with CR in the acute phase was numerically smaller in the palonosetron 20 mcg/kg arm (25%) than the ondansetron arm (38%). However, the subjects enrolled at sites in Russia and Ukraine only encompassed ~16% of subjects in the FAS population and the subjects enrolled at sites in the United States only encompassed ~5% of subjects in the FAS population.

Table 29. Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) During First Cycle by Geographic Region (FAS Population)

Region	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3 x 0.15 mg/kg
United States	N=11	N=8	N=8
Subjects with CR, n (%)	1 (9.1)	2 (25.0)	3 (37.5)
95% CI of CR Rate	[0.5, 42.9]	[4.5, 64.4]	[10.2, 74.1]
Russia and Ukraine	N=25	N=26	N=26
Subjects with CR, n (%)	11 (44.0)	18 (69.2)	15 (57.7)
95% CI of CR Rate	[25.0, 64.7]	[48.1, 84.9]	[37.2, 76.0]
Europe	N=112	N=108	N=117
Subjects with CR, n (%)	70 (62.5)	66 (61.1)	70 (59.8)
95% CI of CR Rate	[52.8, 71.3]	[51.2, 70.2]	[50.3, 68.7]
Latin America	N=18	N=23	N=11
Subjects with CR, n (%)	8 (44.4)	12 (52.2)	7 (63.6)
95% CI of CR Rate	[22.4, 68.7]	[31.1, 72.6]	[31.6, 87.6]

Abbreviations: CI, confidence interval; CR, complete response. **CIs are presented for an information comparison only.**
Source: Reviewer's table, adapted from Table 33, page 135, CSR of PALO-10-20.

Reviewer comments: *Given the low percentage of subjects in regions other than Europe, it is difficult to draw meaningful conclusions about the potential impact of the CR rates in these regions on the overall primary efficacy endpoint analysis results.*

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Doses of palonosetron tested in the proof of concept study PALO-99-07 (3 mcg/kg or 10 mcg/kg) were selected on the basis of the results of the phase 2 dose-ranging study (2330) in which adult cancer subjects were randomized to receive 1 of 5 I.V. palonosetron doses (0.3-1, 3, 10, 30, or 90 mcg/kg). In addition, the adult CINV development program tested 0.25 mg (3 mcg/kg) and 0.75 mg (10 mcg/kg), where

ultimately 0.25 mg was selected and approved for prevention of CINV in adult subjects receiving HEC or MEC. All palonosetron doses were administered as an I.V. bolus over 30 seconds, 30 minutes prior to chemotherapy.

According to the Sponsor, data from PALO-99-07 suggested that palonosetron doses of 3 mcg/kg or 10 mcg/kg (up to a maximum total dose of 0.25 mg or 0.75 mg, respectively) administered as a single I.V. bolus over 30 seconds, 30 minutes prior to chemotherapy were effective in the prevention of CINV in pediatric subjects receiving MEC or HEC. Based on evaluation of the overall comparative efficacy results in pediatric and adult cancer subjects, PK considerations, and considerations of ontogenic factors for renal elimination and hepatic metabolism, the Sponsor determined that a 10 mcg/kg dose might be the lowest effective dose for further evaluation in PALO-10-20, and that an additional higher dose may be useful to confirm the lowest effective dose in the pediatric cancer population. In the original protocol for PALO-10-20 (submitted to FDA on 30 Nov 2010), the Sponsor proposed (b) (4) as the additional higher dose to be tested. However, the Agency, in an Advice Letter (dated 3 Feb 2011), recommended changing the (b) (4) dose to 20 mcg/kg in order to increase the chances of detecting a dose/exposure-response relationship for efficacy.

The Sponsor modified the protocol for PALO-10-20 to study the 10 mcg/kg and 20 mcg/kg doses of palonosetron. Moreover, the Sponsor changed the administration of palonosetron in PALO-10-20 from a 30 second bolus used in PALO-99-07 and the adult development program to a 15 minute infusion to accommodate additional volume administered to pediatric subjects and to correspond to the labeled administration of ondansetron and allow for ease of blinding during the trial. The 20 mcg/kg single dose given by I.V. infusion in PALO-10-20 demonstrated non-inferiority compared to ondansetron as standard therapy in the prevention of acute CINV.

Reviewer comments: *The Sponsor's rationale for studying the 10 mcg/kg and 20 mcg/kg doses in PALO-10-20 is supported by data from adult studies and data from PALO-99-07. Moreover, FDA agreed with the proposed study doses. The 20 mcg/kg dose met pre-specified primary efficacy endpoint definitions, while the 10 mcg/kg dose did not.*

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The efficacy of palonosetron in the prevention of CINV in pediatric subjects over repeated cycles of MEC or HEC was assessed in the phase 3 study PALO-10-20. Pediatric subjects were allowed to continue receiving chemotherapy together with the same antiemetic regimen to which they were randomized in cycle 1 for up to 4 consecutive cycles of MEC or HEC. Subjects could receive study treatment for up to 4 cycles if they were scheduled to receive at least one of the moderately or highly emetogenic chemotherapeutic agents (the most emetogenic agent) on study day 1 of

these subsequent cycles. During cycles 2 to 4, subjects were treated with the same study drug as in the first cycle

Table 30 summarizes the proportion of FAS subjects with CR in the acute phase and the delayed phase of cycle 2, cycle 3, and cycle 4.

Table 30. Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) and Delayed Phase (>24-120 Hours) During Cycles 2, 3, and 4 (FAS Population)

Cycle	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3 x 0.15 mg/kg
Cycle 2	N=82	N=90	N=86
Acute Phase			
Subjects with CR, n (%)	54 (66.7)	59 (65.6)	51 (59.3)
95% CI of CR Rate	[55.2, 76.5]	[54.7, 75.1]	[48.2, 69.6]
Delayed Phase			
Subjects with CR, n (%)	29 (35.8)	35 (38.9)	28 (32.6)
95% CI of CR Rate	[25.7, 47.3]	[29.0, 49.8]	[23.1, 43.6]
Cycle 3	N=43	N=59	N=44
Acute Phase			
Subjects with CR, n (%)	19 (44.2)	48 (81.4)	28 (63.6)
95% CI of CR Rate	[29.4, 60.0]	[68.7, 89.9]	[47.7, 77.2]
Delayed Phase			
Subjects with CR, n (%)	13 (30.2)	25 (42.4)	12 (27.3)
95% CI of CR Rate	[17.7, 46.3]	[29.8, 55.9]	[15.5, 43.0]
Cycle 4	N=19	N=31	N=19
Acute Phase			
Subjects with CR, n (%)	9 (47.4)	20 (64.5)	10 (52.6)
95% CI of CR Rate	[25.2, 70.5]	[45.4, 80.2]	[29.5, 74.8]
Delayed Phase			
Subjects with CR, n (%)	6 (31.6)	10 (32.3)	5 (26.3)
95% CI of CR Rate	[13.6, 56.5]	[17.3, 51.5]	[10.1, 51.4]

Abbreviations: CI, confidence interval; CR, complete response. **CIs are presented for an information comparison only.**
Source: Reviewer's table, adapted from Table 2-42, page 65, Summary of Clinical Efficacy.

Reviewer comments: *Subject attrition through the four cycles was considerable across all dose arms, approximately halving the sample size at each consecutive cycle. However, the attrition was relatively balanced across the treatment arms in each subsequent cycle. Although comparison of CR rates across treatment arms beyond cycle 1 is somewhat limited by the smaller sample sizes, the CR rate for palonosetron 20 mcg/kg is numerically greater than the CR rate for ondansetron both in the acute phase and the delayed phase of cycle 2, cycle 3, and cycle 4. This consistent finding across the cycles supports efficacy of palonosetron 20 mcg/kg for prevention of CINV with repeat cycles.*

For cycle 2, cycle 3, and cycle 4, the Sponsor also assessed the proportion of subjects with no vomiting, the proportion of subjects with no emetic episodes, and the proportion

of subjects with no nausea. Overall, the results were consistent across cycles and similar to the results for cycle 1 (see Table 14, Table 15, and Table 17 for cycle 1 results).

6.1.10 Additional Efficacy Issues/Analyses

Reclassification of emetogenicity of anthracyclines + cyclophosphamide
Combined anthracycline and cyclophosphamide (AC) regimens were re-classified from MEC to HEC in 2011 by the American Society of Clinical Oncology (ASCO) based on the high emetogenic potential of the agents when used together.[1] Emetogenicity classification in study PALO-10-20, however, was based on the older 2006 ASCO guidelines (see Appendix 3: Emetogenic Classification of Chemotherapy Agents). As such, in PALO-10-20, subjects that received AC would be classified as receiving HEC only if the cyclophosphamide dose was ≥1500 mg/m^2 (otherwise, they were classified as receiving MEC). On review of the concomitant medication raw dataset for PALO-10-20, this medical officer determined that in the FAS for cycle 1, 7 subjects (4%) in the palonosetron 10 mcg/kg arm, 11 subjects (7%) in the palonosetron 20 mcg/kg arm, and 6 subjects (4%) in the ondansetron arm received AC and were classified as receiving MEC.

Reviewer comments: *In this medical officer's assessment, because PALO-10-20 studied subjects receiving HEC and subjects receiving MEC in a single study, an exploratory re-analysis of the primary efficacy endpoint (CR in the acute phase) in which subjects in PALO-10-20 that received AC in cycle 1 were re-classified as receiving HEC rather than MEC would not be expected to meaningfully affect the primary efficacy analysis results. Moreover, such a re-analysis would not inform product labeling.*

Revision of emetogenicity of chemotherapy by Sponsor
The Sponsor noted that for the purpose of statistical analysis, the emetogenicity as entered by the investigators at randomization was revised, based on the effectively administered chemotherapy. According to the Sponsor, this reassessment was compelled at the time of the blind data review meeting (before unblinding of the data) by various reasons:

- Errors declared by investigators after randomization (these could not be modified in the system, since randomization was stratified by emetogenicity);
- Incorrect interpretation of the protocol regarding emetogenicity (as described in Appendix 3: Emetogenic Classification of Chemotherapy Agents – HEC or LEC instead of MEC, MEC instead of HEC);
- Subjects treated on the same day with MEC and HEC chemotherapy. In most cases these subjects started with MEC and received HEC some hours later. This combined therapy was not described in the protocol; therefore most investigators randomized the subjects to MEC since it was given first. In order to follow the worst-case-scenario, the sponsor changed these settings to HEC.

Table 31 compares the proportion of subjects with CR in the acute phase during cycle 1 by age group and emetogenicity as entered by investigators at randomization and as revised by the Sponsor at the time of the blind data review meeting.

Table 31. Proportion of Subjects with CR in the Acute Phase (0-24 Hours) During First Cycle by Age Group and Emetogenicity of Chemotherapy – Analysis Population (FAS Population)

Age Group – Emetogenicity	Palonosetron 10 mcg/kg n/N (%)	Palonosetron 20 mcg/kg n/N (%)	Ondansetron 3 x 0.15 mg/kg n/N (%)
<2 years – HEC			
Emetogenicity at Randomization	2/7 (28.6)	4/7 (57.1)	3/7 (42.9)
Corrected Emetogenicity	2/7 (28.6)	4/7 (57.1)	2/6 (33.3)
2 to <6 years – HEC			
Emetogenicity at Randomization	12/17 (70.6)	8/15 (53.3)	10/16 (62.5)
Corrected Emetogenicity	14/19 (73.7)	8/14 (57.1)	10/18 (55.6)
6 to <12 years – HEC			
Emetogenicity at Randomization	3/13 (23.1)	7/12 (58.3)	6/13 (46.2)
Corrected Emetogenicity	4/14 (28.6)	8/13 (61.5)	4/11 (36.4)
12 to <17 years – HEC			
Emetogenicity at Randomization	4/15 (26.7)	5/15 (33.3)	6/13 (33.3)
Corrected Emetogenicity	3/14 (21.4)	5/15 (33.3)	5/16 (31.3)
All Ages – HEC			
Emetogenicity at Randomization	21/52 (40.4)	24/49 (49.0)	25/49 (51.0)
Corrected Emetogenicity	23/54 (42.6)	25/49 (51.0)	21/51 (41.2)
<2 years – MEC			
Emetogenicity at Randomization	5/8 (62.5)	5/8 (62.5)	5/8 (62.5)
Corrected Emetogenicity	5/8 (62.5)	5/8 (62.5)	6/9 (66.7)
2 to <6 years – MEC			
Emetogenicity at Randomization	26/37 (70.3)	32/39 (82.1)	22/38 (57.9)
Corrected Emetogenicity	24/35 (68.6)	32/40 (80.0)	22/36 (61.1)
6 to <12 years – MEC			
Emetogenicity at Randomization	16/33 (48.5)	16/34 (47.1)	20/31 (64.5)
Corrected Emetogenicity	15/32 (46.9)	15/33 (45.5)	22/33 (66.7)
12 to <17 years – MEC			
Emetogenicity at Randomization	22/36 (61.1)	21/35 (60.0)	24/34 (70.6)
Corrected Emetogenicity	23/37 (62.2)	21/35 (60.0)	24/33 (72.7)
All Ages – MEC			
Emetogenicity at Randomization	69/114 (60.5)	74/116 (63.8)	71/111 (64.0)
Corrected Emetogenicity	67/112 (59.8)	73/116 (62.9)	74/111 (66.7)

Note: n = number of subjects with Complete Response; N = number of subjects in the subgroup
Source: Reviewer's table, adapted from Table 64, page 191, CSR of PALO-10-20.

A total of 22 subjects had their corresponding emetogenicity corrected at the time of the blind data review meeting. The Sponsor performed an additional analysis to assess the

impact of the revised emetogenicity on the CR rates. To ensure that such reassessment had not impacted the results, the outcomes of the original assessments and the reassigned assessments were compared for the primary efficacy endpoint. Table 32 summarizes the results of the comparison.

Table 32. Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) During First Cycle (FAS Population): Difference Between Treatments for Emetogenicity Defined by the Investigator and Emetogenicity Defined by the Sponsor

	Delta Palonosetron 10 mcg/kg Minus Ondansetron	Delta Palonosetron 20 mcg/kg Minus Ondansetron
HEC/MEC Defined by Investigator		
Overall – Weighted Sum of Delta CR[1], (%)	-4.55	0.66
97.5% CI[2]	[-16.7, 7.5]	[-11.4, 12.8]
HEC/MEC Defined by Sponsor		
Overall – Weighted Sum of Delta CR[1], (%)	-4.41	0.36
97.5% CI[2]	[-16.4, 7.6]	[-11.7, 12.4]

Abbreviations: CI, confidence interval; CR, complete response
[1] Delta CR = Difference of rates of subjects showing complete response (CR palonosetron – CR ondansetron).
[2] Computed from the stratum adjusted Mantel-Haenszel method.
Source: Reviewer's table, adapted from Sponsor's Table 65, page 192, CSR of PALO-10-20.

Reviewer comments: *Overall, it appears that the emetogenicity as entered by the investigators at randomization based on the effectively administered chemotherapy, had almost no impact on the primary efficacy analysis results. This is not unexpected, especially given that PALO-10-20 assessed efficacy of study drug in MEC and HEC within a single study. In this medical officer's assessment, the Sponsor's revisions, which were performed prior to data unblinding, are reasonable.*

Palonosetron 10 mcg/kg versus ondansetron

In PALO-10-20, for the primary efficacy endpoint of CR in the acute phase of the first cycle, as shown in Table 9, the difference between treatments [Mantel-Haenszel 97.5% CI] for palonosetron 10 mcg/kg and ondansetron was -4.41% [-16.4%; 7.6%]. The lower bound of the 97.5% CI was not strictly superior to the non-inferiority margin of -15%. Thus, the null hypothesis for palonosetron 10 mcg/kg (i.e., $H_{0\ 10\ mcg/kg}$) was not rejected.

Although the reason why palonosetron 10 mcg/kg failed to demonstrate non-inferiority to ondansetron on the primary endpoint is not entirely clear, the Sponsor proposed one possible explanation. As previously discussed at the beginning of section 6.1.6 Other Endpoints, CR data may have been influenced by the chemotherapy schedules used in many pediatric subjects where HEC or MEC was administered during consecutive days. Subjects undergoing such schedules also received prophylactic antiemetic treatments and were therefore considered as treatment failures. In order to better understand the efficacy of the study treatments on one-day chemotherapy, the Sponsor performed an exploratory sub-analysis on subjects receiving HEC or MEC only on Day 1, and none during the delayed phase. Table 33 presents the number of subjects undergoing chemotherapy only on Day 1 or on multiple days.

Table 33. Number of Subjects Undergoing Chemotherapy Only on Day 1 or on Multiple Days of Cycle 1 (FAS Population)

Population	Palonosetron 10 mcg/kg (N=166)	Palonosetron 20 mcg/kg (N=165)	Ondansetron 3 x 0.15 mg/kg (N=162)
Chemotherapy on Day 1 Only, n (%)	79 (47.6)	83 (50.3)	92 (56.8)
Chemotherapy Also on Days 2-6,[1] n (%)	87 (52.4)	82 (49.7)	70 (43.2)

[1] Chemotherapy on Days 2-6 reports the number of subjects receiving HEC/MEC on Days 2-6, calculated as the difference between subjects in the FAS and subjects in the subset receiving HEC/MEC only on Day 1.
Source: Reviewer's table, adapted from Sponsor's Table 58, page 181, CSR of PALO-10-20.

The Sponsor notes that whereas palonosetron 20 mcg/kg included approximately the same number of subjects from the two sub-populations, palonosetron 10 mcg/kg and ondansetron showed opposite distributions. The Sponsor posits that differences in distributions likely favored against palonosetron 10 mcg/kg in both the primary analysis and secondary analyses, because a greater proportion of subjects in this treatment group received chemotherapies also during Day 2 to 6. Table 34 summarizes CR rates in the acute phase of cycle 1 for subjects undergoing chemotherapy only on Day 1.

Table 34. CR in the Acute Phase (0-24 Hours) During First Cycle for Subjects Undergoing Chemotherapy Only on Day 1 (FAS Population)

Variable	Palonosetron 10 mcg/kg (N=79)	Palonosetron 20 mcg/kg (N=83)	Ondansetron 3 x 0.15 mg/kg (N=92)
Subjects with CR, n (%)	52 (65.8)	62 (74.7)	62 (67.4)
95% CI of CR Rate	[54.2, 75.9]	[63.8, 83.3]	[56.7, 76.6]

Abbreviations: CI, confidence interval; CR, complete response. **CIs are presented for an information comparison only.**
Source: Reviewer's table, adapted from Sponsor's Table 59, page 183, CSR of PALO-10-20.

Reviewer comments: *As predicted by the Sponsor, the CR rates for all three study arms during the acute phase of cycle 1 were greater for subjects undergoing chemotherapy only on Day 1 than subjects who also received chemotherapy on Days 2-6 (66% versus 54% for palonosetron 10 mcg/kg, 75% versus 59% for palonosetron 20 mcg/kg, and 67% versus 59% for ondansetron). Nonetheless, numerically, the CR rate for palonosetron 10 mcg/kg (66%) was still slightly lower than the CR rate for ondansetron (67%). Therefore, it is not clear to this medical officer that the failure of the 10 mcg/kg palonosetron dose to demonstrate non-inferiority to ondansetron on the primary endpoint was due entirely to differences in the subpopulations (i.e., subjects that received chemotherapy only on Day 1 and subjects that received chemotherapy also on Days 2-6) between the 10 mcg/kg and 20 mcg/kg doses.*

A simpler possible explanation for the failure of the 10 mcg/kg palonosetron dose to demonstrate noninferiority compared with ondansetron would be that the 10 mcg/kg dose was an inadequate dose. As noted previously, the Sponsor had originally proposed to study 10 mcg/kg and (b) (4) *in PALO-10-20. However, FDA*

recommended that the Sponsor study 20 mcg/kg, in order to increase the chances of detecting a dose/exposure-response relationship for efficacy. The reader is referred to section 2.5 Summary of Presubmission Regulatory Activity Related to Submission for additional discussion of this issue.

Use of corticosteroids

According to antiemetic guidelines[2,3] recommending the use of corticosteroids in the prevention of CINV in pediatric cancer patients receiving HEC/MEC, subjects in PALO-10-20 also received corticosteroids (e.g., dexamethasone) as a co-medication as determined by the investigator, unless this was contraindicated or if corticosteroids were already included in the chemotherapy cycle. A portion of the subjects did not receive concomitant corticosteroids as an adjuvant antiemetic (46% of palonosetron 10 mcg/kg subjects, 44% of palonosetron 20 mcg/kg subjects, and 45% of ondansetron subjects). The Sponsor performed an additional analysis to assess the impact of corticosteroid use on the CR rates. Table 35 summarizes the results.

Table 35. Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) During First Cycle by Corticosteroid Use (FAS Population)

	Palonosetron 10 mcg/kg n/N (%)	Palonosetron 20 mcg/kg n/N (%)	Ondansetron 3 x 0.15 mg/kg n/N (%)
Overall			
With Steroids	42/90 (46.7)	57/92 (62.0)	55/89 (61.8)
No Steroids	48/76 (63.2)	41/73 (56.2)	40/73 (54.8)
HEC			
With Steroids	5/22 (22.7)	8/19 (42.0)	7/21 (33.3)
No Steroids	18/32 (56.3)	17/30 (56.7)	14/30 (46.7)
MEC			
With Steroids	37/68 (54.4)	49/73 (67.1)	48/68 (70.6)
No Steroids	30/44 (68.2)	24/43 (55.8)	26/43 (60.5)

Note: n = number of subjects with Complete Response; N = number of subjects in the subgroup
Source: Reviewer's table, adapted from Table 63, page 189, CSR of PALO-10-20.

Reviewer comments: *Subjects that received steroids as adjuvants had CR rates of 47%, 62%, and 62%, whereas subjects that did not receive steroids had CR rates of 63%, 56%, and 55%, for the palonosetron 10 mcg/kg, palonosetron 20 mcg/kg, and ondansetron arms, respectively. Overall, the impact of steroid administration on the three treatment groups was not consistent and meaningful conclusions are limited.*

[2] Kris MG, Hesketh PJ, Somerfield MR, et al. American Society of Clinical Oncology guideline for antiemetics in oncology. *J Clin Oncol*. 2006;24(18):1-16.
[3] Multinational Association of Supportive Care in Cancer (MASCC) antiemetic guidelines – update 2010. www.mascc.org/mc/page.do?sitePageId=88041.

7 Review of Safety

Safety Summary

Assessment of a possible association between adverse events (AEs) and study drug in the CINV studies of pediatric cancer subjects (i.e., PALO-99-07 and PALO-10-20) is limited for a number of reasons. First, the study population is generally quite sick at baseline with underlying malignancies at various stages and of varying degrees of severity. Additionally, shortly after receiving study drug, all study subjects received potentially toxic chemotherapeutic agents with extensive adverse reaction profiles. Finally, the pediatric studies were not safety studies and were thus not powered or designed to test safety-related hypotheses. Despite these limitations, no clear safety signals emerged from this medical officer's review of safety data from the pediatric CINV studies. Moreover, with respect to AEs, there was no clear or consistent dose-response trend, trend in specific subgroups (e.g., age groups), or trend with repeat cycles of study drug administration in the pediatric CINV studies. Additionally, the safety database did not demonstrate an increased risk of AEs mentioned in the WR as AEs of interest (e.g., infusion site reactions including thrombophlebitis), AEs anticipated as a result of exposure to disodium edetate (EDTA), which is contained in palonosetron HCl injection (e.g., hypocalcemia, hypotension, syncope), or other AEs of interest (e.g., hypersensitivity reactions, convulsive events).

There were no deaths reported in CINV study PALO-99-07. In CINV study PALO-10-20, there were 6 deaths reported during the study (3 palonosetron subjects and 3 ondansetron subjects) and 1 death reported after the follow-up period (ondansetron subject). No deaths were causally associated with study drug.

In the CINV integrated safety population, which included subjects in PALO-99-07 and subjects in cycle 1 of PALO-10-20, there were 177 subjects [13 (7%) palonosetron 3 mcg/kg, 66 (37%) palonosetron 10 mcg/kg, 43 (24%) palonosetron 20 mcg/kg, and 55 (31%) ondansetron] that reported at least 1 serious adverse event (SAE). As adjudicated by this reviewer, all but three of the non-fatal SAEs in subjects receiving palonosetron were described by the investigator as not related to the administration of palonosetron (two were rated as unlikely related, one rated as possibly related). Detailed review of narratives for these three SAEs by this reviewer revealed alternative etiologies for each SAE that confounded attribution of SAE causality to the study drug.

As expected in this pediatric cancer study population, treatment-emergent AEs (TEAEs) in the blood and lymphatic system disorders system organ class (SOC) were the most common overall (54%) and in both treatment groups (51% for palonosetron and 59% for ondansetron). Anemia was the most commonly reported TEAE overall (33%) and in the palonosetron (33%) and ondansetron (34%) treatment groups, followed by thrombocytopenia and neutropenia.

In accordance with 21 CFR 314.50(d)(5)(vi)(b), on March 24, 2014, the Sponsor provided the 4-month safety update. In the update, the Sponsor noted that an additional literature search covering the period from October 1, 2013 through January 31, 2014 identified no pediatric safety data (i.e., no published pediatric clinical studies) regarding palonosetron. The Sponsor indicated that during this same time period, they received no postmarketing safety reports involving any pediatric patients and palonosetron. Moreover, the Sponsor noted they had no ongoing or completed pediatric clinical trials on palonosetron in the reporting period other than those originally submitted in this sNDA. Therefore, the Sponsor had no additional safety data to report in the 4-month safety update.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The WR clinical pediatric program for palonosetron is comprised of four trials: two trials (proof-of-concept study PALO-07-29 and principal study PALO-10-14) investigating the efficacy and safety of palonosetron for the prevention of post-operative nausea and vomiting (PONV) and two trials (proof-of-concept study PALO-99-07 and principal study PALO-10-20) investigating the efficacy and safety of palonosetron for the prevention of chemotherapy-induced nausea and vomiting (CINV).

The safety data for the PONV trials in pediatric subjects (PALO-07-29 and PALO-10-14) were submitted by the Sponsor in a separate sNDA (S-018), and will be reviewed separately by Dr. Teresa Buracchio. The Sponsor also submitted an integrated safety database for all pediatric subjects enrolled in the four trials (two CINV trials and two PONV trials). The integrated summary of safety (ISS) was structured to display the data for the pediatric subjects treated with the same palonosetron single doses (namely 1, 3, 10, and 20 mcg/kg) irrespective of the source study. Only the 3 mcg/kg dose was used in both indications.

The WR indicated that “safety data from the CINV study also is expected to support the safety of palonosetron for PONV prevention in pediatric patients.” This medical officer will focus this safety review on the pooled safety data from the two CINV studies (PALO-99-07 and PALO-10-20). For completeness, an overview of the ISS (i.e., the safety database combining data from the two PONV trials and the CINV trials) will also be provided in section 7.7 Additional Submissions / Safety Issues. For a detailed assessment of the safety database for the PONV trials, however, the reader is referred to the clinical review by Dr. Buracchio.

Two trials (PALO-99-07 and PALO-10-20) comprise the pediatric development program requested by FDA for CINV as stated in the WR issued on July 23, 2010 and in subsequent amendments issued on September 30, 2010, October 22, 2012, and February 15, 2013. The CINV integrated safety population from the two trials includes

all subjects who received I.V. study medication, who had at least 1 post-treatment safety assessment, and who completed 1 cycle of chemotherapy. PALO-10-20 was a multiple cycle study, and the safety population for subsequent cycles includes all subjects who received I.V. study medication, had at least 1 post-treatment safety assessment and completed up to 4 cycles of chemotherapy. The safety data for subsequent cycles are presented alongside cycle 1 safety data in several subsections as appropriate (e.g., section 7.4 Supportive Safety Results) and separately in section 7.7 Additional Submissions / Safety Issues.

7.1.2 Categorization of Adverse Events

The Sponsor coded adverse events (AEs) using the Medical Dictionary of Regulatory Activities (MedDRA) (version 14.0) and classified by MedDRA system organ class (SOC) and preferred term (PT). In both CINV trials (PALO-99-07 and PALO-10-20), the Sponsor defined a treatment-emergent (TEAE) as an AE that began or worsened in intensity after the start of the administration of the study drug (or on the same day if the start time of the AE was not available).

Reviewer comments: *This reviewer evaluated the appropriateness of the Sponsor's coding by comparing preferred terms to verbatim terms recorded by investigators. Coding was reasonably accurate. Accordingly, this reviewer did not recode any of the AE terms in the safety datasets. This reviewer generated AE incidence rates by treatment arm and confirmed the accuracy of the AE incidence rates presented by the Sponsor.*

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from the two CINV trials (PALO-99-07 and PALO-10-20) were combined and analyzed for the integrated safety evaluation for the CINV indication (i.e., the CINV integrated safety population).

For completeness, data from the two PONV trials (PALO-07-29 and PALO-10-14) and the two CINV trials (PALO-99-07 and PALO-10-20), as presented by the Sponsor in the integrated summary of safety (ISS), were also reviewed. See section 7.7 Additional Submissions / Safety Issues for discussion.

Reviewer comments: *The pooling of data as presented in the Sponsor's CINV integrated safety population and ISS (encompassing the PONV and CINV trials) appears acceptable.*

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 577 pediatric cancer subjects receiving MEC or HEC chemotherapy were included in the 2 trials of I.V. palonosetron for the prevention of CINV (PALO-99-07 and PALO-10-20). Of these subjects, 566 received I.V. study medication with MEC or HEC chemotherapy in cycle 1. Overall, 402 subjects received palonosetron (35 received 3 mcg/kg, 204 received 10 mcg/kg, and 163 received 20 mcg/kg), and 164 subjects received ondansetron. Subjects were assigned to study treatment groups for safety analyses according to the actual treatment received.

Table 36 summarizes subject disposition by treatment arm across the two CINV trials (PALO-99-07 and PALO-10-20).

Table 36. Subject Disposition – CINV Integrated Safety Population (PALO-99-07 and PALO-10-20) for Cycle 1

Subject Disposition	Palo 3 mcg/kg n (%)	Palo 10 mcg/kg n (%)	Palo 20 mcg/kg n (%)	Palo All Doses n (%)	Ondansetron 0.15 mg x 3 n (%)	All Drugs, All Doses n (%)
Safety population (SAF)	35 (100)	204 (100)	163 (100)	402 (100)	164 (100)	566 (100)
Completing the study	35 (100)	203 (99.5)	158 (96.9)	396 (98.5)	161 (98.2)	557 (98.4)
Prematurely terminating study	0	1 (0.5)	5 (3.1)	6 (1.5)	3 (1.8)	9 (1.6)
Reason for Terminating from Study						
Adverse event	0	0	2 (1.2)	2 (0.5)	1 (0.6)	3 (0.5)
Death	0	0	1 (0.6)	1 (0.2)	1 (0.6)	2 (0.4)
Withdrawal of consent	0	0	0	0	1 (0.6)	1 (0.2)
Other reason	0	1 (0.5)	2 (1.2)	3 (0.7)	0	3 (0.5)

Note: For details of reasons for termination from study, see Table 6, which also includes data for all 4 cycles of PALO-10-20.
Source: Reviewer's table, adapted from Table 1-5, page 20, Summary of Clinical Safety.

Of the 402 subjects who received palonosetron, a total of 6 (1.5%) subjects discontinued from the study for other reason (3 subjects, 0.7%), TEAE (2 subjects, 0.5%), and death (1 subject, 0.2%). Of the 164 subjects who received ondansetron, 3 (1.8%) subjects discontinued from the study because of withdrawal of consent, TEAE, and death (1 subject each, 0.6%). Among the subjects who discontinued from the study, the rate of discontinuation was greater in the palonosetron 20 mcg/kg group (3.1%) compared to the palonosetron 10 mcg/kg group (0.5%) and the ondansetron group (1.8%).

Table 37 summarizes subject disposition by treatment arm across the two CINV trials (PALO-99-07 and PALO-10-20).

Table 37. Demographics – CINV Integrated Safety Population (PALO-99-07 and PALO-10-20) for Cycle 1

Subject Disposition	Palo 3 mcg/kg (N=35) n (%)	Palo 10 mcg/kg (N=204) n (%)	Palo 20 mcg/kg (N=163) n (%)	Palo All Doses (N=402) n (%)	Ondansetron 0.15 mg x 3 (N=164) n (%)	All Drugs, All Doses (N=566) n (%)
Age Group, n (%)						
<2 Years	6 (17.1)	21 (10.3)	15 (9.2)	42 (10.4)	15 (9.1)	57 (10.1)
2 to <6 years	4 (11.4)	60 (29.4)	53 (32.5)	117 (29.1)	55 (33.5)	172 (30.4)
6 to <12 years	10 (28.6)	58 (28.4)	45 (27.6)	113 (28.1)	45 (27.4)	158 (27.9)
12 to <18 years	15 (42.9)	65 (31.9)	50 (30.7)	130 (32.3)	49 (29.9)	179 (31.6)
Sex, n (%)						
Female	13 (37.1)	92 (45.1)	88 (54.0)	193 (48.0)	66 (40.2)	259 (45.8)
Male	22 (62.9)	112 (54.9)	75 (46.0)	209 (52.0)	98 (59.8)	307 (54.2)
Race, n (%)						
White	15 (42.9)	177 (86.8)	152 (93.3)	344 (85.6)	161 (98.2)	505 (89.2)
Black	2 (5.7)	2 (1.0)	0	4 (1.0)	0	4 (0.7)
Asian	1 (2.9)	2 (1.0)	0	3 (0.7)	0	3 (0.5)
Multiracial	3 (8.6)	5 (2.5)	11 (6.7)	19 (4.7)	3 (1.8)	22 (3.9)
Missing	14 (40.0)	18 (8.8)	0	32 (8.0)	0	32 (5.7)
Race / Ethnicity, n (%)						
Not Hispanic/Latino	0	142 (69.6)	137 (84.0)	279 (69.4)	151 (92.1)	430 (76.0)
Hispanic/Latino	15 (42.9)	43 (21.1)	26 (16.0)	84 (20.9)	13 (7.9)	97 (17.1)
Missing	20 (57.1)	19 (9.3)	0	39 (9.7)	0	39 (6.9)
Geographic Region, n (%)						
United States	32 (91.4)	42 (20.6)	8 (4.9)	82 (20.4)	8 (4.9)	90 (15.9)
Russia and Ukraine	0	25 (12.3)	26 (16.0)	51 (12.7)	26 (15.9)	77 (13.6)
Europe	0	114 (55.9)	106 (65.0)	220 (54.7)	118 (72.0)	338 (59.7)
Latin America	3 (8.6)	23 (11.3)	23 (14.1)	49 (12.2)	12 (7.3)	61 (10.8)

Source: Reviewer's table, adapted from Table 1-7, page 22, Summary of Clinical Safety.

Enrollment in age groups 2 to <6 years, 6 to <12 years, and 12 to <18 years was approximately 30% of the total in each age group for subjects receiving palonosetron or ondansetron. The enrollment of subjects aged <2 years was notably lower for subjects in both palonosetron (10%) and ondansetron (9%) groups.

Reviewer comments: *The distribution of subjects by age group was balanced overall across treatment groups. As noted by the Sponsor, the enrollment of subjects <2 years was low in all treatment groups due largely to difficulty in obtaining parental consent. Moreover, the enrollment of racial and ethnic minorities was low in all treatment groups. The Sponsor indicated that countries and sites were selected in part to facilitate enrollment of minority subjects. The Sponsor noted, however, that nearly all of those*

participating sites where minorities are prevalent did not enroll any subjects (regardless of race), and those sites in countries where the vast majority of subjects are white enrolled the majority of subjects in study PALO-10-20. For example, sites in Hungary, Poland, Czech Republic, Romania, and Russia, where nearly all of the population is white, were the sites that enrolled the most subjects. Issues with enrollment in the youngest age group and of racial/ethnic minorities were discussed previously in section 6.1.7 Subpopulations. Although enrollment of subjects <2 years was low, this medical officer noted no clear trends in AEs to suggest a greater risk of AEs in the youngest age group. Moreover, given what is known about the mechanism of action of palonosetron and the underlying condition (i.e., cancer), this medical officer would not expect a substantially different AE profile among racial/ethnic minorities as compared with white subjects.

Because the 20 mcg/kg dose of palonosetron is the dose recommended by this medical officer for approval for the prevention of CINV in pediatric patients, exposure data presented below focus on PALO-10-20, which was the only CINV study that evaluated the 20 mcg/kg dose. Table 38 presents the extent of exposure by study arm.

Table 38. Extent of Exposure to Study Drug in Cycle 1 of PALO-10-20 (SAF Population)

Variable	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3 x 0.15 mg/kg
	Total dose in mcg	Total dose in mcg	Total dose in mg
Mean (SD)	287.6 (170.9)	610.5 (347.8)	13.88 (8.8)
Median (Min, Max)	230.0 (52.0, 750.0)	560.0 (108.0, 1500.0)	9.90 (2.10, 33.78)

Abbreviations: Max, maximum; Min, minimum; SD, standard deviation.
Source: Reviewer's table, adapted from Table 82, page 220, CSR of Study PALO-10-20.

Reviewer comments: *As expected with weight-based dosing of study drug, exposures were greater in the palonosetron 20 mcg/kg group than in the palonosetron 10 mcg/kg group.*

Exposure data for subsequent cycles (cycles 2-4) are presented in Table 51 of section 7.7 Additional Submissions / Safety Issues.

Table 39. Extent of Exposure to Study Drug in Cycle 1 of PALO-10-20 by Age Group (SAF)

Variable	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3 x 0.15 mg/kg
	Total dose in mcg	Total dose in mcg	Total dose in mg
Age <2 Years	N=15	N=15	N=15
Mean (SD)	89.13 (21.24)	188.5 (50.25)	4.20 (1.21)
Median (Min, Max)	84.0 (52.0, 120.0)	200.0 (108.0, 260.0)	4.26 (2.10, 6.36)
Age 2 up to <6 years	N=55	N=53	N=55
Mean (SD)	160.8 (40.95)	329.5 (66.96)	6.95 (1.46)
Median (Min, Max)	150.0 (90.0, 276.0)	320.0 (210.0, 600.0)	6.78 (3.66, 10.32)
Age 6 up to <12 years	N=46	N=45	N=45
Mean (SD)	271.7 (90.88)	650.6 (177.0)	12.88 (3.26)
Median (Min, Max)	255.0 (160.0, 600.0)	640.0 (380.0, 1220.0)	13.02 (7.44, 20.28)
Age 12 up to <17 years	N=51	N=50	N=49
Mean (SD)	497.1 (114.2)	998.8 (266.5)	25.54 (5.56)
Median (Min, Max)	470.0 (270.0, 750.0)	936.0 (560.0, 1500.0)	25.14 (14.40, 33.78)

Abbreviations: Max, maximum; Min, minimum; SD, standard deviation.
Source: Reviewer's table, Table 14.3.7.2, Table 14.3.7.3, Table 14.3.7.4, and Table 14.3.7.5, pages 10256-10263, CSR of Study PALO-10-20.

Reviewer comments: *As expected with weight-based dosing of study drug, exposures were greater in the palonosetron 20 mcg/kg group than in the palonosetron 10 mcg/kg across all age groups. Moreover, exposures increased with increasing age.*

Exposure data for subsequent cycles (cycles 2-4) by age group are presented in Table 52 of section 7.7 Additional Submissions / Safety Issues.

7.2.2 Explorations for Dose Response

Dose experience with the study drug for cycle 1 of PALO-10-20 was discussed in section 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations. Dose experience with the study drug for subsequent cycles (cycle 2, 3, and 4) of PALO-10-20, are described in section 7.7 Additional Submissions / Safety Issues. Discussion of explorations for dose dependency for adverse events is provided in section 7.5.1 Dose Dependency for Adverse Events.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

The Sponsor performed adequate monitoring of safety parameters including vital signs, physical exams, and laboratory testing. See section 7.4.2 Laboratory Findings, section 7.4.3 Vital Signs, and section 7.4.4 Electrocardiograms (ECGs).

Reviewer comments: *In this reviewer's assessment, the routine clinical testing of subjects in this sNDA was adequate.*

7.2.5 Metabolic, Clearance, and Interaction Workup

No evaluation of drug interactions was performed in the pediatric population participating in these trials.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

None was conducted. As noted in section 2.4 Important Safety Issues With Consideration to Related Drugs, other 5-HT_3 antagonists (e.g., ondansetron, granisetron, dolasetron) have been associated with QT prolongation. The Sponsor has evaluated previously the effect of palonosetron on QTc interval in a double blind, randomized, parallel, placebo and positive (moxifloxacin) controlled trial in adult men and women. The objective was to evaluate the ECG effects of I.V. administered palonosetron at single doses of 0.25, 0.75 or 2.25 mg in 221 healthy subjects. The study demonstrated no significant effect on any ECG interval including QTc duration (cardiac repolarization) at doses up to 2.25 mg. ECG evaluation was included in the pediatric studies of palonosetron and findings are discussed in section 7.4.4 Electrocardiograms (ECGs).

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in PALO-99-07. In PALO-10-20, there were 6 deaths reported during the study and 1 death reported after the follow-up period. Of the 7 subjects who died, 3 were in the palonosetron 20 mcg/kg group, and 4 were in the ondansetron group. No deaths were reported in the palonosetron 10 mcg/kg group. The Sponsor reported that none of the deaths was considered related to the study drug. Table 40 provides brief narratives of deaths reported in PALO-10-20. The table also lists the probable cause of death as assessed by this medical officer.

Table 40. Brief Narratives of Deaths in PALO-10-20

Narrative	Probable Cause of Death	Study arm	Days from Last Dose
Subject 634-5324: 2-year-old male with diagnosed with brain stem tumor 30 Apr 2012. On 03 Jul 2012, he received palonosetron prior to his 3rd cycle of HEC (dacarbazine 125 mg and etoposide 50 mg). (b) (6) days later ((b) (6)), his condition worsened and he was diagnosed with hydrocephalus. Following a ventriculo-peritoneal bypass on (b) (6), his condition improved. On (b) (6), an MRI revealed progression of the brain stem tumor. He was discharged from the hospital on (b) (6) (b) (6) and later died from progression of the brain stem tumor on (b) (6).	Progression of brain stem tumor	Palonosetron 20 mcg/kg	21
Subject 652-5156: 11-year-old male diagnosed with acute lymphoblastic leukemia on 21 Feb 2012. On 13 Mar 2012, he received palonosetron prior to his 1st cycle of MEC (doxorubicin 37.8 mg). Seven days later (20 Mar 2012), he complained of stomach discomfort and retrosternal pain. On the following day (21 Mar 2012), laboratory test results documented anemia, thrombocytopenia and leukopenia. Treatment with broad-spectrum antibiotics, filgrastim, and RBC transfusions was initiated. On (b) (6), he suddenly lost consciousness, stopped breathing, and experienced cardiac arrest. Cardio-pulmonary resuscitation was started, and he was transferred to the ICU. A Chest X-ray showed acute respiratory distress syndrome. Severe anemia was also present. A second episode of cardiac arrest occurred resulting in death.	Acute respiratory distress syndrome	Palonosetron 20 mcg/kg	10
Subject 672-5358: 9-year-old male diagnosed with acute lymphocytic leukemia on 17 May 2012. On 05 Jun 2012, he received palonosetron prior to his 3rd cycle of MEC (doxorubicin 36 mg, vincristine 1.8 mg, and prednisolone). (b) (6) he had a hemorrhagic stroke and cerebral edema with clonic convulsions, and became comatose. Intensive therapy and ventilation was started. He was subsequently diagnosed with neuroleukemia and cerebral edema. He received symptomatic therapy but his condition progressively worsened. On (b) (6) (b) (6), he died from progressive respiratory failure and cardiovascular collapse.	Progression of leukemia	Palonosetron 20 mcg/kg	1
Subject 515-5320: 15-year-old female diagnosed with osteosarcoma of the right fibula on 04 May 2012. On 18 May 2012, she received ondansetron 0.15 mg/kg prior to her 1st cycle of HEC (cisplatin 234 mg and doxorubicin 146 mg). (b) (6) days later (b) (6)), she developed sores in the mouth, difficulty breathing, and hemoptysis. She was admitted to the hospital with a presumptive diagnosis of sepsis, pneumonia, and cardiac arrest. Intensive therapy, including ventilation, was started immediately. Her condition worsened, and she developed multi-organ failure, pneumonia, pulmonary hemorrhage, ventricular fibrillation, and sepsis. On (b) (6), she experienced asystole resulting in death.	Multi-organ failure	Ondansetron 3 x 0.15 mg/kg	13

Narrative	Probable Cause of Death	Study arm	Days from Last Dose
Subject 542-5359: 13-year-old female diagnosed with acute promyelocytic leukemia in February 2012. On 31 May 2012, she received ondansetron 0.15 mg/kg prior to her 1st cycle of MEC (idarubicin 20 mg and cytarabine 240 mg). (b) (6) days later ((b) (6) (b) (6)), she developed fever, was diagnosed with febrile neutropenia, and was admitted to the hospital the next day. Hematology test results revealed pancytopenia. *Candida tropicalis* was isolated from the blood cultures and sepsis due to *C. tropicalis* was diagnosed on (b) (6) Broad spectrum antibiotics and anti-fungal medications were started. Despite treatment, her condition worsened and she developed multi-organ failure. She was treated with inotropics, and mechanical ventilation, but later died on (b) (6)	Sepsis and multi-organ failure	Ondansetron 3 x 0.15 mg/kg	10
Subject 551-5282: 15-year-old male diagnosed with acute lymphoblastic leukemia on 02 May 2011. On 29 Jun 2012, he received ondansetron 0.15 mg/kg prior to his 2nd cycle of MEC (cytarabine 3800 mg). On (b) (6), he was hospitalized for fever, pain, and breathlessness. Hematology test results revealed leukocytosis with blastemia, anemia, and thrombocytopenia. Despite the treatment, he died the following day ((b) (6)) from respiratory failure.	Progression of leukemia	Ondansetron 3 x 0.15 mg/kg	28
Subject 551-5240: 2-year-old female diagnosed with acute lymphoblastic leukemia on 03 Sep 2011. She received ondansetron 0.15 mg/kg on 17 Apr 2012 prior to her 1st cycle of MEC (fludarabine, cytarabine and idarubicin). On (b) (6) she was diagnosed with thrombocytopenia and febrile neutropenia. On (b) (6) she developed enterocolitis. All events except for thrombocytopenia had resolved and the subject was discharged from the hospital on (b) (6) but died on (b) (6) (b) (6) due to respiratory failure.	Respiratory failure	Ondansetron 3 x 0.15 mg/kg	After observational period

Source: Reviewer's table, based on narratives from pages 44-46 of Summary of Clinical Safety and PALO-10-20 CSR.

Reviewer comments: *In this reviewer's assessment, the cause of these subjects' deaths does not appear to be related to the study drug.*

7.3.2 Nonfatal Serious Adverse Events

In the CINV integrated safety population, there were 177 subjects [13 (7%) palonosetron 3 mcg/kg, 66 (37%) palonosetron 10 mcg/kg, 43 (24%) palonosetron 20 mcg/kg, and 55 (31%) ondansetron] that reported at least 1 serious adverse event (SAE) during cycle 1. A total of 343 SAEs were reported by the 177 subjects. The incidence of SAEs was 30% in subjects who received palonosetron compared with 34% in subjects who received ondansetron. At the SOC level, serious TEAEs in the blood and lymphatic system disorder SOC were the most common overall (22%) and in both treatment groups (21% for palonosetron and 24% for ondansetron). The serious TEAE febrile neutropenia was the most commonly reported PT overall (11%), with 11% in the palonosetron and 12% in the ondansetron treatment groups.

Among the remaining most commonly reported serious TEAEs, only pyrexia was reported in a SOC other than blood and lymphatic system disorder. Pyrexia was reported in 21 (5%) subjects receiving palonosetron compared with 5 (3%) subjects receiving ondansetron. None of the serious TEAEs reported in the first cycle of the studies was assessed by the investigators as drug-related.

This medical officer reviewed all nonfatal SAEs, including narrative summaries. Table 41 summarizes the nonfatal SAEs that, in this medical officer's assessment, were clinically relevant [i.e., those that relate to labeled adverse reactions (ARs) with palonosetron (e.g., constipation, headache, hypersensitivity reactions, convulsions (labeled as a potential AR in the case of overdose)), those potentially related to palonosetron hydrochloride injection (e.g., hypotension, syncope, infusion reactions, hypocalcemia), and those that resulted in withdrawal from the study]. Table 41 includes nonfatal SAEs from the CINV integrated safety population (i.e., PALO-99-07 and PALO-10-20) for cycle 1 and nonfatal SAEs from cycles 2-4 of PALO-10-20.

Table 41. Summary of Clinically Relevant Nonfatal Serious Adverse Events for Subjects that Received Palonosetron in PALO-99-07 and PALO-10-20 (SAF)

Treatment/ Subject ID	Age (years)/Gender	Cycle	Time to AE (days)	Preferred Term/Verbatim Term Description	Relationship*
PALONOSETRON 10 MCG/KG					
537-5417	6/M	1	1	Convulsion / Seizure See Reviewer comments below this table.	Unlikely
541-5554	2/F	1	21	Constipation / Constipation Subject with Wilm's tumor that received HEC and developed abdominal pain, fever, and constipation 21 days after first dose of palonosetron 10 mcg/kg. Hospitalized and received antibiotics. Imaging did not reveal obstruction or perforations. Events resolved the next day.	Not related
582-5139	15/F	4	18	Renal tubular disorder / Toxic tubulopathy Subject with Ewing's sarcoma that received MEC preceded by palonosetron 10 mcg/kg. Eighteen days after last administration of palonosetron, she was hospitalized due to renal tubular disorder (hypocalcemia, hypophosphatemia).	Not related
622-5003	15/M	1	8	Grand mal convulsion / Grand mal epileptic seizure Subject with pre-B cell acute lymphoblastic leukemia that received MEC (including asparaginase and vincristine) preceded by palonosetron 10 mcg/kg. Eight days later, he had a convulsion with loss of consciousness for one minute. MRI brain showed a small subcortical white matter signal disturbance in the left parietal region.	Not related
622-5113	15/M	2	15	Ventricular fibrillation / Ventricular fibrillation Circulatory collapse / Circulation failure Subject with osteosarcoma that received MEC preceded by palonosetron 10 mcg/kg. Fifteen days after last dose of palonosetron, he was accidentally given a I.V. bolus injection of 12 mL of 7.4% solution of potassium. This led immediately to ventricular fibrillation and circulatory collapse. He was resuscitated and placed on mechanical ventilation.	Not related
711-7267	11/F	1	6	Hypotension / Hypotension See Reviewer comments below this table.	Unlikely

Treatment/ Subject ID	Age (years)/Gender	Cycle	Time to AE (days)	Preferred Term/Verbatim Term Description	Relationship*
714-7218	15/F	1	1	Drug hypersensitivity / Allergic Reaction to VP-16 Subject with undifferentiated high-grade sarcoma that received MEC preceded by palonosetron 10 mcg/kg. The next day, she experienced 10 minutes of dyspnea, nausea, and flushing 10 minutes after receiving 40 mg of I.V. etopsoide (VP-16).	Not related
718-7338	2/F	1	7	Hypotension / Hypotension Subject with thoracic neuroblastoma that received HEC preceded by palonosetron 10 mcg/kg. Seven days later, she developed hypotension in the setting of sepsis and was hospitalized.	Not related
PALONOSETRON 20 MCG/KG					
515-5032	6/M	1	9	Febrile neutropenia / Febrile neutropenia Subject with metastatic adrenal neuroblastoma that received HEC (cisplatin, etoposide, and dexamethasone) preceded by palonosetron 20 mcg/kg. Nine days later, he developed febrile neutropenia. He recovered from the event 9 days later, but was withdrawn from the study.	Not related
581-5162	3/F	1	12	Neurotoxicity / Central neurotoxicity Subject with acute leukemia that received MEC (included cytarabine) preceded by palonosetron 20 mcg/kg. Twelve days later, she experienced a short period of unconsciousness followed by generalized convulsions 2 days later. EEG showed slowing over the left hemisphere. Explanation for event included concomitant medications, particularly cytarabine.	Not related
583-5464	4/F	1	11	Convulsion / Generalized convulsion Subject with acute lymphoblastic leukemia that received MEC preceded by palonosetron 20 mcg/kg. Eleven days later, she developed convulsions and acute respiratory failure. She was intubated and subsequently extubated. MRI brain showed lesions in two regions of the brain.	Not related
631-5185	1/M	2	8	Diarrhea / Diarrhea Dehydration / Dehydration See Reviewer comments below this table.	Possible

Note: Time to AE reflects number of days to AE after last administration of study medication.
* Relationship to study drug as assessed by the investigator.
Source: Reviewer's table, based on narratives on pages 9518-9531 of CSR PALO-10-20 and pages 1-39 of Appendix 2, module 5.3.5.3 ISS.

Reviewer comments: *This medical officer assessed all the non-fatal SAEs by CRFs, narratives and/or datasets provided by the Sponsor. As adjudicated by this reviewer, all of the non-fatal SAEs in subjects receiving palonosetron were described by the investigator as not related to the administration of palonosetron, with the exception of three SAEs. These three cases are reviewed below:*

- *Subject 537-5417's SAE of convulsion was determined as unlikely related to the study drug (palonosetron 10 mcg/kg) by the investigator. This subject, a 6-year-old male, was diagnosed with primary Ewing's sarcoma on 18 Jun 2012. On 11 Jul 2012 he received the first cycle of palonosetron 10 mcg/kg prior to MEC (I.V. vincristine 1.5 mg, I.V. etoposide 150 mg, I.V. doxorubicin 20 mg, and I.V. ifosfamide 3000 mg). On (b) (6) 1 h and 41 min after the second administration of palonosetron, he developed a seizure that lasted for approximately 5 minutes and then resolved spontaneously. An hour later he had another convulsion. He was given I.V. lorazepam and convulsion resolved within several minutes. Brain CT was reported as normal. Due to the event, it was decided not to administer the third dose of the study drug. The event was considered by the investigator as unlikely related to the study drug. Alternative explanation was concomitant medications (i.e., chemotherapy).*

  This reviewer notes that concomitant chemotherapy may have been the source of the subject's seizures. Seizures are listed as a potential toxicity in approved labeling for etoposide. Moreover, labeling for doxorubicin indicates that seizures and coma have been reported in subjects treated with doxorubicin in combination with cisplatin or vincristine (this subject received doxorubicin in combination with vincristine). Additionally, seizures and other CNS toxicities are a labeled warning in the Package Insert for ifosfamide.

- *Subject 631-5185's SAEs of diarrhea and dehydration were determined as possibly related to the study drug (palonosetron 20 mcg/kg) by the investigator. This subject, a 10-month-old male, was diagnosed with embryonic rhabdomyosarcoma on 31 Aug 2011. He had a history of cystectomy, prostatectomy, bilateral urethral cutaneous fistula and urinary tract infection from Nov 2011. On 04 Apr 2012, he received the second cycle of MEC (cyclophosphamide 105 mg and vinblastine 0.63 mg) preceded by palonosetron 20 mcg/kg. On (b) (6) he had loose stools and was hospitalized 5 days later with the diagnosis of diarrhea. On admission the subject also presented with dehydration and febrile neutropenia. Treatment with antibiotics and infusions of fluids was initiated. All events resolved without sequelae (diarrhea on (b) (6), dehydration on (b) (6), and febrile neutropenia on (b) (6) and the subject was discharged from the hospital on (b) (6) Diarrhea and dehydration were rated by the investigator as possibly related to study drug.*

  This reviewer notes that diarrhea is a labeled adverse reaction from adult CINV trials of palonosetron. Even though diarrhea may occur following palonosetron

exposure, the subject's loose stools began (b) (6) days following exposure to palonosetron, making it unlikely that the AE was related to the study drug. Moreover, it is likely that the loose stools that occurred five days prior to subject's hospitalization resulted in excessive loss of fluids and minerals and caused dehydration.

- *Subject 711-7267's SAE of hypotension was determined as unlikely related to the study drug (palonosetron 10 mcg/kg) by the investigator. This 11-year-old female was diagnosed with ovarian cancer and received HEC preceded by palonosetron 10 mcg/kg. Six days later, she was hospitalized with hypotension and was found to have gastroenteritis. Hypotension resolved the next day.*

  Given the time lag between onset of hypotension and the dose of palonosetron, there is no clear temporal association between the AE and the study drug. Moreover, gastroenteritis is an alternative etiology for the hypotension.

In conclusion, this reviewer does not note any SAEs that suggest a new safety signal with palonosetron in pediatric cancer subjects receiving the drug for prevention of CINV. Moreover, review of SAE listings did not demonstrate a dose response trend with increasing palonosetron dose.

7.3.3 Dropouts and/or Discontinuations

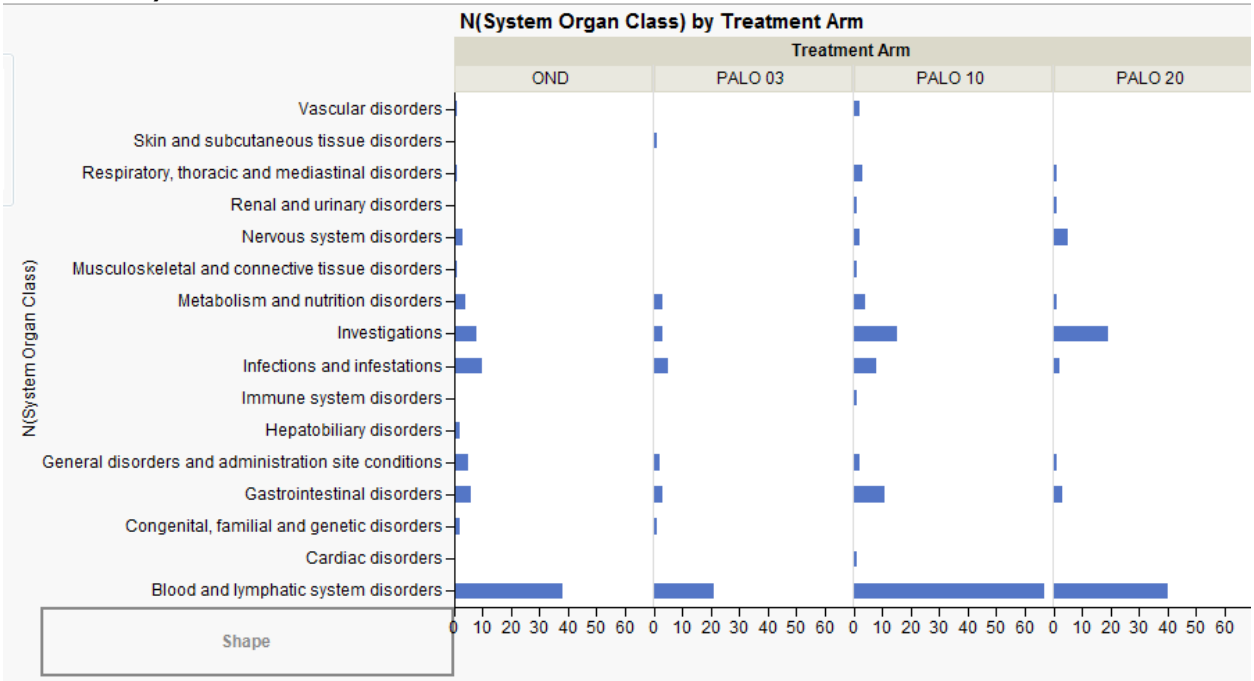
During Cycle 1, 2 (0.5%) subjects in the palonosetron 20 mcg/kg group (subject 515-5032 and subject 672-5358) and 1 (0.6%) subjects in the ondansetron group (subject 505-5161) were withdrawn from the studies because of a TEAE. The events that led to withdrawal in the palonosetron subjects were described in section 7.3.1 Deaths and section 7.3.2 Nonfatal Serious Adverse Events.

7.3.4 Significant Adverse Events

AEs leading to discontinuation were discussed in section 7.3.3 Dropouts and/or Discontinuations.

As illustrated in Figure 2, the majority of AEs that were characterized by the investigators as severe in intensity were in the Blood and lymphatic system disorders SOC, with anemia, febrile neutropenia, and thrombocytopenia among the most frequently encountered PTs.

Figure 2. Count of Severe TEAEs by SOC – CINV Integrated Safety Population (PALO-99-07 and PALO-10-20)



Abbreviations: Ond, ondansetron; PALO 03, palonosetron 3 mcg/kg; PALO 10, palonosetron 10 mcg/kg; PALO 20, palonosetron 20 mcg/kg.
Note: The numbers on the x-axis represent the number of subjects in each treatment arm that experienced an AE (by SOC). Subjects who experienced the same AE (by SOC) are counted only once for that AE.
Source: Reviewer's table, generated in JMP from the subset of subjects in the integrated CINV AE dataset (obtained by joining PALO-10-20 cycle 1 ADAE in module 5.3.5.1 with PALO-99-07 ADAE in module 5.3.5.1) who were in the safety population (SAFFL=Y), whose AE was considered treatment emergent (TRTEMFL=Y), and whose AE was categorized as severe by the investigator (AESEV=SEVERE).

Reviewer comments: *Severe TEAEs were principally hematologic in nature, as would be reasonably expected in a trial enrolling pediatric subjects with cancer who receive chemotherapy. In the Investigations SOC, the severe TEAEs (by PT) that occurred in ≥2% of subjects in at least one of the treatment arms were blood culture positive, blood uric acid increased, hematocrit decreased, neutrophil count decreased, platelet count decreased, and white blood cell count decreased. Again, such TEAEs would be expected from a pediatric cancer trial. Overall, this medical officer noted no trends with respect to severe TEAEs that would suggest a specific safety risk with palonosetron vs. ondansetron.*

7.3.5 Submission Specific Primary Safety Concerns

Infusion site reactions

The WR stated that the Sponsor should "carefully monitor infusion site reactions including thrombophlebitis in studies of the I.V. formulation." The Sponsor notes that they monitored closely for infusion site reactions (thrombophlebitis) during the studies.

Injection site reactions described as related to the study drug were reported in 2 subjects, for a total of 3 related TEAEs. The 3 AEs were all non-serious and are described briefly below:

- Subject 572-5145: 5-year-old female in the palonosetron 10 mcg/kg group who received MEC. The onset of *infusion site reaction* was on the day of treatment of the first cycle, while the onset of *infusion site erythema* was on the day of treatment of the second cycle. Both TEAEs resolved within one day. Both TEAEs were considered by the investigator to be of mild intensity and possibly related to study drug.

- Subject 643-5096: 3-year-old female in the palonosetron 10 mcg/kg group. *Infusion site pain* started and resolved on the day of treatment of the first cycle. The investigator considered this TEAE to be of moderate intensity and probably related to study drug.

Table 42 summarizes TEAEs with PTs potentially encompassing infusion/injection site reactions and thrombophlebitis/phlebitis. PTs selected were those that, in this medical officer's assessment, might relate to infusion/injection site reactions or thrombophlebitis/phlebitis. None of the reported events was serious, and except for the events described above in subject 572-5145 and subject 643-5096, none of the events was considered related to study drug.

Table 42. Incidence of TEAEs Potentially Encompassing Infusion/Injection Site Reactions or Thrombophlebitis – CINV Integrated Safety Population (PALO-99-07 and PALO-10-20)

MedDRA System Organ Class MedDRA Preferred Term	Palo 3 (N=35) n (%)	Palo 10 (N=204) n (%)	Palo 20 (N=163) n (%)	Palo All (N=402) n (%)	Ondansetron (N=164) n (%)	Total (N=566) n (%)
General Disorders and Administration						
Administration site pain	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)
Catheter site pain	0	1 (0.5)	1 (0.6)	2 (0.5)	1 (0.6)	3 (0.5)
Infusion site erythema	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)
Infusion site pain	0	0	1 (0.6)	1 (0.2)	0	1 (0.2)
Infusion site reaction	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)
Injection site extravasation	0	2 (1.0)	0	2 (0.5)	0	2 (0.4)
Injection site urticaria	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)
Vessel puncture site inflammation	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)
Vessel puncture site pain	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)
Vascular Disorders						
Phlebitis	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)
Thrombophlebitis	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)

Source: Reviewer's table, adapted from Table 3.11A and 3.11B, pages 666-729, Integrated Summary of Safety.

Reviewer comments: *Although palonosetron subjects had a numerically greater incidence of TEAEs potentially encompassing infusion/injection site reactions or*

thrombophlebitis/phlebitis than ondansetron subjects, there is no trend for an increasing incidence of these TEAEs with increasing palonosetron dose.

Hypersensitivity reactions

Hypersensitivity reactions were recently added to the WARNINGS AND PRECAUTIONS section of approved ALOXI labeling (labeling supplement approved February 6, 2014). Therefore, this medical officer evaluated the pediatric safety database for AEs relating to hypersensitivity. Table 43 summarizes the incidence of TEAEs with PTs relating to hypersensitivity.

Table 43. Incidence of TEAEs Relating to Hypersensitivity – CINV Integrated Safety Population (PALO-99-07 and PALO-10-20)

MedDRA System Organ Class MedDRA Preferred Term	Palo 3 (N=35) n (%)	Palo 10 (N=204) n (%)	Palo 20 (N=163) n (%)	Palo All (N=402) n (%)	Ondansetron (N=164) n (%)	Total (N=566) n (%)
Immune System Disorders						
Drug hypersensitivity	0	1 (0.5)	1 (0.6)	2 (0.5)	0	2 (0.4)
Hypersensitivity	1 (2.9)	1 (0.5)	0	2 (0.5)	1 (0.6)	3 (0.5)

Source: Reviewer's table, adapted from Table 3.11A and 3.11B, pages 666-729, Integrated Summary of Safety.

Reviewer comments: *None of the events were considered related to study drug. Verbatim terms for the AEs coded to the PT "drug hypersensitivity" and the PT "hypersensitivity" included "allergic reaction during chemotherapy", "allergic reaction to VP-16", "rash on neck and shoulders post morphine", and "allergic reaction to platelet transfusion". Current labeling for palonosetron includes a description of the potential for hypersensitivity reactions, including anaphylaxis, in subjects receiving I.V. palonosetron. There were no reported cases of anaphylaxis in the pediatric studies of palonosetron.*

Adverse events potentially related to disodium edetate (EDTA)

Palonosetron hydrochloride injection for intravenous administration contains disodium edetate (EDTA). As noted in the PMHS review of the original protocol for PALO-10-20 (see review by Dr. Virginia Elgin in DARRTS, dated February 4, 2011 under IND 37,797), EDTA has been associated with hypocalcemia, hypotension, and syncope. Given the presence of EDTA in the injectable formulation of palonosetron, and given that a higher dose of 20 mcg/kg was studied in PALO-10-20, the Sponsor agreed to increase monitoring for the aforementioned known reactions associated with EDTA.

Table 44 summarizes the incidence of TEAEs with PTs, which in this medical officer's assessment potentially encompass syncope, hypotension, or hypocalcemia. None of the events was considered by the investigator as related to study drug.

Table 44. Incidence of TEAEs Potentially Relating to EDTA – CINV Integrated Safety Population (PALO-99-07 and PALO-10-20)

MedDRA System Organ Class MedDRA Preferred Term	Palo 3 (N=35) n (%)	Palo 10 (N=204) n (%)	Palo 20 (N=163) n (%)	Palo All (N=402) n (%)	Ondansetron (N=164) n (%)	Total (N=566) n (%)
Syncope-Related						
Nervous System Disorders						
Dizziness	0	4 (2.0)	1 (0.6)	5 (1.2)	1 (0.6)	6 (1.1)
Syncope	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)
Hypotension-Related						
Vascular Disorders						
Hypoperfusion	1 (2.9)	0	0	1 (0.2)	0	1 (0.2)
Hypotension	0	4 (2.0)	1 (0.6)	5 (1.2)	0	5 (0.9)
Low Calcium-Related						
Metabolism and nutrition disorders						
Hypocalcemia	1 (2.9)	2 (1.0)	2 (1.2)	5 (1.2)	5 (3.0)	10 (1.8)

Source: Reviewer's table, adapted from Table 3.11A and 3.11B, pages 666-729, Integrated Summary of Safety.

Reviewer comments: *None of the dizziness TEAEs were considered serious and none were associated with concurrent hypotension or hypoperfusion. The one subject who experienced a TEAE of syncope (subject 651-5235) did not have documented concurrent hypotension or hypoperfusion on the day of the syncopal event. The syncopal event was classified as mild and not related to study drug by the investigator.*

Five palonosetron subjects had at least one TEAE of hypotension, and the event was considered a nonfatal SAE for two of these subjects (subject 711-7267 and subject 718-7338, both in the palonosetron 10 mcg/kg arm). The narratives for these subjects, which were provided in section 7.3.2 Nonfatal Serious Adverse Events, reveal alternative explanations for the hypotension (e.g., sepsis). The one subject with a TEAE of hypoperfusion (received palonosetron 3 mcg/kg) had been diagnosed with staphylococcal sepsis the day prior to the hypoperfusion event.

Regarding hypocalcemia, there is no clear trend for increasing incidence with increasing palonosetron dose. Moreover, the incidence of hypocalcemia was lower in the palonosetron arm (1%) than the ondansetron arm (3%). Hypocalcemia as a potential AE with palonosetron is also discussed in section 7.4.2 Laboratory Findings.

In this medical officer's assessment, the pediatric CINV studies demonstrated no safety signal relating to EDTA exposure with palonosetron in pediatric subjects. Moreover, there appear to be no trends in the incidence of known potential AEs associated with EDTA (e.g., syncope, hypotension, hypocalcemia) with increasing palonosetron dose.

Convulsive events

Several of the SAEs in the CINV safety database related to convulsions/seizures (the reader is referred to Table 41). In this medical officer's assessment, none of these SAEs

were related to study drug. For completeness, however, this reviewer further evaluated the safety database for TEAEs which in this medical officer's assessment potentially encompass convulsive events. Table 45 summarizes the results.

Table 45. Incidence of TEAEs Related to Convulsive Events – CINV Integrated Safety Population (PALO-99-07 and PALO-10-20)

MedDRA System Organ Class MedDRA Preferred Term	Palo 3 (N=35) n (%)	Palo 10 (N=204) n (%)	Palo 20 (N=163) n (%)	Palo All (N=402) n (%)	Ondansetron (N=164) n (%)	Total (N=566) n (%)
Nervous System Disorders						
Convulsion	0	2 (1.0)	3 (1.8)	5 (1.2)	1 (0.6)	6 (1.1)
Grand mal convulsion	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)
Neurotoxicity	0	0	1 (0.6)	1 (0.2)	0	1 (0.2)

Source: Reviewer's table, adapted from Table 3.11A and 3.11B, pages 666-729, Integrated Summary of Safety.

Of the 8 subjects that experienced at least 1 TEAE relating to convulsive events (i.e., convulsion, grand mal convulsion, neurotoxicity), 3 (38%) received palonosetron 10 mcg/kg, 4 (50%) received palonosetron 20 mcg/kg, and 1 (12%) received ondansetron. Of the 7 palonosetron subjects with at least 1 TEAE relating to convulsive events, 4 (57%) had TEAEs that were considered as nonfatal SAEs. The convulsive TEAE of the one ondansetron subject was also considered a nonfatal SAE. Narratives for the 4 subjects with nonfatal SAEs related to convulsive events were provided in section 7.3.2 Nonfatal Serious Adverse Events.

Reviewer comments: *Although palonosetron subjects had a numerically greater incidence of TEAEs related to convulsive events than ondansetron subjects, there was no clear causal link between the convulsive event and administration of palonosetron. As illustrated in the case of the four subjects with serious TEAEs related to convulsive events, all the subjects had a more plausible explanation for the event (e.g., chemotherapy, underlying malignancy). Moreover, there is no clear trend for increasing TEAEs related to convulsive events with increasing palonosetron dose.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the Sponsor's presentation of common TEAEs in the integrated safety population (PALO-99-07 and PALO-10-20), the Sponsor defined the most common TEAEs as those reported in ≥2% of subjects in any treatment group. Because the palonosetron 3 mcg/kg arm contained only 35 subjects, a TEAE that occurred in only 1 subject in the 3 mcg/kg arm would yield an AE incidence rate of ≥2%, but this medical officer would not necessarily consider a TEAE occurring in 1 of 35 subjects as a common AE. Therefore, Table 46 below presents those TEAEs in cycle 1 that occurred with a frequency of ≥5% of subjects in any treatment group.

Table 46. Incidence of Most Common Adverse Events (≥5% of Subjects in Any Treatment Group) – CINV Integrated Safety Population (PALO-99-07 and PALO-10-20)

MedDRA System Organ Class MedDRA Preferred Term	Palo 3 (N=35) n (%)	Palo 10 (N=204) n (%)	Palo 20 (N=163) n (%)	Palo All (N=402) n (%)	Ondansetron (N=164) n (%)	Total (N=566) n (%)
Number of subjects with TEAE	28 (80.0)	170 (83.3)	113 (69.3)	311 (77.4)	134 (81.7)	445 (78.6)
Blood and Lymphatic System Disorders						
Anemia	11(31.4)	72 (35.3)	50 (30.7)	133 (33.1)	55 (33.5)	188 (33.2)
Febrile neutropenia	5 (14.3)	25 (12.3)	22 (13.5)	52 (12.9)	21 (12.8)	73 (12.9)
Leukopenia	1 (2.9)	33 (16.2)	24 (14.7)	58 (14.4)	34 (20.7)	92 (16.3)
Neutropenia	7 (20.0)	39 (19.1)	24 (14.7)	70 (17.4)	23 (14.0)	93 (16.4)
Pancytopenia	3 (8.6)	8 (3.9)	2 (1.2)	13 (3.2)	5 (3.0)	18 (3.2)
Thrombocytopenia	10 (28.6)	37 (18.1)	26 (16.0)	73 (18.2)	33 (20.1)	106 (18.7)
Gastrointestinal Disorders						
Abdominal pain	1 (2.9)	16 (7.8)	10 (6.1)	27 (6.7)	12 (7.3)	39 (6.9)
Abdominal pain upper	2 (5.7)	4 (2.0)	3 (1.8)	9 (2.2)	4 (2.4)	13 (2.3)
Constipation	4 (11.4)	12 (5.9)	9 (5.5)	25 (6.2)	7 (4.3)	32 (5.7)
Diarrhea	3 (8.6)	14 (6.9)	4 (2.5)	21 (5.2)	8 (4.9)	29 (5.1)
Nausea	3 (8.6)	8 (3.9)	4 (2.5)	15 (3.7)	10 (6.1)	25 (4.4)
Proctalgia	2 (5.7)	1 (0.5)	0	3 (0.7)	2 (1.2)	5 (0.9)
Vomiting	6 (17.1)	16 (7.8)	13 (8.0)	35 (8.7)	14 (8.5)	49 (8.7)
General Disorders and Administration Conditions						
Chills	2 (5.7)	1 (0.5)	0	3 (0.7)	0	3 (0.5)
Fatigue	2 (5.7)	7 (3.4)	2 (1.2)	11 (2.7)	2 (1.2)	13 (2.3)
Irritability	2 (5.7)	0	0	2 (0.5)	1 (0.6)	3 (0.5)
Pyrexia	9 (25.7)	38 (18.6)	14 (8.6)	61 (15.2)	20 (12.2)	81 (14.3)
Infections and Infestations						
Oral candidiasis	2 (5.7)	0	0	2 (0.5)	0	2 (0.4)
Injury, Poisoning, and Procedural Complications						
Transfusion reaction	2 (5.7)	0	0	2 (0.5)	0	2 (0.4)
Investigations						
Platelet count decreased	0	8 (3.9)	11 (6.7)	19 (4.7)	7 (4.3)	26 (4.6)
White blood cell count decreased	0	9 (4.4)	15 (9.2)	24 (6.0)	14 (8.5)	38 (6.7)
Metabolism and Nutrition Disorders						
Fluid overload	3 (8.6)	2 (1.0)	0	5 (1.2)	0	5 (0.9)
Hypomagnesemia	2 (5.7)	1 (0.5)	2 (1.2)	5 (1.2)	0	5 (0.9)
Hypophagia	4 (11.4)	3 (1.5)	0	7 (1.7)	0	7 (1.2)
Nervous System Disorders						
Headache	3 (8.6)	16 (7.8)	7 (4.3)	26 (6.5)	17 (10.4)	43 (7.6)
Paresthesia	2 (5.7)	1 (0.5)	0	3 (0.7)	0	3 (0.5)
Respiratory, Thoracic and Mediastinal Disorders						
Nasal congestion	2 (5.7)	0	1 (0.6)	3 (0.7)	0	3 (0.5)
Skin and Subcutaneous Tissue Disorders						
Ecchymosis	2 (5.7)	0	0	2 (0.5)	0	2 (0.4)
Erythema	2 (5.7)	0	0	2 (0.5)	1 (0.6)	3 (0.5)
Pruritus	2 (5.7)	2 (1.0)	1 (0.6)	5 (1.2)	1 (0.6)	6 (1.1)
Rash	2 (5.7)	2 (1.0)	3 (1.8)	7 (1.7)	1 (0.6)	8 (1.4)
Vascular Disorders						
Pallor	2 (5.7)	1 (0.5)	0	3 (0.7)	1 (0.6)	4 (0.7)

Source: Reviewer's table, adapted from Table 1-7, pages 38-42, Summary of Clinical Safety.

Reviewer comments: *As expected in this cancer subject population, TEAEs in the Blood and lymphatic system disorders SOC were the most common overall (54%) and in both treatment groups (51% for palonosetron and 59% for ondansetron). Anemia was the most commonly reported TEAE overall (33%) and in the palonosetron (33%) and ondansetron (34%) treatment groups followed by thrombocytopenia (19% overall; 18% palonosetron, 20% ondansetron), neutropenia (16% overall; 17% palonosetron, 14% ondansetron) and leukopenia (16% overall; 14% palonosetron, 21% ondansetron). For these commonly reported TEAEs in the Blood and lymphatic system disorders SOC, there were no notable differences in the frequencies of individual TEAEs between the palonosetron 10 mcg/kg group and the palonosetron 20 mcg/kg group. Differences in the frequencies of individual events in the palonosetron 3 mcg/kg group compared with the palonosetron 10 mcg/kg and 20 mcg/kg groups are most likely attributable to the small number of subjects in the palonosetron 3 mcg/kg treatment group (N = 35).*

As discussed further in section 7.5.1 Dose Dependency for Adverse Events, there was no clear suggestion of a dose response with respect to adverse events. For example constipation, a labeled adverse reaction associated with I.V. palonosetron, did not appear to increase in incidence with increasing palonosetron dose.

Investigators characterized the relationship of each TEAE to study drug as definite, probable, possible, unassessable, unlikely, or unrelated. The Sponsor considered drug-related TEAEs to be those whose relationship to the study drug was characterized by the investigator as definite, probable, possible, or unassessable. Table 47 summarizes the results.

Table 47. Incidence of Adverse Events Considered by Investigators as Drug-Related[1] – CINV Integrated Safety Population (PALO-99-07 and PALO-10-20)

MedDRA System Organ Class MedDRA Preferred Term	Palo 3 (N=35) n (%)	Palo 10 (N=204) n (%)	Palo 20 (N=163) n (%)	Palo All (N=402) n (%)	Ondansetron (N=164) n (%)	Total (N=566) n (%)
Number of subjects with Related TEAE	2 (5.7)	8 (3.9)	7 (4.3)	17 (4.2)	7 (4.3)	24 (4.2)
Cardiac Disorders						
Conduction disorder	0	1 (0.5)	0	1 (0.2)	1 (0.6)	2 (0.4)
Sinus tachycardia	0	1 (0.5)	0	1 (0.2)	2 (1.2)	3 (0.5)
General Disorders and Administration Conditions						
Infusion site pain	0	0	1 (0.6)	1 (0.2)	0	1 (0.2)
Infusion site reaction	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)
Pain	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)
Pyrexia	1 (2.9)	0	0	1 (0.2)	0	1 (0.2)
Investigations						
Electrocardiogram QT prolonged	0	0	1 (0.6)	1 (0.2)	2 (1.2)	3 (0.5)
Musculoskeletal and Connective Tissue Disorders						
Muscle spasms	0	0	0	0	1 (0.6)	1 (0.2)
Nervous System Disorders						
Dizziness	0	1 (0.5)	1 (0.6)	2 (0.5)	0	2 (0.4)
Dyskinesia	0	0	1 (0.6)	1 (0.2)	0	1 (0.2)
Headache	0	3 (1.5)	1 (0.6)	4 (1.0)	2 (1.2)	6 (1.1)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)
Dyspnea	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)
Epistaxis	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)
Skin and Subcutaneous Tissue Disorders						
Dermatitis allergic	0	0	1 (0.6)	1 (0.2)	0	1 (0.2)
Pruritus	1 (2.9)	0	0	1 (0.2)	0	1 (0.2)
Skin disorder[2]	0	0	1 (0.6)	1 (0.2)	0	1 (0.2)
Urticaria	0	0	0	0	1 (0.6)	1 (0.2)

[1] Drug-related TEAEs are TEAEs assessed by the investigator as definite, probable, possible, or unassessable with regard to relationship to study drug.
[2] The verbatim term for the PT skin disorder for the subject in the palonosetron 20 mcg/kg arm was "skin changes during chemotherapy". The investigator indicated that the AE was possibly related to study drug.
Source: Reviewer's table, adapted from Table 2-4, page 33, Summary of Clinical Safety.

Reviewer comments: *Review of drug-related TEAEs as judged by the investigators reveals that the profile of drug-related TEAEs is similar to the labeled adverse reactions for the adult CINV studies. None of the drug-related TEAEs reported in the palonosetron 20 mcg/g arm were reported at a frequency >1%.*

7.4.2 Laboratory Findings

In study PALO-99-07, blood and urine samples for routine hematology and chemistry evaluations and urinalysis were obtained at screening (Visit 1), on Day 2 (Visit 3), and on Day 7, 8, 9 or 10 (Visit 4).

In study PALO-10-20, blood samples for routine hematology and chemistry evaluations were drawn at screening (Visit 1) and on Day 7, 8, 9 or 10 (Visit 7) of each cycle.

Additionally, 1 sample for serum chemistry was taken at Visit 2 of each cycle, at the end of the first study drug administration.

The following parameters were determined:

- Hematology: hematocrit, hemoglobin, erythrocytes (RBC), platelets, leucocytes (WBC), neutrophils, lymphocytes, basophils, eosinophils, and monocytes.
- Serum chemistry: creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, potassium, albumin, total protein, blood glucose, total creatine kinase, and ionized calcium (in PALO-10-20 only).
- Urinalysis (if the subject was capable of providing a urine sample): protein, glucose, WBC, RBC, nitrites, and bacteria.

Newly occurring abnormal clinically relevant values during the studies were considered to be laboratory AEs. The clinically significant abnormal laboratory values were not to be recorded on the electronic case report form (eCRF) pages as AEs. The etiology of the abnormality was to be identified, and any clinical signs, symptoms, or diagnoses which corresponded to the laboratory AE were recorded as AEs.

The Sponsor provided shift tables for laboratory parameters in the CINV integrated safety population (PALO-99-07 and PALO-10-20). Overall, the Sponsor noted no clinically significant shifts in the laboratory parameters evaluated.

Hematology

Table 48 shows shifts in key values (e.g., hematocrit, platelet count, and leukocyte count).

Table 48. Shift Table of Key Hematology Lab Values – CINV Integrated Safety Population (PALO-99-07 and PALO-10-20)

Serum Laboratory Parameter	Palo 3 (N=35) n (%)	Palo 10 (N=204) n (%)	Palo 20 (N=163) n (%)	Palo All (N=402) n (%)	Ondansetron (N=164) n (%)	Total (N=566) n (%)
Hematocrit						
Normal to Low	4 (11.4)	18 (8.8)	23 (14.1)	45 (11.2)	27 (16.5)	72 (12.7)
Normal to High	0	0	0	0	1 (0.6)	1 (0.2)
Platelet Count						
Normal to Low	11 (31.4)	45 (22.1)	19 (11.7)	75 (18.7)	25 (15.2)	100 (17.7)
Normal to High	0	2 (1.0)	3 (1.8)	5 (1.2)	1 (0.6)	6 (1.1)
Leukocyte Count						
Normal to Low	8 (22.9)	46 (22.5)	35 (21.5)	89 (22.1)	38 (23.2)	127 (22.4)
Normal to High	1 (2.9)	0	1 (0.6)	2 (0.5)	2 (1.2)	4 (0.7)

Source: Reviewer's table, adapted from Sponsor's Table 3-1, page 76, Summary of Clinical Safety.

Reviewer comments: *The shifts in clinically important hematology parameters discussed above are consistent with shifts that would be expected in cancer subjects undergoing*

chemotherapy and demonstrate no clear dose-response trend for palonosetron. Shifts from normal to low or high were comparable between palonosetron and ondansetron subjects. The findings are in line with the established safety profile of palonosetron in adults, which has not demonstrated clinically important effects on hematologic parameters.

Serum Chemistry

The Sponsor provided shift tables for serum chemistry parameters, including hepatic enzymes. Given the potential of the EDTA that is contained palonosetron for injection to cause hypocalcemia, this reviewer focused on ionized calcium trends in the CINV integrated safety population.

Table 49 shows shifts in ionized calcium from normal to low by cycle in study PALO-10-20 (ionized calcium levels were not measured in PALO-99-07).

Table 49. Shift Table of Ionized Calcium Values by Cycle – PALO-10-20 (Safety Population)

Ionized Calcium Shift	Palo 10 n (%)	Palo 20 n (%)	Palo All n (%)	Ondansetron n (%)
Cycle 1	N=167	N=163	N=330	N=164
Normal to Low	1 (0.6)	2 (1.2)	3 (0.9)	1 (0.6)
Cycle 2	N=84	N=90	N=174	N=86
Normal to Low	1 (1.2)	1 (1.1)	2 (1.1)	0
Cycle 3	N=43	N=59	N=102	N=44
Normal to Low	0	0	0	0
Cycle 4	N=20	N=31	N=51	N=18
Normal to Low	0	1 (3.2)	1 (2.0)	0

Source: Reviewer's table, adapted from Sponsor's Table 14.3.5.2.12.1, pages 9853-9854, CSR of PALO-10-20.

Reviewer comments: *Shifts in ionized calcium levels from normal to low were infrequent and the incidence rate was too low to allow for robust conclusions about a dose response trend or a trend with repeat administration. Overall, there appears to be no safety signal of hypocalcemia from EDTA exposure from palonosetron at clinically relevant doses, including the higher 20 mcg/kg dose.*

This medical officer reviewed shift tables for serum chemistry parameters and also reviewed AEs related to serum chemistry parameters. Although isolated instances of laboratory abnormalities were seen in studies submitted for this sNDA, no trends or consistent patterns were seen. Causality associations between serum chemistry abnormalities and study drug were in many cases confounded by underlying disease (e.g., abnormal hepatic enzymes in the setting of metastatic malignancy) or concurrent medications (e.g., chemotherapy agents). Moreover, shift tables did not suggest a dose-response trend in laboratory value shifts from normal to high or normal to low. Because the study drug was administered only once in PALO-99-07, limited comparisons were available and no signal of an effect of palonosetron was observed. No trends for

laboratory abnormalities were apparent in study PALO-10-20, in which palonosetron was administered for up to 4 cycles of chemotherapy.

7.4.3 Vital Signs

Vital signs measurements (body weight, heart rate and systolic and diastolic blood pressure) were carried out at screening (Visit 1), on Day 2 (Visit 3) and on Day 7, 8, 9 or 10 (Visit 4) in study PALO-99-07 and at screening (Visit 1), on Day 1 (Visit 2) and on Day 7, 8, 9 or 10 (Visit 7) in study PALO-10-20. Vital signs data were not pooled in the integrated database.

In study PALO-99-07, the Sponsor noted no pronounced changes in the mean values of vital signs from baseline (V1) to Visit 3 and Visit 4 in either treatment group. The observed changes tended to be slightly greater in subjects treated in the open-label period compared with those treated in the double-blind period.

In study PALO-10-20, the Sponsor noted that changes from baseline in systolic blood pressure, diastolic blood pressure, and pulse rate were generally similar across treatment groups overall and within age groups. One drug-related TEAE (hypertension) was reported for 1 (0.6%) subject in the ondansetron treatment group.

Reviewer comments: None of the pediatric CINV trials was powered or designed to test specific safety-related hypotheses. Moreover, the small number of subjects in PALO-99-07, the small number of subjects in the <2 years old age group in PALO-10-20, and the progressively decreasing numbers of subjects in cycles 2, 3, and 4 of PALO-10-20 preclude a robust assessment of these results. The totality of the data however, does not raise concerns about adverse effects of palonosetron on vital signs in the pediatric population. The incidence of hypotension, which has been associated with disodium edetate (EDTA), was examined separately in section 7.3.5 Submission Specific Primary Safety Concerns. No causal link between hypotension and palonosetron could be established, and there does not appear to be a dose-related trend in the incidence of hypotension.

7.4.4 Electrocardiograms (ECGs)

In study PALO-99-07, triplicate 12-lead electrocardiograms (ECGs) were to be performed at screening (Visit 1), on Day 1 (Visit 2) and on Day 2 (Visit 3). In addition, subjects aged 2 to 17 years were to have Holter monitoring from 2 hours before to 22 hours after study drug administration. In PALO-10-20, triplicate 12-lead ECGs were to be performed at screening (Visit 1) and on Day 7, 8, 9 or 10 (Visit 7) of each cycle. Additionally, during Visit 2 a single ECG was to be recorded at the end of the first study drug administration. If a subsequent cycle was performed within 2 weeks after the previous cycle, the ECGs at screening were not performed. The ECG interpretation included the analysis of the hearth rate, morphology, rhythm, conduction, ST segment,

PR, RR, QRS, QT and QTc intervals, T waves, U waves, and the presence or absence of any pathological changes (PALO-10-20 only). ECG data were integrated for cycle 1 across the two studies.

In cycle 1, the most common ECG abnormalities were increases from baseline in heart rate ≥25% and heart rate values >100 beats/min (6% for palonosetron 3 mcg/kg, 10% for palonosetron 10 mcg/kg, 9% for palonosetron 20 mcg/kg, and 12% for ondansetron), changes in QTcB values from ≤450 msec at baseline to >450 msec post-baseline (11% for palonosetron 3 mcg/kg, 14% for palonosetron 10 mcg/kg, 17% for palonosetron 20 mcg/kg, and 22% for ondansetron), and changes from baseline in QTcB values of >30 msec to ≤60 msec (9% for palonosetron 3 mcg/kg, 8% for palonosetron 10 mcg/kg, 7% for palonosetron 20 mcg/kg, and 10% for ondansetron).

Three subjects had *electrocardiogram QT prolonged* (PT) reported as a TEAE (all three TEAEs were considered by the investigator as possibly related to the study drug). One subject (0.6%) was in the palonosetron 20 mcg/kg group and 2 subjects (1.2%) were in the ondansetron group. All the *electrocardiogram QT prolonged* events were non-serious.

Reviewer comments: *In cycle 1, the most frequently reported ECG abnormalities occurred with greater frequency in the ondansetron group compared with the palonosetron group. Small differences were observed between palonosetron doses, but no clear trend was identified for differing effects of palonosetron doses on ECG findings. Subgroup analyses by age, although limited by small sample size, did not reveal any trends in the incidence of ECG abnormalities in specific age groups (e.g., the youngest age groups). A similar pattern was seen for subsequent cycles (cycles 2-4). Moreover, a prior adult thorough QT study of palonosetron demonstrated no significant effect on any ECG interval including QTc duration (cardiac repolarization) at doses up to 2.25 mg. These findings, taken together, reassure this medical officer of the safety of palonosetron with respect to cardiac electrophysiology in the pediatric population.*

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies/clinical trials were conducted for this sNDA.

7.4.6 Immunogenicity

Palonosetron is not a peptide or protein. Immunogenicity studies were not performed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the CINV integrated safety population, the proportion of subjects reporting at least 1 TEAE was 69% in the palonosetron 20 mcg/kg group, compared with 83% in the 10 mcg/kg group, and 80% in the 3 mcg/kg group. Moreover the proportion of subjects with serious TEAEs was 26% in the palonosetron 20 mcg/kg group, compared with 32% in the 10 mcg/kg group, and 37% in the 3 mcg/kg group. Comparable proportions of subjects of both genders reported at least 1 TEAE in the palonosetron 20 mcg/kg group (71% male vs. 68% female) compared with the 10 mcg/kg (78% male vs. 90% female) and 3 mcg/kg (68% male vs. 100% female) groups.

Reviewer comments: *In the palonosetron dose groups, there was no apparent effect of dose on the frequency of TEAEs. There was also no clear effect of palonosetron dose in any age group in subjects who were reported with at least 1 TEAE. Although small differences were observed across age groups and between treatments, this reviewer identified no consistent trends. There was also no apparent effect of palonosetron dose in male or female subjects reporting at least 1 TEAE.*

Overall, no dose-response trends were noted for TEAEs in general or for specific TEAEs (see section 7.3.5 Submission Specific Primary Safety Concerns and section 7.4 Supportive Safety Results for incidence tables by dose arm and additional discussion).

7.5.2 Time Dependency for Adverse Events

The Sponsor did not perform any analyses of cumulative AE incidence rates. Mean terminal elimination half-life of palonosetron I.V. in adults is approximately 40 hours.

7.5.3 Drug-Demographic Interactions

Age Group
In the CINV integrated safety population, in subjects aged <2 years, the proportion of subjects with at least 1 TEAE was 74% in the palonosetron group vs. 80% in the ondansetron group. In subjects aged 2 to <6 years, the proportion of subjects with at least 1 TEAE was 84% in the palonosetron group vs. 75% in the ondansetron group. In subjects aged 6 to <12 years, the proportion of subjects with at least 1 TEAE was 76% in the palonosetron group vs. 87% in the ondansetron group. In subjects aged 12 to <18 years, the proportion of subjects with at least 1 TEAE was 74% in the palonosetron group vs. 86% in the ondansetron group.

Reviewer comments: *This medical officer also reviewed safety data for trends across age groups with regard to specific AEs (by PT), particularly those that are labeled as*

adverse reactions with palonosetron (e.g., constipation, headache). Overall, there appears to be no particular consistent trend in the incidence of TEAEs or specific AEs (by PT) in the comparison between age groups. For example, constipation was more frequent in the palonosetron 20 mcg/kg arm (8%) than in the ondansetron arm (4%) in the 2 to <6 years age group, and the 12 to <18 years age (8% in the palonosetron 20 mcg/kg arm vs. 2% in the ondansetron arm). In the 6 to <12 years age group, constipation was less frequent in the palonosetron 20 mcg/kg arm (2%) than in the ondansetron arm (9%). Review of individual AEs (by PT) precluded meaningful comparisons across groups for many AEs due to the low overall incidence of many AEs and the further reduction in incidence rate that occurred when these AEs were examined across four age groups. Moreover, the TEAE incidence rate among palonosetron subjects is generally comparable to the TEAE incidence rate among ondansetron subjects within each of the four age groups.

Gender
The proportion of subjects with at least 1 TEAE was lower in males (76%) than females (82%) overall but was slightly greater in the ondansetron group for males (79%) and females (86%) compared with males (74%) and females (81%) who received palonosetron. The proportion of subjects who reported serious TEAEs was comparable in both genders.

Reviewer comments: *The small differences observed between genders are not likely to be of clinical significance.*

Race and Ethnicity
The Sponsor indicated that because the majority (89%) of subjects who received palonosetron or ondansetron was White with non-Hispanic (75%), Hispanic (8%), or unknown (6%) ethnicities, meaningful interpretation of TEAEs on the basis of race or ethnicity were not possible.

Reviewer comments: *The incidences of all categories of AEs in White subjects were comparable in the palonosetron and ondansetron treatment groups. Meaningful conclusions about non-White subjects are precluded by the small numbers of non-white subjects.*

Region
Overall, the proportions of subjects with at least 1 TEAE were greater in Latin America (87%) and the US (87%) compared with Europe (76%) and Russia/Ukraine (73%). In the US, the proportion of subjects with at least 1 TEAE was 87% in the palonosetron group and 88% in the ondansetron group. In Latin America, the proportion of subjects with at least 1 TEAE was 86% in the palonosetron group and 92% in the ondansetron group. In Europe, the proportion of subjects with at least 1 TEAE was 73% in the palonosetron group and 82% in the ondansetron group. In Russia/Ukraine, the

proportion of subjects with at least 1 TEAE was 73% in the palonosetron group and 73% in the ondansetron group.

Reviewer comments: *Although the incidence of TEAEs was greater in Latin America and the US than in Europe and Russia/Ukraine, within each region, the proportion of subjects with at least 1 TEAE was comparable between the palonosetron and ondansetron dose groups.*

7.5.4 Drug-Disease Interactions

Drug-disease interactions were not evaluated in PALO-10-20 or PALO-99-07.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not evaluated in PALO-10-20 or PALO-99-07.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity trials were not performed as part of this sNDA.

7.6.2 Human Reproduction and Pregnancy Data

The Sponsor reports that no use in pregnant or lactating females occurred during the pediatric program.

ALOXI is a pregnancy category B drug. Teratology studies have been performed in rats at oral doses up to 60 mg/kg/day (1894 times the recommended human intravenous dose based on body surface area) and rabbits at oral doses up to 60 mg/kg/day (3789 times the recommended human intravenous dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to palonosetron. There are, however, no adequate and well-controlled studies in pregnant women.

The Maternal Health Team (MHT) provided labeling recommendations to structure Pregnancy and Nursing Mothers labeling information in the spirit of the Proposed Pregnancy and Lactation Labeling Rule (PLLR). For details, the reader is referred to the MHT review by Dr. Miriam Dinatale, dated April 30, 2014.

7.6.3 Pediatrics and Assessment of Effects on Growth

Effects on growth were not assessed.

Reviewer comments: *Because palonosetron I.V. is not for chronic use, effects on growth would not be anticipated.*

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reported cases of overdose in the pediatric clinical trials of palonosetron.

Reviewer comments: *Given what is known about the mechanism of action of palonosetron, abuse potential, withdrawal, and rebound effects are not expected.*

7.7 Additional Submissions / Safety Issues

Safety Summary for Subsequent Cycles (Cycle 2, 3, and 4)
In PALO-10-20, subjects were scheduled to receive study treatment on study Day 1 of each chemotherapy cycle for up to 4 cycles if they were to receive at least one MEC or HEC agent. Table 50 shows the number of subjects (by age group) included in the safety population (SAF) at each cycle for cycles 2-4.

Table 50. Number of Subjects in the Safety Population in Cycles 2-4 by Age Group (PALO-10-20)

Safety Population (SAF)	Palonosetron 10	Palonosetron 20	Ondansetron
Cycle 2	N=84	N=90	N=86
Age <2 years, n (%)	8 (9.5)	8 (8.9)	8 (9.3)
Age 2 up to <6 years, n (%)	31 (36.9)	26 (28.9)	33 (38.4)
Age 6 up to <12 years, n (%)	20 (23.8)	26 (28.9)	20 (23.3)
Age 12 up to <17 years, n (%)	25 (29.8)	30 (33.3)	25 (29.1)
Cycle 3	N=43	N=59	N=44
Age <2 years, n (%)	5 (11.6)	6 (10.2)	5 (11.4)
Age 2 up to <6 years, n (%)	15 (34.9)	16 (27.1)	15 (34.1)
Age 6 up to <12 years, n (%)	14 (32.6)	16 (27.1)	11 (25.0)
Age 12 up to <17 years, n (%)	9 (20.9)	21 (35.6)	13 (29.5)
Cycle 4	N=20	N=31	N=18
Age <2 years, n (%)	3 (15.0)	4 (12.9)	1 (5.6)
Age 2 up to <6 years, n (%)	7 (35.0)	5 (16.1)	8 (44.4)
Age 6 up to <12 years, n (%)	6 (30.0)	8 (25.8)	5 (27.8)
Age 12 up to <17 years, n (%)	4 (20.0)	14 (45.2)	4 (22.2)

Note: Regarding the overall exposure to study drugs in each study cycle, each individual subject received the same study treatment in all cycles except for one subject [582/5088] randomized to ondansetron, who was erroneously treated with palonosetron 10 mcg/kg during cycle 4.
Source: Reviewer's table, adapted from Table 1-6, page 21, Summary of Clinical Safety.

From the safety population, 20 (12%) subjects in the palonosetron 10 mcg/kg group, 31 (19%) subjects in the palonosetron 20 mcg/kg group, and 18 (11%) subjects in the ondansetron group completed 4 study cycles. Overall, 69 (14%) subjects completed 4 cycles in study PALO-10-20.

Reviewer comments: *In the palonosetron 20 mcg/kg arm, the number of subjects remaining on study through the 4 cycles was numerically greater than in the other treatment groups. Although there was a substantial stepwise decline in sample size with each cycle, in this medical officer's assessment, the number of subjects was adequate for a general safety evaluation through 4 cycles. Additionally, the number of subjects was generally balanced across treatment arms through repeat cycles.*

Exposure to study drug

Table 51 summarizes exposure data by treatment arm for cycles 2-4 of PALO-10-20.

Table 51. Extent of Exposure to Study Drug in Cycles 2-4 of PALO-10-20 (SAF Population)

Variable	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3 x 0.15 mg/kg
	Total dose in mcg	Total dose in mcg	Total dose in mg
Cycle 2			
Mean (SD)	287.9 (172.3)	642.2 (372.9)	13.35 (8.7)
Median (Min, Max)	221.0 (55.0, 747.0)	541.0 (112.0, 1500.0)	9.00 (2.22, 33.78)
Cycle 3			
Mean (SD)	262.2 (156.9)	656.9 (384.3)	13.27 (8.87)
Median (Min, Max)	210.0 (52.0, 615.0)	530.0 (132.0, 1500.0)	9.57 (2.22, 33.78)
Cycle 4			
Mean (SD)	260.9 (161.1)	753.6 (412.9)	11.41 (7.16)
Median (Min, Max)	203.5 (55.0, 620.0)	820.0 (140.0, 1500.0)	8.91 (4.08, 25.68)

Abbreviations: Min, minimum; Max, maximum; SD, standard deviation.
Source: Reviewer's table, adapted from Table 82, page 220, CSR of Study PALO-10-20.

Reviewer comments: *Because the number of subjects treated decreased substantially from cycle 2 to cycle 4, conclusions about exposures with repeat courses are somewhat limited. Nonetheless, within treatment arms, the mean total dose administered was similar across study cycles. Moreover, as expected, exposures were greater in the palonosetron 20 mcg/kg arm than the palonosetron 10 mcg/kg arm across cycles 2-4.*

Table 52 summarizes exposure data by age group across the treatment arms during cycles 2-4 of PALO-10-20.

Table 52. Exposure to Study Drug in Cycles 2-4 of PALO-10-20 by Age Group (SAF Population)

Variable	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3 x 0.15 mg/kg
	Total dose in mcg	Total dose in mcg	Total dose in mg
Cycle 2			
Age <2 Years	N=8	N=8	N=8
Mean (SD)	89.75 (19.91)	178.8 (59.96)	4.19 (1.19)
Median (Min, Max)	87.5 (55.0, 115.0)	175.0 (112.0, 260.0)	4.44 (2.22, 5.40)
Age 2 up to <6 years	N=31	N=26	N=33
Mean (SD)	169.9 (39.50)	324.5 (54.45)	7.06 (1.38)
Median (Min, Max)	160.0 (110.0, 272.0)	320.0 (212.0, 434.0)	7.02 (4.50, 9.66)
Age 6 up to <12 years	N=20	N=26	N=20
Mean (SD)	285.4 (92.08)	629.2 (196.0)	12.70 (2.97)
Median (Min, Max)	262.5 (170.0, 490.0)	618.0 (392.0, 1252.0)	13.86 (8.52, 16.62)
Age 12 up to <17 years	N=25	N=30	N=25
Mean (SD)	499.7 (126.8)	1053 (257.0)	25.10 (5.43)
Median (Min, Max)	490.0 (260.0, 747.0)	990.0 (674.0, 1500.0)	25.14 (16.20, 33.78)
Cycle 3			
Age <2 Years	N=5	N=6	N=5
Mean (SD)	82.8 (20.29)	200.0 (53.98)	3.71 (1.16)
Median (Min, Max)	81.0 (52.0, 106.0)	220.0 (132.0, 270.0)	3.96 (2.22, 5.22)
Age 2 up to <6 years	N=15	N=16	N=15
Mean (SD)	163.1 (40.98)	334.0 (64.54)	6.59 (1.42)
Median (Min, Max)	156.0 (111.0, 270.0)	345.0 (230.0, 430.0)	6.78 (4.38, 9.24)
Age 6 up to <12 years	N=14	N=16	N=11
Mean (SD)	284.1 (111.5)	588.8 (167.5)	12.66 (2.77)
Median (Min, Max)	246.0 (160.0, 570.0)	530.0 (400.0, 950.0)	12.60 (8.64, 16.62)
Age 12 up to <17 years	N=9	N=21	N=13
Mean (SD)	493.2 (80.22)	1085 (246.8)	25.18 (4.98)
Median (Min, Max)	486.0 (395.0, 615.0)	1086 (770.0, 1500.0)	25.26 (16.62, 33.78)
Cycle 4			
Age <2 Years	N=3	N=4	N=1
Mean (SD)	79.67 (24.5)	215.0 (57.54)	4.08 (N/A)
Median (Min, Max)	80.0 (55.0, 104.0)	220.0 (140.0, 280.0)	4.08 (4.08, 4.08)
Age 2 up to <6 years	N=7	N=5	N=8
Mean (SD)	175.3 (26.99)	332.8 (47.17)	6.52 (1.29)
Median (Min, Max)	173.0 (130.0, 215.0)	350.0 (280.0, 390.0)	6.36 (5.16, 9.24)
Age 6 up to <12 years	N=6	N=8	N=5
Mean (SD)	286.2 (112.5)	632.3 (190.7)	11.44 (3.25)
Median (Min, Max)	275.0 (167.0, 490.0)	586.0 (420.0, 980.0)	9.42 (8.76, 15.48)
Age 12 up to <17 years	N=4	N=14	N=4
Mean (SD)	508.8 (91.09)	1127 (236.2)	23.00 (3.44)
Median (Min, Max)	507.5 (400.0, 620.0)	1130 (860.0, 1500.0)	23.94 (18.42, 25.68)

Abbreviations: Min, minimum; Max, maximum; SD, standard deviation.
Source: Reviewer's table, adapted from Table 14.3.7.2, Table 14.3.7.3, Table 14.3.7.4, and Table 14.3.7.5, pages 10256-10263, CSR of Study PALO-10-20.

Deaths and nonfatal SAEs
For details of subject deaths, see Table 40 in section 7.3.1 Deaths.

During cycle 2, there were 73 subjects [28 (38%) palonosetron 10 mcg/kg, 20 (27%) palonosetron 20 mcg/kg, and 25 (34%) ondansetron] that reported at least 1 nonfatal SAE. During cycle 3, there were 32 subjects [11 (34%) palonosetron 10 mcg/kg, 11 (34%) palonosetron 20 mcg/kg, and 10 (31%) ondansetron] that reported at least 1 nonfatal SAE. During cycle 4, there were 21 subjects [6 (29%) palonosetron 10 mcg/kg, 8 (38%) palonosetron 20 mcg/kg, and 7 (33%) ondansetron] that reported at least 1 nonfatal SAE.

Details of clinically relevant SAEs in cycles 2-4 were previously described in Table 41 in section 7.3.2 Nonfatal Serious Adverse Events.

Table 53 provides an overview of TEAEs by cycle for cycles 2-4 in PALO-10-20.

Table 53. Summary of Subjects with TEAEs by Cycle of PALO-10-20 (Cycles 2-4) (SAF Population)

TEAE category	Palonosetron 10 mcg/kg n (%)	Palonosetron 20 mcg/kg n (%)	Ondansetron 3 x 0.15 mg/kg n (%)
Cycle 2	N=84	N=90	N=86
Any TEAE	64 (76.2)	58 (64.4)	71 (82.6)
Serious TEAE	28 (33.3)	20 (22.2)	25 (29.1)
Cycle 3	N=43	N=59	N=44
Any TEAE	31 (72.1)	33 (55.9)	30 (68.2)
Serious TEAE	11 (25.6)	11 (18.6)	10 (22.7)
Cycle 4	N=20	N=31	N=18
Any TEAE	15 (75.0)	15 (48.4)	13 (72.2)
Serious TEAE	6 (30.0)	8 (25.8)	7 (38.9)

Abbreviations: TEAE, treatment emergent adverse event.
Source: Reviewer's table, adapted from Table 2-11, pages 61-62, Summary of Clinical Safety.

Reviewer comments: *Robust conclusions about trends in the incidence of TEAEs and SAEs are limited in part by the decreasing sample size with each subsequent cycle. Numerically, the palonosetron 20 mcg/kg dose arm demonstrates a consistently smaller incidence of TEAEs and SAEs than the palonosetron 10 mcg/kg and ondansetron dose arms for cycle 2, cycle 3, and cycle 4.*

Detailed review by this medical officer of deaths, nonfatal SAEs, common AEs, and other supportive safety data (e.g., laboratory findings, vital signs) did not reveal any patterns, shifts, or trends across cycles 2-4 that would suggest meaningful differences in the safety of palonosetron between cycle 1 and subsequent cycles of therapy.

Integrated Summary of Safety – PONV and CINV Studies

The safety data for the PONV studies in pediatric subjects (PALO-07-29 and PALO-10-14) were submitted by the Sponsor in a separate sNDA (S-018). For detailed review of safety data in the PONV studies, the reader is referred to the medical officer review of S-018 by Dr. Teresa Buracchio. The Sponsor also submitted an integrated safety database for all pediatric subjects enrolled in the four studies (two CINV studies and two PONV studies). The integrated summary of safety (ISS) was structured to display the data for the pediatric subjects treated with the same palonosetron single doses (namely 1, 3, 10, and 20 mcg/kg) irrespective of the source study. Only the 3 mcg/kg dose was used in both indications. For completeness, this medical officer also reviewed the ISS and findings are summarized briefly below.

The integrated safety population for PONV and CINV studies in pediatric subjects was comprised of 1377 subjects. Of these 1377 subjects, 883 were treated with palonosetron and 494 were treated with ondansetron.

Among the subjects treated with palonosetron, 405 subjects received 1 mcg/kg (74 subjects in PALO-07-29 and 331 subjects in PALO-10-14); 111 subjects 3 mcg/kg (76 subjects in PALO-07-29 and 35 subjects in PALO-99-07); 204 subjects 10 mcg/kg (37 subjects in PALO-99-07 and 167 subjects in PALO-10-20) and 163 subjects 20 mcg/kg (all in PALO-10-20). Of the subjects treated with ondansetron 330 subjects received 0.1 mg/kg (all in PALO-10-14); and 164 subjects received 3 x 0.15 mg/kg (all in PALO-10-20).

Table 54 summarizes the demographics and baseline characteristics for subjects who received at least a single I.V. dose of palonosetron or ondansetron (1 or 3 doses).

Table 54. Demographics and Baseline Characteristics in CINV & PONV Phase 3 Pediatric Studies

		Palonosetron all doses N = 883 (100.0%)	Ondansetron all doses N = 494 (100.0%)	All Patients All doses N =1377 (100.0%)
Patients completing the studies		872 (98.8%)	490 (99.2%)	1362 (98.9%)
Gender	Male	501 (56.7%)	298 (60.3%)	799 (58.0%)
	Female	382 (43.3%)	196 (39.7%)	578 (42.0%)
Age group, No. (%)	< 2 years	71 (8.0%)	39 (7.9%)	110 (8.0%)
	2 to < 6 years	275 (31.1%)	178 (36.0%)	453 (32.9%)
	6 to < 12 years	292 (33.1%)	162 (32.8%)	454 (33.0%)
	12 to <18 years	245 (27.7%)	115 (23.3%)	360 (26.1%)
Region	USA	171 (19.4%)	79 (16.0%)	250 (18.2%)
	Latin America	56 (6.3%)	18 (3.6%)	74 (5.4%)
	Russia and Ukraine	284 (32.2%)	138 (27.9%)	422 (30.6%)
	Europe	372 (42.1%)	259 (52.4%)	631 (45.8%)
Therapeutic indication	Prevention of CINV	402 (45.5%)	164 (33.2%)	566 (41.1%)
	Prevention of PONV	481 (54.5%)	330 (66.8%)	811 (58.9%)

Source: Sponsor's table, Table 1-1, page 6, Summary of Clinical Safety.

Of the 883 subjects who received palonosetron in the phase 3 studies, 481 (55 %) subjects were treated in PONV studies and 402 (46%) were treated in CINV studies. Of the 494 subjects who received ondansetron, 330 (67%) subjects were treated in PONV studies and 164 (33%) were treated in CINV studies.

A total of 872 of 883 (99%) subjects receiving palonosetron and 490 of 494 (99%) subjects receiving ondansetron completed treatment in the studies.

The Sponsor reported no deaths, serious TEAEs, or discontinuations due to TEAEs in PONV study PALO-07-29. In PONV study PALO-10-14, the Sponsor reported that no subjects died and that no subjects discontinued due to TEAEs. There were 15 subjects (4 palonosetron 1 mcg/kg, 11 ondansetron 0.1mg/kg) that reported at least 1 SAE. A total of 30 SAEs were reported by the 15 subjects. The incidence of SAEs was 1% in subjects who received palonosetron compared with 3% in subjects who received ondansetron. At the SOC level, serious TEAEs in the gastrointestinal disorder SOC were the most common overall (1%) and in both treatment groups. The serious TEAE post procedural hemorrhage was the most commonly reported PT overall (1%).

Reviewer comments: *Narratives for all subjects who had a serious TEAE in the PONV studies were reviewed by this medical officer. The majority of serious TEAEs appeared to be complications related to the procedure (e.g., postoperative hemorrhage, wound bleeding, ileus following heminephrectomy).*

Because the maximum dose of palonosetron evaluated in the pediatric PONV program was 3 mcg/kg, review of the PONV safety database was of limited utility in assessing for potential AEs at the higher doses relevant to the CINV study population (e.g., 20 mcg/kg). Nonetheless, no safety signal emerged from this medical officer's review of the PONV safety database or the integrated safety database for all pediatric subjects enrolled in the four studies (two CINV studies and two PONV studies).

8 Postmarket Experience

The Sponsor presented safety data on pediatric use and other off-label uses of palonosetron during postmarketing experience for the reporting period from 2003 (year of initial ALOXI approval) to September 30, 2013. The Sponsor reports that a total of 4 reports have been collected regarding the use of palonosetron in pediatric patients aged 0 to 18 years inclusive. These cases are summarized briefly below:

- An 8-year-old female received 0.25 mg I.V. palonosetron in multiple cycles for CINV prevention. She vomited once per cycle, which was reportedly an improvement compared to the frequency of emetic episodes with previous ondansetron therapy.
- A 7-year-old female received unknown dose of I.V. palonosetron apparently for CINV prevention, but experienced no relief (i.e., lack of efficacy). No AEs were reported.

- A 12-year-old female with lupus received 0.75 mg I.V. palonosetron prior to treatment with cyclophosphamide. She erroneously received palonosetron for 2 consecutive days. No AEs were reported.
- A 17-year-old male with recurrent precursor B-lymphoblastic lymphoma under chemotherapy with thiotepa received 0.25 mg I.V. palonosetron for CINV prevention. The subject was also receiving furosemide. Following completion of chemotherapy, the subject developed tremor and foot cramps. Blood tests revealed hyponatremia.

Reviewer comments: *Spontaneous adverse event reports relating to I.V. palonosetron in the pediatric population are sparse. Despite the limited interpretability of spontaneous postmarketing reports, the cases presented above demonstrate no clear causal link between the AE reported (if any) and palonosetron.*

9 Appendices

Appendix 1: Discussion of Individual Trials: PALO-10-20

Title
A multicenter, randomized, double-blind, parallel group study to evaluate the efficacy and safety of two different doses of palonosetron compared to ondansetron in the prevention of CINV in pediatric patients undergoing single and repeated cycles of MEC or HEC

Primary Objective
"To evaluate the efficacy of two different doses of I.V. palonosetron in the prevention of chemotherapy induced nausea and vomiting in MEC and HEC subjects through 120 hours after start of chemotherapy in single and repeated chemotherapy cycles"

Trial Design
Active-controlled, double-blind, randomized, parallel group, stratified, phase 3 study involving 3 study groups receiving palonosetron in two different doses or ondansetron standard therapy

Duration
The first subject was enrolled on September 12, 2011 and the last subject's last visit was on October 26, 2012. Database lock occurred on February 11, 2013.

Study Sites
A total of 71 investigative sites were initiated in 17 countries. Subjects were enrolled into the study at 59 sites, including 11 sites in the United States, 7 in Russia, 5 in Poland, 4 sites each in Chile, Czech Republic, Romania, and Ukraine, 3 sites each in Bulgaria, France, Hungary, and Peru, 2 sites each in Argentina, Austria, and Serbia, and 1 site each in Estonia and Germany. Subjects from 57 of these sites enrolled subjects included the FAS population.

Key Inclusion Criteria
1. Written informed consent signed by parent(s)/legal guardians of the pediatric subject in compliance with the local laws and regulations. In addition signed pediatric subjects' assent form according to local requirements.
2. Male or female in- or out-patients from neonates (full term) to <17 years at the time of randomization.
3. Subject weight at least 3.2 kg.
4. Histologically, and/or cytologically (or imaging in the case of brain tumors) confirmed malignant disease.
5. Naïve or non-naïve to chemotherapy.

6. Scheduled and eligible to receive at least one of the moderately or highly emetogenic chemotherapeutic agents (the most emetogenic agent) on Study Day 1. See Table 57 for emetogenic risk classification.
7. For subjects aged ≥10 years to <17 years: Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤2 (see Table 59).
8. For subjects with known hepatic impairment (defined as AST >2.5 X upper limit of normal (ULN) or ALT >2.5 X ULN or total bilirubin >1.5 X ULN): in the investigator's opinion the impairment should not jeopardize subject's safety during the study.
9. For subjects with known renal impairment (defined as creatinine >1.5 X ULN): in the investigator's opinion the impairment should not jeopardize subject's safety during the study.
10. For subjects with known history or predisposition to cardiac abnormalities: in the investigator's opinion the history/predisposition should not jeopardize subject's safety during the study.
11. For subjects with known clinically relevant abnormal laboratory values: in the investigator's opinion the abnormality should not jeopardize the subject's safety during the study.
12. Fertile subjects (male or female) must use reliable contraceptive measures (such measures, for subjects and sexual partners, include: implants, injectables, combined oral contraceptives, intrauterine devices, vasectomized/sterilized partner, use of a double barrier method or sexual abstinence).
13. Female subjects who have attained menarche must have a negative pregnancy test at the screening visit (Visit 1) and at study treatment visit (Visit 2). The subject and her parent(s) must be counseled on the importance of not becoming pregnant before or during the study.

Key Exclusion Criteria

1. The subject and/or parents/caregivers are expected by the investigator to be noncompliant with the study procedures.
2. Lactating or pregnant female subject.
3. Subject has received total body irradiation, upper abdomen radiotherapy, radiotherapy of the cranium, craniospinal regions or the pelvis within 1 week prior to study entry (screening).
4. Scheduled to receive concomitant total body irradiation, radiotherapy of the upper abdomen, lower thorax region, or cranium/craniospinal regions up to 24 hours after study drug administration.
5. Known history of allergy to any component or other contraindications to any 5-HT_3 receptor antagonists.
6. Active infection.
7. Uncontrolled medical condition (e.g., uncontrolled insulin-dependent diabetes mellitus).

8. Marked baseline prolongation of QTc interval [QTcB or QTcF >460 msec] in any of the ECG assessments at screening. For this purpose, assessment will rely on the automatic interpretation by the ECG machine.
9. Subject suffering from ongoing vomiting from any organic etiology (including subjects with history of gastric outlet obstruction or intestinal obstruction due to adhesions or volvulus) or subjects with hydrocephalus.
10. Subject who experienced any vomiting, retching, or nausea within 24 hours prior to the administration of the study drug.
11. Subject who received any drug with potential antiemetic effect within 24 hours prior to administration of study treatment, including but not limited to:
    - NK_1-receptor antagonists (e.g. aprepitant)
    - 5-HT_3 antagonists (e.g., ondansetron, granisetron, dolasetron);
    - Phenothiazines (e.g., perphenazine, prochlorperazine, promethazine, fluphenazine, chlorpromazine, thiethylperazine);
    - Butyrophenones (e.g., droperidol, haloperidol);
    - Benzamides (e.g., metoclopramide, alizapride);
    - Corticosteroids (e.g., prednisone, methylprednisolone; except inhaled steroids for respiratory disorders and topical steroids for skin disease with doses of ≤10 mg of prednisone daily or its equivalent); Corticosteroids foreseen in the chemotherapy regimen or to reduce intracranial pressure are allowed. According to guidelines,[2,3] subjects will receive also corticosteroids (e.g., dexamethasone) as a co-medication in accordance with standard clinical practice and if deemed appropriate by the Investigator.
    - Dimenhydrinate, Hydroxyzine, Domperidone, Lorazepam, Cyclizine, Cannabinoids, Scopolamine, Trimetobenzamide HCl, Meclizine hydrochloride, Pseudoephedrine HCl;
    - Over the Counter (OTC) antiemetics, OTC cold or OTC allergy medications;
    - Herbal preparations containing ephedra or ginger.
12. Subject aged ≤6 years who received any investigational drug (defined as a medication with no marketing authorization granted for any age group and any indication) within 90 days prior to Day 1, or subject aged >6 years who received any investigational drug within 30 days prior to Day 1 or is expected to receive investigational drugs prior to study completion.
13. Subject who participated in any previous trial with palonosetron.

Randomization

Subjects who met all eligibility criteria and who had not had vomiting, retching or nausea within 24 hours prior to administration of study drug were randomized in a 1:1:1 ratio to one of three treatment groups (palonosetron 10 mcg/kg, palonosetron 20 mcg/kg, or ondansetron). Treatment assignment was managed through a static central permuted block randomization stratified by age class (<2 years, 2 years to <6 years, 6 years to <12 years, 12 years to <17 years) and by chemotherapy emetogenicity (HEC or MEC).

Trial Conduct
See Figure 3 for a detailed study flow chart.

Visit 1: Day -14 to -1; Day -7 to -1 for subjects aged <2 years – Determine eligibility for study inclusion

- Informed consent of parent(s) or legal guardian(s) and assent of the child
- Demographic data (gender, race, date of birth), medical history, history of nausea and vomiting, prior and concomitant medication, recording of any AE (starting after signature of informed consent)
- Current cancer history, CNS leukemia status (for subjects with leukemia only), ECOG PS assessment (for subjects aged ≥10 years to <17 years)
- Physical examination, vital signs (pulse, systolic/diastolic blood pressure), height/length measurement (as appropriate for various pediatric age groups)
- 12-lead electrocardiogram, blood and urine samples for serum chemistry, hematology, urinalysis, urine pregnancy test for post-menarchal females
- Instruction on how to complete the subject diary

Visit 2: Day 1 – Randomization (using IWRS)[4]

- Randomize subjects who meet all eligibility criteria and who have not had vomiting, retching or nausea within 24 hours prior to administration of study drug to one of three treatment groups (palonosetron 10 mcg/kg, palonosetron 20 mcg/kg, or ondansetron).
- Record weight, concomitant medications and any pretreatment AEs
- Corticosteroid (e.g., dexamethasone) administration unless contraindicated or part of chemotherapy regimen
- Study drug administration 30 (± 5) minutes before the start of the first agent considered by the investigator as the most highly or moderately emetogenic chemotherapy
- Blood samples for PK measurements
- Vital signs (pulse, blood pressure) at the end of the first study drug administration, and 1 hour (± 10 min) and 3 hours (± 60 min) after end of first study drug administration
- Single 12-lead ECG at the end of the first study drug administration
- Administration of chemotherapy
- Administration of second and third dose of ondansetron/placebo starting at 4 and 8 hours (± 30 minutes) after first dose (i.e. 3.5 and 7.5 hours respectively after start of chemotherapy)

[4] If a subject is eligible at Visit 1 and the study medication and chemotherapy administration can be accomplished on that day, then Visit 1 and Visit 2 procedures including screening, randomization, study drug and highly or moderately emetogenic chemotherapy administration can be accomplished on the same day, as long as written informed consent and written assent, if applicable, are obtained prior to initiating any screening or study procedures.

- Recording of rescue medication (if any), other used medication (if any), emetic episodes (if any), any AEs
- Supply diary covering 120 hours after T_0

Visit 3: Day 2 (24 hours or more after T_0)
- Assess subject's safety (concomitant medication, rescue medication, AEs)
- Review and collect data of the first 24 hours of the completed diary
- Evaluate subject's nausea (in subjects aged ≥6 years)
- PK sampling for a subset of subjects

Visit 4: Day 3 (48 hours after T_0) – For subjects included in the PK sub-study only
- PK sampling for a subset of subjects
- Review and collect data of the first 24 hours of the completed diary

Visit 5: Day 4 (72 hours after T_0) – For subjects included in the PK sub-study only
- PK sampling for a subset of subjects

Visit 6: Day 6 (120 hours after T_0)
- Assess subject's safety (concomitant medication, rescue medication, AEs)
- Review and collect the completed diary
- Evaluate subject's nausea (in subjects aged ≥6 years)
- PK sampling for a subset of subjects

Visit 7: Day 7 to 10
- Physical examination, vital signs, 12-lead ECG blood and urine samples for serum chemistry, hematology, and urinalysis
- Review and collect the completed diary for subjects having performed Visit 3 and/or Visit 6 by phone
- PK sampling for a subset of subjects

Visit 8: Follow-up telephone contact (Day 15 to 18)
- Assess for any new or ongoing AEs and changes in concomitant medications since the last visit

Study procedures at subsequent cycles
Subjects could undergo study treatment for up to 4 cycles if they were scheduled to receive at least one of the moderately or highly emetogenic chemotherapeutic agents (the most emetogenic agent) on Study Day 1 of these subsequent cycles. Emetogenicity of Day 1 chemotherapeutic agents (HEC or MEC) could be different at each cycle.

During cycles 2 to 4 the subjects were administered the same treatment as in first cycle. The dose administered was calculated basing on the actual body weight. During cycles

2 to 4 the same study procedures as during the first cycle were performed, except for the subject diary which was not used during the subsequent cycles. Efficacy data were collected only during Visit 3 and Visit 6 (presence/absence of nausea, vomiting and retching, use of rescue medication).

The interval between two consecutive study drug administrations (i.e., the time interval between two consecutive 'Study Day 1' in chemotherapy cycles) was to be at least fourteen days. Study drug administration for the fourth cycle was to be performed within 12 weeks after administration of the first cycle.

Visit 1 and Visit 2 of cycles 2 to 4 could be performed on the same day. If two separate visits were foreseen within the same cycle, the maximum interval allowed between the two visits was 3 days. Before administration of study drug during any subsequent cycle all eligibility criteria were to be checked.

If the second/third/fourth cycle started 2 weeks after the start of the previous cycle, then the follow-up of the previous cycle could be performed during the same visit as V1/V2 of the second/third/fourth cycle.

In the case the interval between Visit 7 of a given study cycle and Visit 1 of the next study cycle was ≤5 days, one unique blood and urine sampling was considered sufficient to cover both visits. This unique sampling was to be taken at Visit 7 of the preceding cycle. If more than 5 days had elapsed between Visit 7 of a given cycle and Visit 1 of the next cycle, the blood and urine samplings and analysis were to be repeated at V1 of the next cycle.

Subjects could enter cycles 2 to 4 until the last subject enrolled started the first cycle; then no new cycles could be started for any subject. A subject was defined as "completed" for a given cycle if she/he completed Visit 7 (final visit) of that cycle. Termination at any previous time point was considered as discontinuation of the cycle.

Figure 3. Study PALO-10-20 Flow Chart

	CYCLE 1						CYCLES 2 to 4					
Visit	V1	V2[10]	V3[23]	V6[23]	V7	V8[11]	V1[12,13]	V2[13]	V3[23]	V6[23]	V7	V8[11]
Time point (Day)	-14 to -1; -7 to -1 for <2 years	1	2 (≥24h)[14]	6	7 to 10	15 to 18	-3 to -1	1	2 (≥24h)[14]	6	7 to 10	15 to 18
Assessments	Screening	Randomization/ Treatment/ Chemotherapy	Control Visit	Control Visit	Final Visit	Follow up	Screening	Treatment/ Chemotherapy	Control Visit	Control Visit	Final Visit	Follow up
Informed Consent	X											
Inclusion/Exclusion Criteria[1]	X	X					X	X				
Demography and medical history (including current cancer history, naivety to chemotherapy)	X											
History of nausea and vomiting in previous chemotherapy	X											
Prior and concomitant medication recording	X	X	X[15]	X	X	X	X	X	X[15]	X	X	X
Hematology, Serum chemistry[2], Urinalysis[2]	X	X[21]			X[16]		X[16]	X[21]			X[16]	
Pregnancy test (urine)[3]	X	X						X				
Physical examination	X				X		X				X	
Vital signs	X	X[20]			X		X	X[20]			X	
Height / length	X											
Weight		X						X				
12-lead ECGs[4]	X	X			X[17]		X[17]	X			X[17]	
Randomization		X										
Study drug administration (palonosetron+placebo or ondansetron+placebo)[5]		X						X				
PK sampling at T_T		X[22]										
Study drug administration Ondansetron/placebo6		X						X				
HEC/MEC Chemotherapy		X						X				
Concomitant corticosteroid[7]		X						X				
Record efficacy parameters		Recording up to 120h							X[18]	X		
Patient Diary	Instruction	Filled in up to 120h[19]										
Adverse event recording[8]	X	X	X	X	X	X	X	X	X	X	X	X
ECOG status[9]	X						X					

1 Eligibility criteria were checked prior to randomization during the first cycle and prior to the first infusion of the study drug during each of the following cycles. For the evaluation of inclusion criteria 8 and 9, values from the local laboratory could be used.

2 Blood and urine samples were sent to the central laboratory. A urine sample was obtained if the patient was capable of providing a urine sample.

3 For female patients having reached menarche only.

4 At Visits 1 and 7, ECGs were recorded in triplicate, while at visit 2 only a single ECG was recorded at T_T. The 12-lead ECG was evaluated in a central reading facility.

5 Study drugs were administered in double-blind fashion: 30 (±5) minutes prior to initiating MEC or HEC, palonosetron 10 mcg/kg or palonosetron 20 mcg/kg or ondansetron diluted in isotonic saline solution was given as a 15 minutes infusion. During cycles 2 to 4 the patients were administered the same treatment as in the first cycle.

6 Administration of ondansetron/placebo to be repeated after 4 and 8 hours (±30 minutes) after the first administration of the study drug (i.e. 3.5 and 7.5 hours (±30 minutes) after the start of chemotherapy).

7 Concomitant dexamethasone for the prevention of CINV was given except if this was contraindicated or if corticosteroids were already included in the chemotherapy regimen. Dosage and administration: according to standard practice.

8 Adverse events occurring after signature of informed consent but before first study drug administration were to be reported and treated as pre-treatment AEs.
9 ECOG status was assessed for patients aged ≥10 years to <17 years.
10 If a patient was eligible at Visit 1 and the study medication administration and chemotherapy could be done on that day, Visit 1 and Visit 2 procedures including screening, randomization, study drug administration and chemotherapy could be accomplished on the same day.
11 Follow up Telephone Contact (14 to 17 days after drug administration).
12 If the second/third/fourth cycle started 2 weeks after the start of the previous cycle; the follow-up of the previous cycle could be performed during the same visit as V1/V2 of the second/third/fourth cycle.
13 Visit 1 and Visit 2 of cycles 2 to 4 could be performed on the same day. If two separate visits were foreseen within the same cycle, the maximum interval allowed between the two visits was 3 days.
14 Visit 3 was performed at least 24 after start of chemotherapy on Day 1 of the respective study cycle.
15 Including antiemetic rescue medication.
16 In the case the interval between V7 of a given study cycle and V1 of the next study cycle was less or equal to 5 days, one unique blood and urine sampling was sufficient to cover both visits. This unique sampling was to be taken at V7 of the preceding cycle. If more than 5 days had elapsed between V7 of a given cycle and V1 of the next cycle, the blood and urine samplings and analysis were to be repeated at V1 of the next cycle.
17 In the case the interval between V7 of a given study cycle and V1 of the next study cycle was less or equal to 5 days, one set of ECGs was sufficient to cover both visits. This unique set was to be taken at V7 of the preceding cycle. If more than 5 days had elapsed between V7 of a given cycle and V1 of the next cycle, the ECGs were to be repeated at V1 of the next cycle.
18 Efficacy parameters during Cycles 2-4 were recorded only at Visit 3 and 6 (presence / absence of vomiting, retching and nausea).
19 Data regarding the first 24 hours were reported in the eCRF from the patient diaries at Visit 3 and the relevant diary pages collected. Data regarding the 24 to 120 hours were reported in the eCRF at Visit 6 and the complete diary collected and stored as source data.
20 At Visit 2, vital signs were measured at the end of first study drug administration (T_T), and 1 hour and 3 hours after first study drug administration.
21 On Day 2 of each cycle only sampling for serum chemistry was performed at the end of first study drug administration (T_T),
22 One single PK sample at T_T (end of infusion of first study drug administration) was obtained in all patients, if clinically feasible
23 For patients not included in the PK sub-study and not able to personally reach the study site or no study personnel could reach the patient at his home, this visit could be performed at the phone. In this case, the diary for the first cycle had to be collected during a subsequent visit, but at the latest during Visit 7 (Day 7 to 10).

Source: Table 6, pages 66-68, CSR of PALO-10-20.

Removal of Subjects from Therapy or Assessment

Subjects could be withdrawn from the study for reasons that may include the following:

- An AE that, in the opinion of the investigator, made it unsafe for the subject to continue the study
- Any clinically significant laboratory abnormalities that in the investigator's opinion endangered the subject
- The subject's safety was affected by violation of inclusion or exclusion criteria
- The subject and/or the parent(s)/legal guardian(s) requested withdrawal
- The subject was unwilling or unable to adhere to the study requirements after randomization (e.g., non-compliance)
- If the study blind was broken by the investigator (a protocol violation) the subject was automatically withdrawn from the study
- The subject was lost to follow-up

Withdrawn subjects were not replaced.

Prior and Concurrent Therapy

Information on prior and concomitant medications was collected beginning 14 days prior to administration of first cycle up to the follow-up visit (Day 15-18) of the last cycle.

Medication for the prevention of nausea and vomiting or any other medication with potential antiemetic properties within the 24 hours prior to the start of chemotherapy or during the 120 hours after T_0 were prohibited. For subjects receiving HEC or MEC during study days 2-6, the use of antiemetic medication for the prevention of CINV was allowed starting from 24 hours after start of chemotherapy on Day 1 (T_0). Prohibited medications included the following:

- 5-HT_3 receptor antagonists (including ondansetron, granisetron, dolasetron, tropisetron, ramosetron, palonosetron);
- NK_1-receptor antagonists (e.g., aprepitant or any other new drug of this class);
- Phenothiazines (including perphenazine, prochlorperazine, promethazine, fluphenazine, chlorpromazine, theithylperazine);
- Butyrophenones (including droperidol, haloperidol);
- Domperidone;
- Lorazepam;
- Benzodiazepines (except if the subject was receiving such medication for sleep or anxiety and had been on a stable dose for at least 7 days prior to Day 1);
- Antihistamines (e.g., cyclizine, hydroxyzine, diphenhydramine, chlorphenhyramine), except for prophylactic use for taxane therapy;
- Cannabinoids;
- Anticholinergics (e.g., scopolamine), with the exception of inhaled anticholinergics for respiratory disorders (e.g., ipratropium bromide);
- Benzamides (e.g., metoclopramide, alizapride);
- Corticosteroids (e.g., dexamethasone, prednisone, methylprednisolone; except inhaled steroids for respiratory disorders and topical steroids for skin disease);
- Dimenhydrinate;
- Trimetobenzamide HCl;
- Over the Counter (OTC) antiemetics, OTC cold or OTC allergy medications;
- Meclizine hydrochloride, mirtazapine, olanzapine;
- Pseudoephedrine HCl;
- Herbal preparations containing ephedra or ginger.

Systemic corticosteroid therapy at any dose within 24 hours prior to Day 1 was permitted only if part of the chemotherapy, to reduce intracranial pressure, or in case of topical and inhaled corticosteroids with dose of ≤10 mg of prednisone daily or its equivalent.

Study Medication
The study drugs used in PALO-10-20 were:

- Palonosetron 0.05 mg/mL (5.0 mL vial) given I.V. Each 5 mL vial contains palonosetron (0.25 mg), disodium edetate (2.5 mg), mannitol (207.5 mg), sodium citrate/citric acid (buffer), sodium hydroxide/hydrochloric acid (pH adjustment), and water for injection

- Ondansetron 2.00 gm/mL (4 mL ampule) given I.V. Each 4 mL ampule contains ondansetron hydrochloride dihydrate (8 mg), sodium chloride (36.0 mg), citric acid monohydrate (2.0 mg), sodium citrate dehydrate (1.0 mg), and water for injection

As the placebo for palonosetron, a solution with the same excipients but without palonosetron and disodium edetate (EDTA) was used, while an isotonic saline solution served as the placebo for ondansetron.

Subjects eligible for the study were assigned randomly to one of the three treatment groups:

- Group 1: palonosetron 10 mcg/kg– active palonosetron and placebo to ondansetron
- Group 2: palonosetron 20 mcg/kg – active palonosetron and placebo to ondansetron
- Group 3: ondansetron – active ondansetron and placebo to palonosetron

For neonates an open-label sub-study was planned starting with a palonosetron dose of 3 mcg/kg. Because the investigators were unable to enroll neonates, the open-label sub-study was not carried out.

Palonosetron was administered based on the body weight: 10 mcg/kg, up to a maximum total dose of 0.75 mg in the lower dose group; and 20 mcg/kg up to a total dose of 1.5 mg in the higher dose group. For neonates (<28 days, full term) a dose of 3 mcg/kg was to be tested first. Because the investigators were unable to enroll neonates, the open-label sub-study was not carried out.

Ondansetron was administered in three doses of 0.15 mg/kg for all subjects, up to a maximum total dose of 32 mg. Subjects could also receive corticosteroids (e.g., dexamethasone) as a co-medication, except if this was contraindicated or if corticosteroids were already included in the chemotherapy regimen.

Individual doses of study drugs for each subject were calculated at each study cycle by the IWRS based on the subject's actual body weight. For neonates planned in the open-label sub-study only palonosetron active treatment diluted with isotonic saline solution was to be administered. Because the investigators were unable to enroll neonates, the open-label sub-study was not carried out. Dose adjustment was not allowed.

The first dose of study drug was administered 30 minutes (± 5) prior to initiating moderately or highly emetogenic chemotherapy, while subsequent ondansetron/ matching placebo doses were administered after 4 (± 30 minutes) and 8 hours (± 30 minutes) after the first dose (i.e. 3.5 and 7.5 hours after start of chemotherapy). All study drug doses were administered as a 15 minutes infusion.

Rescue Medications
Rescue medication could be administered to alleviate established, refractory or persistent nausea or vomiting and were permitted on an as-needed basis, not as prevention or to increase the expected antiemetic effects of the study medication. Rescue medication was defined as any drug taken for nausea or vomiting symptoms at any time during the 120-hour time interval after chemotherapy administration. The choice of rescue medication was given at the discretion of the investigator.

Antiemetics considered as rescue medication included the following:

- 5-HT_3 receptor antagonists (e.g. ondansetron);
- Benzamides (aliprazide);
- Phenothiazine antiemetics (e.g., promethazine, prochlorperazine, thiethylperazine and perphenazine);
- Dimenhydrinate;
- Corticosteroids;
- Over the counter (OTC) antiemetics;
- Non-pharmacologic methods (e.g., acupressure)

Use of metoclopramide as rescue medication was not permitted.

Compliance
Subject's compliance with the protocol was assessed on the basis of completion of the diary and subjects' attendance at each visit. Following telephone follow-up calls, subjects may also have been asked to visit the study center for assessment of any AEs by the Investigator.

Study Design and Statistical Analysis
The efficacy evaluation was based on the comparison between palonosetron and ondansetron doses according to a non-inferiority test. The efficacy sample size was estimated to be 492 evaluable subjects equally distributed to three treatment groups (164 per treatment arm). The sample size computation was based on overall type I error of 5% (2-sided), a type II error of 20% (power of 80%), an overall power of 80%, a non-inferiority threshold of -15%, and a response rate for the proportion of CR of 60%. Because the primary efficacy analysis hypothesis (null hypothesis $H_0 = \{H_{0\ 20\ mcg/kg} \cap H_{0\ 10\ mcg/kg}\}$) was composite, both type I and type II error had to be adjusted and at least one dose of palonosetron had to demonstrate non-inferiority versus the ondansetron dose in order to demonstrate efficacy of palonosetron. To keep the overall type I error at 5%, the conservative correction of Bonferroni was applied and the 2-sided significance level was set to 2.5% for each elementary test.

Sponsor's Plan for Handling of Missing Data
Conservative approaches were applied and are described below.

Emetic episodes and nausea
For the binary outcomes (presence/absence of retching/vomiting/nausea), the value defined as lack of efficacy was used to classify the missing value(s). CR was assessed after imputation of missing values.

In cycle 1, vomiting and retching were considered as missing when no information was available for the global experience of vomiting and retching, and no information was available for specific episode assessment. Because the assessment of emetic episodes was stated in the subject diary, and the diary part about the assessment of the first 24 hours could be collected separately from the part of the diary about the assessment of the delayed phase (after the first 24 hours until 120 hours after T_0), the acute and delayed assessments were handled separately. Nausea was considered as missing when no information was available for the global experience. As the assessment of nausea was stated at Visit 3 (T_0+24 hours) and Visit 6 (T_0+120 hours), acute and delayed assessments were handled separately.

For subsequent cycles, vomiting, retching, and nausea were considered as missing when no information was available for the global experience. Because the assessments were stated at Visit 3 (T_0+24 hours) and Visit 6 (T_0+120 hours), acute and delayed assessments were handled separately.

Time to event
For the time to event analysis (time to first vomiting, time to first emetic episode, time to first administration of rescue medication, time to treatment failure), the rules for binary endpoints applied. Additionally the missing time-to-event were handled as follows:

- If a time was known but the event was missing then the missing event was replaced by the value for lack of efficacy at the time known.
- If there was no evidence that no event happened (i.e., time was missing, event was missing, and the box for no event was not ticked), then the missing event was replaced by the value defined as lack of efficacy at T_0+24 hours for the acute phase and T_0+120 hours for the delayed phase.

The time to treatment failure was defined after the replacement of missing data for the time to first emetic episode and the time to first administration of rescue medication.

Efficacy Outcome Measures
Primary Efficacy Endpoint
See section 6.1.4 Analysis of Primary Endpoint(s).

Secondary Efficacy Endpoints
See section 6.1.5 Analysis of Secondary Endpoints(s).

Primary and Secondary Analyses
See section 6.1.4 Analysis of Primary Endpoint(s) and section 6.1.5 Analysis of Secondary Endpoints(s).

Protocol Amendments
The protocol version approved in most of the countries was Version 3.0 dated April 27, 2011 (this is the protocol version that is summarized in this Appendix). The following country-specific modifications to the protocol were implemented at the request of Competent Authorities and/or Ethics Committees. The final version and date of the protocol used in each country are shown below. According to the Sponsor, no other amendments were implemented.

Argentina, Version 3.1 AR dated June 20, 2011

- Inclusion criteria: Modified inclusion criterion #2 “Male or female in- or out-subjects from 2 years to <17 years at the time of randomization.”

France, Version 3.1 FR dated July 22, 2011

- Exclusion criteria: Additional exclusion criterion #14 “Subject receiving chemotherapy including any vinca alkaloids or their analogues.”
- Withdrawal criteria: Additional withdrawal criterion: “Subjects experiencing persistent constipation.”
- Other changes: Requirements for careful monitoring of subjects with constipation or abdominal distention and for attentive supervision of subjects taking any medication that can cause constipation or paralysis in the gastrointestinal tract (particularly cholinergic blockers or morphine etc.) were added.

Ukraine, Version 3.1 UA, dated July 22, 2011

- Inclusion criteria: Modified inclusion criterion #2 “Male or female in- or out-subjects from 28 days to <17 years at the time of randomization.”

Statistical Analysis Plan Amendments
The initial SAP (version 1.0) was dated November 24, 2010. The SAP was amended three times:

- Version 2.0, dated March 27, 2012: Updated SAP according to Version 3.0 of the protocol and made changes to descriptive analyses. The changes in the conduct of the planned analyses notes that “no changes from the powered statistical analyses planned in the protocol have been implemented.”
- Version 2.1, dated November 9, 2012: Added tables, figures, and listings; corrected a typo and added descriptive analyses
- Version 2.2, dated January 24, 2013: Added details on derivation rules and added exploratory analyses according to Blind Data Review Meeting Discussion (which occurred on December 18-19, 2013)

Protocol Deviations and Violations
See section 6.1.3 Subject Disposition, specifically Table 7.

Appendix 2: Discussion of Individual Trials: PALO-99-07

Title
Double-blind Pediatric Study to Assess the Safety, Pharmacokinetics and Efficacy of Single I.V. Doses of Palonosetron, 3.0 mcg/kg or 10.0 mcg/kg, in the Prevention of Chemotherapy-Induced Nausea and Vomiting

Objectives
- To evaluate the safety and tolerability of single I.V. doses of palonosetron, 3 mcg/kg and 10 mcg/kg, administered to pediatric subjects who were undergoing moderately or highly emetogenic chemotherapy
- To assess the PK of palonosetron, administered prophylactically I.V., in pediatric subjects
- To evaluate the efficacy of single I.V. doses of palonosetron, 3 mcg/kg or 10 mcg/kg, in preventing chemotherapy-induced nausea and vomiting in pediatric subjects

Trial Design
Uncontrolled, double-blind, randomized, parallel group study involving 2 study groups receiving palonosetron in two different doses

Duration
The first subject was enrolled on December 2, 2002 and the last subject's last visit was on August 1, 2005.

Study Sites
PALO-99-07 was performed at 7 investigative sites in the U.S. and at 1 site in Mexico.

Key Inclusion Criteria
1. Male or female in- or out-patients aged >28 days if full term (or >128 days if premature) to 17 years.
2. Histologically, and/or cytologically (or imaging in the case of brain tumors) confirmed malignant disease.
3. Naïve or non-naïve to chemotherapy.
4. Scheduled to receive a single dose of moderately or highly emetogenic chemotherapeutic agents (the most emetogenic agent) on Study Day 1. See Table 58 for emetogenic risk classification.
5. Written informed consent (permission) provided by parent or legal guardian of the pediatric subject.
6. If female of childbearing potential, the subject and her parent/legal guardian had to be counseled on the importance of not becoming pregnant before or during the

study and the subject had to have a negative pregnancy test at the screening visit.
7. Subjects with hepatic abnormalities, scheduled to receive the above mentioned chemotherapeutic agents, could be enrolled in this study at the discretion of the investigator.

Key Exclusion Criteria

1. Subject and/or families who were expected to be noncompliant with the study procedures.
2. Subjects who received any investigational drug 30 days before study entry or were expected to receive investigational drugs prior to study completion.
3. Have received any drug with potential antiemetic efficacy within 24 hours prior to study drug administration, including but not limited to 5-HT_3 antagonists, phenothiazines, scopolamine, diphenhydramine, chlorpheniramine maleate, trimethobenzamide, propofol, all benzodiazepines except temazepam or triazolam used once nightly for sleep, haloperidol, droperidol, tetrahdrycannabinol, or nabilone, any corticosteroid including dexamethasone, hydrocortisone, methylprednisolone, prednisone (excluding topical or inhaled preparations).
4. Clinically unstable seizure disorder with seizure activity requiring anticonvulsant medication; (prophylactic anticonvulsant medication for subjects free of seizure activity was allowed).
5. Any vomiting, retching, or NCI Common Toxicity Criteria grade 2 or 3 nausea in the 24 hours prior to the administration of the study drug.
6. Ongoing vomiting from any organic etiology.
7. Serum transaminase values ≥3 times upper limit of normal for the subject's age, bilirubin values ≥1.5 mg/dL (25.65 µmol/L), serum creatinine values above normal limits for the subject's age.
8. Known contraindication to 5-HT_3 receptor antagonists.
9. Treated with chemotherapy that required corticosteroids on Study Day 1.

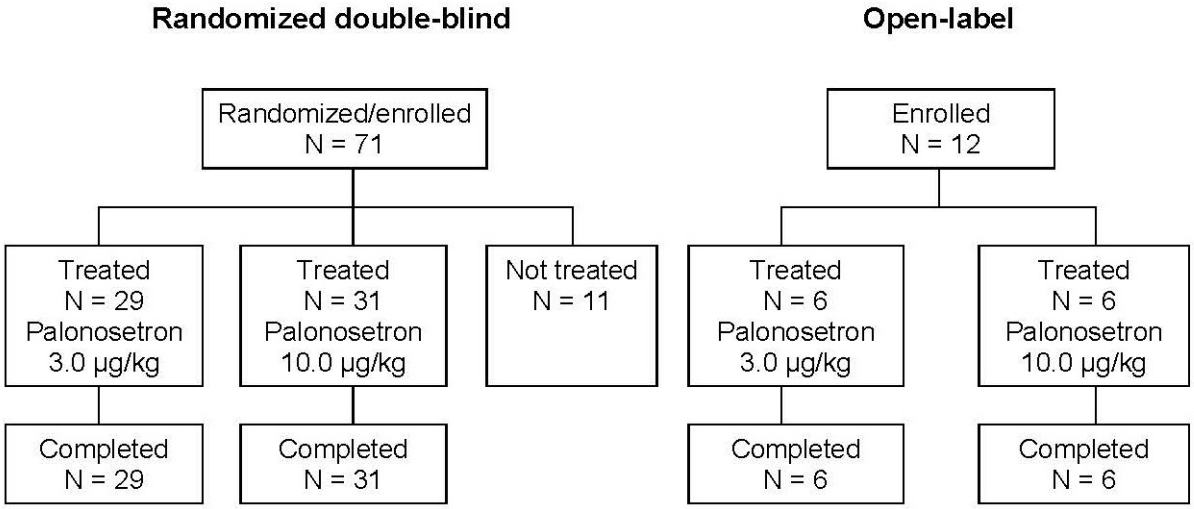
Study Design and Statistical Analysis

The number of subjects to include and randomize in the study was estimated to be 60, distributed in 2 dose groups (i.e., 30 subjects per group). In addition, 12 subjects (aged >28 days to 23 months) were planned to be included into an open-label treatment segment. Considering a sample size of 72 subjects (including the open-label treatment) the probability (power) to observe at least one adverse event was 77% given an incidence of 2%. Analyses of efficacy endpoints were based on the intent-to-treat (ITT) population, which included all subjects who received study drug and at least MEC. For the ITT analysis, subjects who received study drug different from that to which they were randomly assigned were evaluated according to the planned treatment. All the statistical analyses were descriptive, and hypothesis testing to detect differences between the 2 treatment groups was not conducted.

Demographics and Subject Disposition

Figure 4 summarizes the flow of subjects in study PALO-99-07.

Figure 4. Subject Disposition in Study PALO-99-07



Note: Of the 11 subjects that were not treated (i.e., screen failures), 1 (9%) was not treated due to a non-serious AE (subject 750-7702 with AE of febrile neutropenia); 6 (55%) were not treated due to violation of inclusion/exclusion criteria (violations included not being scheduled to receive MEC/HEC, abnormal baseline transaminase levels and/or creatinine, and vomiting/retching in the 24 hours prior to scheduled administration of study drug); 1 (9%) was not treated due to withdrawal of consent; and 3 (27%) were not treated due to other reason (1 subject was scheduled for sedation with propofol after having been consented; 1 subject was a screen failure due to liver function test results; 1 subject did not receive study drug due to study coordinator family emergency).
Source: Figure 6.1-a, page 85, CSR of study PALO-99-07.

For randomized subjects, the cancers treated most often were acute lymphocytic leukemia in the palonosetron 3 mcg/kg group [5 (17%) subjects] and rhabdomyosarcoma NOS in the palonosetron 10 mcg/kg group [7 (23%) subjects]. For open-label subjects the cancers most frequently treated (in more than 1 subject) was acute myeloid leukemia NOS in the palonosetron 3 mcg/kg group [2 (33%) subjects] and nephroblastoma in the palonosetron 10 mcg/kg group [2 (33%) subjects].

Cyclophosphamide was the most frequent chemotherapeutic treatment given on day 1 for the total population, followed by methotrexate, ifosfamide, cisplatin, cytarabine, carboplatin and doxorubicin. For randomized subjects, cyclophosphamide was the most emetogenic agent usually given in both treatment groups. For open-label subjects, the most emetogenic treatments given included cytarabine in the palonosetron 3 mcg/kg group (4 subjects) and cisplatin and dactinomycin in the palonosetron 10 mcg/kg group (2 subjects each).

Efficacy Outcome Measures

Primary Efficacy Endpoint

A primary efficacy endpoint was not defined. The efficacy endpoint of major interest was the proportion of subjects with CR (defined as no emetic episode and no rescue

medication) during the first 24 hours after the start of chemotherapy. Table 55 summarizes the results.

Table 55. Proportion of Subjects with Complete Response During the First 24 Hours After Chemotherapy in Study PALO-99-07 (ITT Population)

Variable	Open-Label		Randomized		Total	
	3 mcg/kg (N=6)	10 mcg/kg (N=6)	3 mcg/kg (N=29)	10 mcg/kg (N=31)	3 mcg/kg (N=35)	10 mcg/kg (N=37)
Subjects with CR, n (%)	3 (50.0)	6 (100.0)	10 (34.5)	14 (45.2)	13 (37.1)	20 (54.1)
95% CI of CR Rate	[13.9, 86.1]	[51.7, 100]	[18.6, 54.3]	[27.8, 63.7]	[22.0, 55.1]	[37.1, 70.2]

Abbreviations: CI, confidence interval; CR, complete response. **CIs are presented for an information comparison only.**
Note: CR was defined as no emetic episode and no rescue medication.
Source: Reviewer's table, adapted from Sponsor's Table 2-2, page 28, Summary of Clinical Efficacy.

Additional Efficacy Endpoints

The following additional efficacy parameters were evaluated during the first 24 hours after the start of chemotherapy administration:

- Complete Control 0-24h (subjects aged ≥ 6 y); Complete control was defined as Complete Response and no more than mild nausea
- Number of emetic episodes 0-24h
- Need for rescue therapy 0-24h
- Time to the first emetic episode
- Time to administration of rescue therapy
- Time to treatment failure
- Severity of nausea 0-24h (subjects aged ≥ 6 years)

Changes to the planned analysis

The PALO-99-07 study completed enrollment in August 2005, and the PALO-99-07 CSR was submitted to IND 39,797 in February 2007. Subsequent to the IND submission of the original CSR data, the FDA issued a WR to the Sponsor to perform limited re-analysis of PALO-99-07 study data using the following age groups: (a) <2 years; (b) 2 to <6 years; (c) 6 to <12 years; and (d) 12 to <18 years. Because the WR age groups differed from those evaluated in the original PALO-99-07 CSR (>28 days to 23 months, 2 to 11 years and 12 to 17 years), the PALO-99-07 study data were re-analyzed according to the WR age groups described above. The re-analysis by age group also included new analyses by gender and race/ethnicity and analyses of emetogenicity for all subjects who received chemotherapy. The WR also required the analysis of the PALO-99-07 study data to include the endpoint of CR (defined as no vomiting, no retching, and no use of rescue medication) from 0 to 24 hours after the first chemotherapy dose was administered. The results of these analyses are summarized below. None of the statistics included in the re-analyses are powered. In compliance with the WR for PALO-99-07, statistical methods are descriptive in nature only.

Proportion of subjects with complete response 0-24 Hours by WR subpopulations

Table 56 summarizes the results of the post hoc analysis (as required by the WR) of CR in the first 24 hours by age group, gender, race/ethnicity, and emetogenicity.

Table 56. Proportion of Subjects with CR (0-24 Hours) by Subgroup in PALO-99-07 (ITT)

Subpopulation	Palonosetron 3 mcg/kg (Total N=35)	Palonosetron 10 mcg/kg (Total N=37)
AGE GROUP		
Age <2 years	N=6	N=6
Subjects with CR, n (%)	3 (50.0)	6 (100.0)
95% CI of CR Rate	[13.9, 86.1]	[51.7, 100.0]
Age 2 up to <6 years	N=4	N=5
Subjects with CR, n (%)	3 (75.0)	3 (60.0)
95% CI of CR Rate	[21.9, 98.7]	[17.0, 92.7]
Age 6 up to <12 years	N=10	N=12
Subjects with CR, n (%)	3 (30.0)	4 (33.3)
95% CI of CR Rate	[8.1, 64.6]	[11.3, 64.6]
Age 12 up to <18 years	N=15	N=14
Subjects with CR, n (%)	4 (26.7)	7 (50.0)
95% CI of CR Rate	[8.9, 55.2]	[24.0, 76.0]
GENDER		
Female	N=13	N=15
Subjects with CR, n (%)	5 (38.5)	6 (40.0)
95% CI of CR Rate	[15.1, 67.7]	[17.5, 67.1]
Male	N=22	N=22
Subjects with CR, n (%)	8 (36.4)	14 (63.6)
95% CI of CR Rate	[18.0, 59.2]	[40.8, 82.0]
RACE/ETHNICITY		
White	N=15	N=20
Subjects with CR, n (%)	6 (40.0)	9 (45.0)
95% CI of CR Rate	[17.5, 67.1]	[23.8, 68.0]
Hispanic	N=15	N=18
Subjects with CR, n (%)	6 (40.0)	11 (61.1)
95% CI of CR Rate	[17.5, 67.1]	[36.1, 81.7]
EMETOGENECITY		
HEC	N=25	N=24
Subjects with CR, n (%)	9 (36.0)	12 (50.0)
95% CI of CR Rate	[18.7, 57.4]	[29.6, 70.4]
MEC	N=10	N=13
Subjects with CR, n (%)	4 (40.0)	8 (61.5)
95% CI of CR Rate	[13.7, 72.6]	[32.3, 84.9]

Abbreviations: CI, confidence interval; CR, complete response; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy. **CIs are presented for an information comparison only.**
Source: Reviewer's table, adapted from Table 3-10, pages 16-23, Addendum to CSR of PALO-99-07.

Reviewer comments: *Subjects in the 10 mcg/kg arm showed greater response rates than the 3 mcg/kg arm in all age groups except for the 2 to <6 years group. Although the*

younger age groups had numerically greater CR rates than subjects ≥6 years old, the number of subjects in each of the age groups was probably too small to draw any meaningful conclusions. Moreover, with respect to gender, race/ethnicity, and emetogenicity, subjects in the 10 mcg/kg arm showed numerically greater response rates than the 3 mcg/kg arm. The small sample size, however, precludes meaningful assessment of any trends or patterns in various subpopulations.

Appendix 3: Emetogenic Classification of Chemotherapy Agents

Table 57. Emetic Risk Group Classification for Single Antineoplastic Agents in Study PALO-10-20

EMETIC RISK GROUPS – SINGLE ANTINEOPLASTIC AGENTS		
HIGH (> 90%)	Cisplatin Carmustine Cyclophosphamide ≥ 1500 mg/m^2 Dacarbazine Dactinomycin	Mechlorethamine Lomustine Pentostatin Streptozocin
MODERATE (30% to 90%)	Alemtuzumab Altretamine Azacitidine Bendamustine Carboplatin Cytarabine > 1gm/m^2 Cyclophosphamide <1500 mg/m^2 Clofarabine Daunorubicin Doxorubicin $^{\Delta}$	Epirubicin Idarubicin Ifosfamide Melphalan Mitoxantrone >12 mg/m^2 Oxaliplatin Irinotecan Temozolomide Trabectedin Treosulfan
LOW (10% to 30%)	Paclitaxel Docetaxel Mitoxantrone Topotecan Etoposide Pemetrexed Methotrexate	Mitomycin Gemcitabine Cytarabine ≤1 gm/ m2 Fluorouracil Bortezomib Cetuximab Trastuzumab
MINIMAL **(<10%)**	Bevacizumab Bleomycin Busulfan 2-Chlorodeoxyadenosine Fludarabine	Rituximab Vinblastine Vincristine Vinorelbine

For combination chemotherapy, the emetogenicity is determined by the most emetogenic agent as described in the table above.

$^{\Delta}$ Doxorubicin is sometimes used in extremely low doses not requiring any antiemetic treatment in clinical practice. Patients undergoing such therapy shall not be included in the study.
Source: Appendix E of PALO-10-20 Protocol, page 97.

Table 58. Emetic Risk Group Classification for Single Antineoplastic Agents in Study PALO-99-07

Moderately emetogenic	Highly emetogenic
Actinomycin-D	Carboplatin
Cyclophosphamide $\leq$ 750 mg/m^2	Cyclophosphamide > 750 mg/m^2
Cytarabine 250-1000 mg/m^2	Cytarabine > 1000 mg/m^2
Doxorubicin $\leq$ 60 mg/m^2	Doxorubicin > 60 mg/m^2
Epirubicin	Carmustine
Hexamethylmelamine	Cisplatin
Idarubicin	Dacarbazine
Ifosfamide	Mechlorethamine
Methotrexate 250-1000 mg/m^2	Methotrexate > 1000 mg/m^2
Irinotecan	Procarbazine
Mitoxantrone	Streptozocin

Source: Section 5.3.1 of PALO-99-07 CSR, page 39.

Appendix 4: Eastern Cooperative Oncology Group (ECOG) Performance Status

Table 59. ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Reviewer's table, adapted from Appendix D of PALO-10-20 protocol, page 96.

Appendix 5: Definition of Efficacy Parameters Analyzed in PALO-99-07 and PALO-10-20

Study	DEFINITION OF PARAMETERS ANALYZED
Complete Response (CR)	
PALO-99-07	Nno emetic episode and no rescue medication.
PALO-10-20	No emetic episode (no retching, no vomiting) and no use of antiemetic rescue medication.
Time to treatment failure	
PALO-99-07	Time to the first emetic episode or to first administration of rescue therapy (whichever occurs first).
PALO-10-20	Time to first emetic episode or administration of rescue medication, whichever occurred first.
Complete Control (CC)	
PALO-99-07	Complete response and no more than mild nausea (patients aged 6-17 years)
PALO-10-20	Not analyzed
Emetic episode	
PALO-99-07	One occurrence of vomiting or a sequence of occurrences in very close succession not relieved by a period of relaxation of at least 1 minute, any number of occurrences of unproductive emesis (retches) in a unique 5-minute period, or an episode of retching of less than 5 minutes duration combined with vomiting not relieved by a period of relaxation of at least 1 minute.
PALO-10-20	One or more continuous vomits (expulsion of stomach contents through the mouth) or retches (an attempt to vomit that is not productive of stomach contents). Regurgitation (defined as the sudden effortless return of small volumes of gastric contents into the pharynx and mouth, typically after breastfeeding or bottle feeding) was regarded as a physiological event and was not considered as an emetic episode for patients up to 12 months of age.
Time to the first emetic episode	
PALO-99-07	The difference between the start time of the first emetic episode and the start time of the chemotherapy.
PALO-10-20	The difference between the start time of the first emetic episode and the start time of the chemotherapy (T_0).
Intake of rescue	
PALO-99-07	All anti-emetic medications taken/administered within 24 hours after chemotherapy.
PALO-10-20	Any medication with potential antiemetic properties taken within 120 hours after T_0. In line with the protocol, the only exception consisted of corticosteroids administered as part of the chemotherapy regimen or as a mean to reduce intracranial pressure, which were not accounted as rescue medications.
Time to the first intake of rescue medication	
PALO-99-07	The difference between the start time of the first rescue medication and the start of chemotherapy.
PALO-10-20	The difference between the start time of the first rescue medication and the start of chemotherapy (T_0).
Nausea	
PALO-99-07	The severity of nausea measured by the Likert scale was collected for the patients aged 6-17 years.
PALO-10-20	The nausea was assessed in the eCRF as a yes/no question (in patients aged ≥6 years).
Vomiting	
PALO-99-07	Not analyzed.
PALO-10-20	Each single episode of vomiting was to be collected in the patient's diary during Cycle1. During Cycles 2 to 4. Vomiting was assessed in the eCRF as a yes/no question
Time to first vomiting	
PALO-99-07	Not analyzed
PALO-10-20	The difference between the start of the first vomiting and the start of chemotherapy (T_0).

Source: Sponsor's Table 1-3, page 16, Summary of Clinical Efficacy.

Appendix 6: Clinical Investigator Financial Disclosure

Covered Clinical Study (Name and/or Number): PALO-99-07

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 85 (includes investigators and subinvestigators)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Sponsor provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangements with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). The Sponsor also certified that each clinical investigator had no proprietary interest in this product or significant equity in the Sponsor as defined by 21 CFR 54.2(b). As defined by 21 CFR 54.2(f), the Sponsor certified that no clinical investigator received any significant payments of any sorts.

Covered Clinical Study (Name and/or Number): PALO-10-20

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 310 (includes investigators and subinvestigators)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Sponsor provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangements with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). The Sponsor also certified that each clinical investigator had no proprietary interest in this product or significant equity in the Sponsor as defined by 21 CFR 54.2(b). As defined by 21 CFR 54.2(f), the Sponsor certified that no clinical investigator received any significant payments of any sorts.

9.1 Literature Review/References

Kris MG, Hesketh PJ, Somerfield MR, et al. American Society of Clinical Oncology guideline for antiemetics in oncology. *J Clin Oncol*. 2006;24(18):1-16.

Multinational Association of Supportive Care in Cancer (MASCC) antiemetic guidelines – update 2010. www.mascc.org/mc/page.do?sitePageId=88041.

9.2 Labeling Recommendations

Labeling discussions are ongoing at the time of this review. See final label.

1 INDICATIONS AND USAGE
The principal study used to support approval of palonosetron I.V. for the prevention of CINV in pediatric cancer patients (i.e., PALO-10-20) used ondansetron I.V. as the active comparator. Ondansetron I.V. is currently labeled for prevention of CINV as follows:

> **1.1 Prevention of Nausea and Vomiting Associated with Initial and Repeat Courses of Emetogenic Cancer**
> ZOFRAN Injection is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin [*see Clinical Studies (14.1)*].
> ZOFRAN is approved for patients aged 6 months and older.

The Sponsor's proposed indication statement for palonosetron I.V. for the prevention of CINV in pediatric cancer patients mirrors the labeled indication for palonosetron I.V. for the prevention of CINV in adult cancer patients. Specifically, the Sponsor proposes the following (for pediatric patients aged >1 month):

For a discussion of the basis for the above indication statement for palonosetron I.V. for the prevention of CINV in adult cancer patients, the reader is referred to section 6.1 Indication.

Unlike, the adult CINV program, in which subjects receiving HEC and subjects receiving MEC were studied in separate adequate and well-controlled studies, the principal pediatric CINV study (i.e., PALO-10-20) included HEC and MEC within the same study.

Moreover, the adult CINV program demonstrated superiority of palonosetron 0.25 mg I.V. to Zofran 32 mg I.V. in both the acute and delayed phases in the MEC study and demonstrated noninferiority of palonosetron 0.25 mg I.V. to Zofran 32 mg I.V. in both the acute and delayed phases in the HEC study. Importantly, Zofran I.V. is not labeled for the delayed phase indication. As noted by the medical officer (Dr. Narayan Nair) in his clinical review for the adult palonosetron studies (see clinical review of NDA 21372 in DARRTS, dated July 8, 2003):

> "The results demonstrated the non-inferiority of ... palonosetron 0.25 mg ... when compared to ondansetron. Again, the lower limit of the 97.5% confidence interval for the difference in complete response rates between the ondansetron and the palonosetron groups during the first 24 hours after chemotherapy was above the preset 15% delta. However, these trials did not establish that palonosetron 0.25 mg was efficacious for delayed prevention (24-120 hours) of highly emetogenic CINV. While the results did show non-inferiority to the comparator arms, the comparator drug is not indicated for delayed prevention of CINV. Thus, in order to show efficacy the study drug should demonstrate superiority to the comparator drug. It did not do so. There was no statistically significant difference between palonosetron and ondansetron for delayed prevention of highly emetogenic CINV. The evidence the applicant has presented does not substantiate an efficacy claim for this indication."

Accordingly, for the adult program, the indication statement included the acute and delayed phases for MEC, but only the acute phase for HEC. In PALO-10-20, however, the Sponsor demonstrated noninferiority of palonosetron 20 mcg/kg I.V. to Zofran 3 x 0.15 mg I.V. in both the acute and delayed phases. As noted previously, Zofran I.V. is not labeled for the delayed phase indication. Therefore, in order to demonstrate efficacy in the delayed phase, palonosetron 20 mcg/kg I.V. would need to demonstrate superiority to Zofran 3 x 0.15 mg I.V. Because it did not do so, this medical officer recommends the following indication statement for prevention of CINV in pediatric patients aged 1 month and older:

> ALOXI is indicated for the prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy.

Instead of distinguishing between MEC and HEC in the indication statement, this medical officer recommends describing the most frequently administered chemotherapy agents in the CLINICAL STUDIES section of labeling.

2 DOSAGE AND ADMINISTRATION

This medical officer recommends displaying the dosage information in a table for clarity and to highlight the differences in dosing between pediatric patients (i.e., 20 mcg/kg to a maximum of 1.5 mg) and adults (0.25 mg) for the prevention of CINV. Moreover, this

medical officer recommends that units for dosing be presented in mcg/kg (i.e., 20 mcg/kg) for pediatric CINV instead of in mg/kg (i.e., 0.02 mg/kg). To illustrate the rationale for this recommendation, this reviewer presents two hypothetical "worst case" scenarios of how each of these dosing units might be misread by a prescriber and their potential outcomes in a pediatric patient weighing 5 kg:

- Scenario 1: Dose is written in label as 0.02 mg/kg and is misread by the prescriber as 0.2 mg/kg. Given patient's weight of 5 kg, the prescriber orders 1 mg of palonosetron. Each 5 mL vial of palonosetron contains 0.25 mg, so 4 vials (i.e., 20 mL) would contain 1 mg of palonosetron. Given that the 1 mg dose is less than the maximum of 1.5 mg, the prescriber error may not be detected by the pharmacist and the patient could receive 10 times the dose he/she should receive based on weight.
- Scenario 2: Dose is written in the label as 20 mcg/kg dose and is misread by the prescriber as 20 mg/kg. Given patient's weight of 5 kg, the prescriber orders 100 mg of palonosetron. Each 5 mL vial of palonosetron contains 0.25 mg, so 400 vials (i.e., 2000 mL) would contain 100 mg of palonosetron. Given that the 100 mg dose is much greater than the maximum of 1.5 mg and that 400 vials would be needed to fulfill the order, the pharmacist would readily detect the error and the prescriber error would be intercepted.

6 ADVERSE REACTIONS

According to 21 CFR 201.57(c)(3)(ii) DOSAGE AND ADMINISTRATION, dosing regimens must not be implied or suggested in other sections of labeling if not included in the DOSAGE AND ADMINISTRATION section. Therefore, this medical officer's proposed language for the ADVERSE REACTIONS section focuses on the subjects in the 20 mcg/kg palonosetron dose arm.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

This medical officer's proposed language for the Pediatric Use subsection is based on *FDA Guidance for Industry: Pediatric Information Incorporated into Human Prescription Drug and Biological Products*.

14 CLINICAL STUDIES

According to 21 CFR 201.57(c)(15)(i) CLINICAL STUDIES, for drug products other than biological products, any clinical study that is discussed in prescription drug labeling that relates to an indication or use of the drug must be adequate and well-controlled as described in 21 CFR 314.126(b) of the chapter and must not imply or suggest indications or uses or dosing regimens not stated in the INIDCATIONS AND USAGE or DOSAGE AND ADMINISTRATION section. Therefore, this medical officer's proposed language for the CLINICAL STUDIES section focuses on the subjects in the 20 mcg/kg palonosetron dose arm. This medical officer's proposed language for the CLINICAL STUDIES section is also based on *FDA Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products*.

9.3 Advisory Committee Meeting

No advisory committee (AC) meeting was held.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FARROKH SOHRABI
05/05/2014

RUYI HE
05/05/2014