CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	sNDA 21-372/S-018
Priority or Standard	Priority
Submit Date(s)	November 27, 2013
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Division / Office	CDER/ODE III/DGIEP
Reviewer Name(s)	Teresa Buracchio, MD
Review Completion Date	May 5, 2014
Established Name	Palonosetron
(Proposed) Trade Name	Aloxi
Therapeutic Class	5-HT receptor antagonist
Applicant	Helsinn Healthcare SA
Formulation(s)	Aqueous solution
Dosing Regimen	1mcg/kg IV single dose
Indication(s)	Prevention of post-operative nausea and vomiting
Intended Population(s)	Pediatric patients ages >28 days-17 years old

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

1.2 Risk Benefit Assessment

Efficacy for PONV in the pediatric population was not proven based on study PALO-10-14. The proportion of treated patients with Complete Response (CR) at 24 hours was 78.2% in the palonosetron 1mcg/kg group and 82.7% in the ondansetron 0.1 mg/kg group. The primary efficacy analysis assessed the non-inferiority of palonosetron to ondansetron based on the stratum adjusted Mantel-Haenszel method for the Full Analysis Set comparing proportions of patients with CR at 0-24 hours. The difference between treatments was -4.4% (-10.5%, 1.7%). The lower bound of the confidence interval did not meet the pre-specified non-inferiority margin of 10%; therefore, non-inferiority of palonosetron to ondansetron was not proven. Three pre-specified co-primary efficacy analyses and six sensitivity analyses supported the primary efficacy analysis conclusions.

Review of the safety database from the pediatric PONV studies demonstrated no clear safety signals. With respect to adverse events (AEs), there was no clear or consistent dose-response trend or trend in specific subgroups such as age, gender, or race/ethnicity. Additionally, the safety database did not demonstrate an increased risk of AEs identified as AEs of interest (e.g., infusion site reactions including thrombophlebitis). The overall safety profile was generally consistent with that of the adult PONV safety profile in the current Aloxi label.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended for this sNDA. Continuation of routine surveillance for adverse events would be adequate.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for additional postmarket requirements and commitments.

2 Introduction and Regulatory Background

Post-operative nausea and vomiting (PONV) is a common morbidity in children undergoing surgical procedures. It causes discomfort for the patient and is a source of distress for both patients and their families. Potential complications related to PONV may include dehydration, pulmonary aspiration, electrolyte disturbance, and wound dehiscence. These complications increase the risk for prolonged hospitalization and hospital readmission.[1]

PONV occurs twice as frequently in children than in adults. The incidence of PONV increases with age until puberty at which point it begins to decline to adult rates.[2] Vomiting is more frequently reported in children than nausea, since the subjective nature of nausea may be difficult to capture in young patients. Risk factors for PONV include the type of surgery, increasing age, history of post-operative vomiting, history of motion sickness, use of post-operative opioid medications, duration of general anesthesia >30 minutes, and use of inhalation anesthetics.[2] Higher rates of PONV are seen with tonsillectomy and strabismus surgeries.[3]

PONV is triggered by the release of 5-HT into the CNS and gastrointestinal tract. The $5HT_3$ receptor selectively participates in the emetic response.[1]

Multiple medications may be used to treat PONV but there are currently only three drugs approved for the prevention of PONV in the pediatric population, the $5HT_3$ receptor antagonists Zofran and Anzemet and the antihistamine Phenergan.

2.1 Product Information

Aloxi (palonosetron) injection is a selective serotonin receptor antagonist that has a strong binding affinity for the subtype 3 ($5HT_3$) receptor. Aloxi injection is currently indicated for the prevention of chemotherapy-induced nausea and vomiting (CINV) and PONV for up to 24 hours following surgery in the adult population. The dosage for CINV in adults is a single 0.25 mg intravenous dose administered over 30 seconds, occurring approximately 30 minutes before the start of chemotherapy. The dosage for PONV in adults is a single 0.075 mg I.V. dose administered over 10 seconds immediately before induction of anesthesia.

2.2 Tables of Currently Available Treatments for Proposed Indications

Zofran (ondansetron) and Anzemet (dolasetron) are currently approved in the US for the prevention of post-operative nausea and vomiting in pediatric patients.[4] Both drugs are 5HT3 receptor antagonists. Zofran is approved for use in patients >1 month of age and Anzemet is approved for children aged 2 years and older. Other unapproved therapies may be used for pediatric patients and these agents are listed in Table 1.[2,3]

Table 1. Therapies used in the prevention and treatment of pediatric PONV

Therapeutic Agent	Class/Mechanism	Approved for adult PONV	Approved for pediatric PONV
Zofran (ondansetron)	5HT3 receptor antagonist	X	X
Anzemet (dolasetron)	5HT3 receptor antagonist	X	X
Kytril (granisetron)	5HT3 receptor antagonist	X	
Phenergan (promethazine)	Phenothiazine/antihistamine/ dopamine antagonist	X	X
Perphenazine	Phenothiazine/antihistamine/ dopamine antagonist		
Dexamethasone	Corticosteroid		
Metoclopromide	Prokinetic/dopamine antagonist		
Droperidol	Butyrophenone/dopamine antagonist		
Dimenhydrinate	Antihistamine		

2.3 Availability of Proposed Active Ingredient in the United States

The IV formulation of Aloxi is available and marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Hypersensitivity reactions may be seen in patients who have shown hypersensitivity reactions to other 5HT3 antagonists. QTc prolongation is reported in the label of other 5HT3 antagonists including ondansetron, dolasetron and granisetron; however, a thorough QT study was performed with Aloxi and there was no evidence of QT prolongation and this warning is no longer in the label for Aloxi. Masking of ileus/distention is in the label for Aloxi and other 5THs antagonists.[5]

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On July 25, 2003, FDA first granted U.S. marketing approval to Aloxi (palonosetron HCl) injection for the indications of prevention of acute nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC) and highly emetogenic cancer chemotherapy (CINV-HEC). On February 29, 2008, marketing approval was also granted for Aloxi injection for the indication of PONV for up to 24 hours following surgery. However, extensive discussions with the FDA for development and planning of the pediatric studies with Aloxi preceded those approvals and began over 13 years ago in April 2000. The major regulatory interactions regarding the pediatric development plan, with specific focus on the pediatric PONV program, are summarized below.

Apr 24, 2000	Proposal for Pediatric Studies Request (PPSR) submitted to IND 39,797 requesting a Written Request (WR) based on performing pediatric study PALO-99-07 in CINV. The pediatric protocol for CINV (PALO-99-07) was submitted with draft study reports for juvenile toxicology studies in rats and dogs on August 14, 2000.
2000-2003	FDA had concerns about an ophthalmologic finding on a 28-day juvenile rat toxicology and requested a repeat of the study and the inclusion of ocular function testing in the pediatric study. On January 20, 2003, Sponsor submitted a repeat rat toxicology study without ocular toxicity findings and requested removal of the ocular testing requirement for pediatric studies. Sponsor submitted PALO-99-07 Amendment #2 to implement omission of eye testing on June 4, 2003
Jun 26, 2003	2nd PPSR submitted based on the revised PALO-99-07 protocol.
2003-2006	FDA had concerns about a potential safety signal of QTc prolongation in some of the first six patients in PALO-99-07, resulting in a partial clinical hold on PALO-99-07 on November 6, 2003. The clinical hold was removed on January 11, 2004 after agreement for additional cardiac monitoring and plans for an adult thorough QT study. The thorough QT study (PALO-03-11) showed no effect of palonosetron on the QT interval. (b) (4)
Nov 9, 2006	A teleconference was held to discuss the results of pediatric study PALO-99-07, adult thorough QT study PALO-03-11, and planned PONV pediatric study PALO-07-29. Key discussion points included: • The pediatric CINV study PALO-99-07 and an FDA-requested population pharmacokinetic (PK) analysis on this dataset (PALO-07-06) would be included in the WR, as that was the only approved indication at the time. • FDA indicated that no further CINV studies would be included in the WR.

- The pediatric PONV studies may possibly be handled as a post-marketing commitment because the PONV studies could not be completed before the sunset date of the BPCA on October 1, 2007.

Feb 14, 2007 3rd PPSR submitted as agreed at the November 9, 2006 meeting.

Feb 29, 2008 FDA approves Aloxi injection for PONV (NDA 21-372/S008).

Jul 10, 2008 The protocol for the pediatric PONV study (PALO-07-29) was submitted to the IND. The study was completed and the clinical study report submitted on July 22, 2009.

Nov 16, 2009 A teleconference was held to discuss the WR outline. The Sponsor and FDA agreed that PALO-99-07 (CINV) and PALO-07-29 (PONV) would serve as pilot studies for larger trials to be requested in the WR.

Jul 23, 2010 WR issued by the FDA: The WR included the two previously conducted pediatric studies PALO-07-29 (WR study 1) and PALO-99-07 (WR study 2) and included the requirement for a larger trials in each indication PONV (WR study 3) and CINV (WR study 4) against a standard of care active comparator. The WR initially included the requirement for the development of a pharmacy compounded palonosetron liquid preparation for oral administration in CINV-MEC. There were three subsequent amendments to the WR.

Sept 30, 2010 Written Request, Amendment #1: The requirements for studies 1 and 2 were revised to be consistent with the conduct of the already completed studies, PALO-07-29 and PALO-99-07.

Nov 11, 2010 The protocol for pediatric PONV study, PALO-10-14 (WR study3) was submitted, including submission of the statistical analysis plan. Communications regarding the protocol included:

- Dec 23, 2010: FDA sent a response letter requesting revisions to the protocol including monitoring for infusion reactions, justification for excluding some surgeries, recommending a revised primary efficacy endpoint statistical analysis, and recommending methods for handling missing data.
- Apr 26, 2011: FDA sent a letter accepting the final protocol.
- Jun 2, 2011: Final protocol submitted to initiate study.
- Additional changes to the statistical analysis plan requested by the FDA on July 28, 2011 and agreed to by Sponsor on November 23, 2011.

2011-2012 Sponsor provided 3 enrollment status updates detailing the difficulty of enrolling patients in the youngest age groups and across races/ethnicities in the PALO-10-14 (PONV) study. Sponsor informed the FDA of their continued efforts in this regard and sought guidance from the FDA on improving enrollment across age groups and races/ethnicities.

Oct 22, 2012 Written Request, Amendment #2: Revisions included changes to wording for safety monitoring, clarified monitoring for infusion reactions,

and eliminated the requirement for the development of a compounded palonosetron liquid preparation for use in pediatric CINV patients.

Dec 4, 2012 Pre-sNDA meeting:

- FDA agreed that Sponsor would reanalyze the age groups in Studies 1 and 2 to be consistent with the WR and include the reanalysis in an addendum to each study report.
- FDA and Sponsor agreed on format and content of the Summary of Clinical Efficacy (SCE), Summary of Clinical Safety, and safety database.
- FDA requested that PONV and CINV indications be submitted as separate sNDAs.

Jan 16, 2013 Type C meeting Written Response:

- Sponsor proposed (b) (4) FDA response: "Separate pediatric PONV and pediatric CINV adverse event tables should be submitted, even if the pediatric adverse event profiles are similar to adults and for the two different indications. We note that the final text for labeling will be a review issue. Your proposed ≥2% cutoff is acceptable."
- FDA indicated that the sNDAs would be granted a Priority Review.

Feb 15, 2013 Written Request, Amendment #3: This amendment clarified wording regarding the development of liquid oral palonosetron, product packaging, and the reporting of PK values.

Nov 27, 2013 Sponsor submitted sNDA for pediatric PONV and CINV indications.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This was an electronic submission. The overall quality of the data submitted by the applicant was adequate for comprehensive review of the data.

3.2 Compliance with Good Clinical Practices

The sponsor stated that the studies were conducted according to study protocols and in compliance with the current International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for GCP.

No site inspections were performed for this study.

3.3 Financial Disclosures

The sponsor and investigators who participated in studies PALO-07-29 and PALO-10-14 stated that they did not enter into any financial agreement. FDA form 3454 was signed and submitted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Since palonosetron is already approved, no new CMC information is included in this sNDA.

4.2 Clinical Microbiology

No new microbiology information is included in this sNDA.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical Pharmacology/Toxicology information is included.

4.4 Clinical Pharmacology

No clinical pharmacology data were submitted for this application.

4.4.1 Mechanism of Action

Palonosetron is a selective serotonin receptor antagonist that has a strong binding affinity for the subtype 3 ($5HT_3$) receptor. PONV is triggered by the release of 5-HT in the CNS and gastrointestinal tract and the $5HT_3$ receptor plays a role in the emetic response.

4.4.2 Pharmacodynamics

There were no clinically significant effects of palonosetron on vital signs or ECG findings in the studies submitted in this application.

4.4.3 Pharmacokinetics

Pharmacokinetic testing was planned for neonates, if they could be enrolled, in PALO-10-14. Since no neonates were enrolled in PALO-10-14, there was no pharmacokinetic data submitted for this application.

5 Sources of Clinical Data

The primary sources of clinical data for this application were two pediatric clinical trials for PONV, PALO-07-29 and PALO-10-14. These studies are summarized in the table below.

5.1 Tables of Studies/Clinical Trials

Table 2. Clinical trials of palonosetron for PONV in pediatric patients

Study	Design	Population	Dose and Duration	Number of Centers and locations
PALO-07-29	Randomized, double-blind, parallel group	N=150 Ages: >28 days to 16 years Pediatric patients undergoing elective surgical procedures requiring general endotracheal inhalation anesthesia and receiving nitrous oxide during the maintenance phase of anesthesia	Single IV palonosetron 1 mcg/kg, max 0.075mg Single IV palonosetron 3mcg/kg, max 0.25 mg	12 sites from Russia and Ukraine
PALO-10-14	Randomized, double-blind, double-dummy, active-controlled, parallel group	N=670 Ages: 30 days to <17 years Pediatric patients undergoing elective surgical procedures requiring general IV anesthesia and receiving nitrous oxide during the maintenance phase of anesthesia	Single IV palonosetron 1 mcg/kg, max 0.075mg Single Ondansetron IV 0.1mg/kg, max 4mg	44 sites from United States, Ukraine, Hungary, Poland, Russia, Czech Republic, and Argentina

Source: Summarized from Sponsor's Listing of Clinical Studies (Module 5.2)

5.2 Review Strategy

Two pediatric PONV trials were submitted for this supplement and were reviewed in detail. PALO-07-29 was a proof-of-concept, dose-finding study and PALO-10-14 was the pivotal Phase 3 efficacy and safety study for PONV. PALO-10-14 was the primary study reviewed for the efficacy evaluation. The safety data of both PALO-07-29 and PALO-10-14 were reviewed for an integrated safety evaluation.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study PALO-07-29

Title: A Multicenter, Double-blind, Randomized, Parallel Group, Stratified Study to Assess the Safety and Efficacy of Single IV Doses of Palonosetron to Prevent Postoperative Nausea and Vomiting in Pediatric Patients

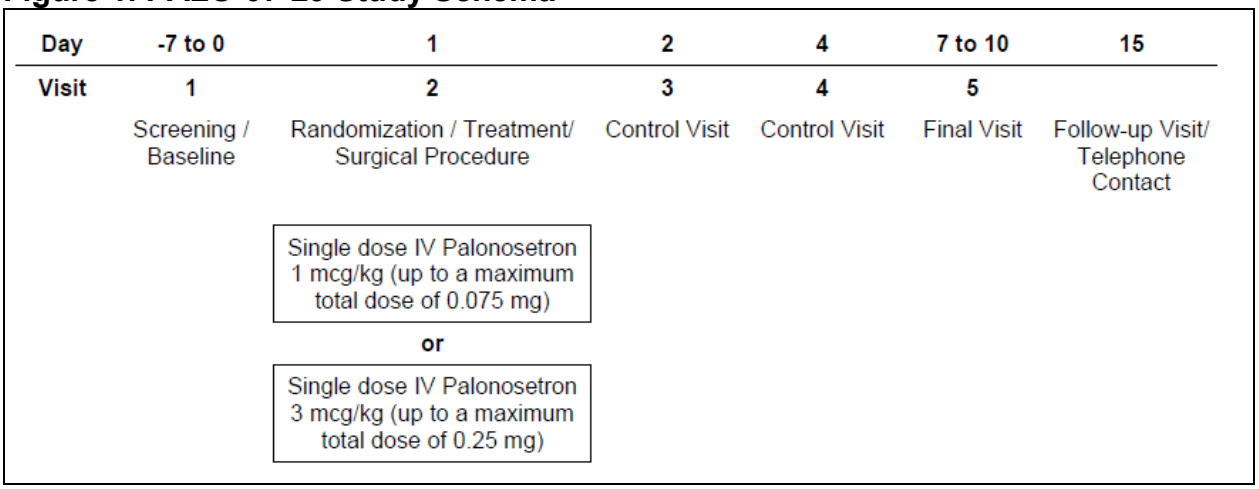
Study Period: August 19, 2008-December 27, 2008

Investigators and Study Centers: A total of 12 investigators from two countries, Russia and Ukraine, participated in the study. The study was conducted at 4 sites in Russia and 8 sites in Ukraine.

Study Objective: The objective of the study was to assess the safety and efficacy of two doses of IV palonosetron each administered as a single dose for the prevention of postoperative nausea and vomiting through 72 hours postoperatively in children aged >28 days up to 16 years undergoing surgical elective procedures requiring general endotracheal inhalation anesthesia.

Study Design: This was a multi-center, randomized, double-blind, stratified, parallel group study. There were two study groups who received either 1mcg/kg or 3mcg/kg of IV palonosetron that was administered IV push within 5 minutes before induction of general endotracheal anesthesia or immediately following placement of an IV line following inhalation anesthesia induction. Patients were stratified by age and country and then randomized to one of the two treatment arms. Patients were followed for 15 days after dosing for scheduled efficacy and safety assessments. The overall trial design is illustrated in Figure 1.

Figure 1. PALO-07-29 Study Schema



Source: Sponsor's Clinical Study Report for PALO-07-29, Figure 9.1 (Module 5.3)

Protocol Amendments: There was 1 protocol amendment after the original protocol dated June 4, 2008 that was specific to Russia. The Central Ethics Committee within the Federal Authority for Healthcare and Social Development Regulation of Russia requested exclusion of the pregnancy surveillance program and this language was removed from the protocol.

Study Population: The study enrolled pediatric patients age >28 days to 16 years who were undergoing elective surgical procedures requiring general endotracheal inhalation anesthesia and receiving nitrous oxide during the maintenance phase of anesthesia. Key inclusion and exclusion criteria are summarized below.

Key Inclusion Criteria

- Male or female patient aged >28 days (full term) up to and including 16 years.
- Inpatient scheduled to undergo any of the following surgical procedures: ear, nose and throat surgery (e.g., tonsillectomy, adenoidectomy); one-side strabismus surgery; orchidopexy; plastic reconstructive surgery (e.g., cleft lip/cleft palate, burn procedures involving the scalp); herniorraphy; orthopedic surgery (e.g., club foot, hip disorders).
- American Society of Anesthesiologists (ASA)1 physical status I, II or III
- Patient scheduled to have an intravenous line placed and functioning prior to surgery, or have an intravenous line placed immediately following induction using inhalation anesthesia.
- Patient scheduled to receive nitrous oxide during the maintenance phase of anesthesia.
- Patient scheduled to be hospitalized for at least 72 hours after wake up of surgery (T0).

Key Exclusion Criteria

- For patient aged more than 6 years: inability to understand or cooperate with the study procedures.
- For infant aged more than 12 months: a history of gastro-esophageal reflux.
- Patient suffering from any concomitant disease uncontrolled by therapy, which, in the judgment of the Investigator, could compromise the outcome of surgery.
- For patient aged 28 days to ≤6 years: patient who received any investigational drugs within 90 days prior to Day 1. For patient aged >6 up to 16 years inclusive: patient who received any investigational drugs within 30 days prior to Day 1.
- Patient scheduled to undergo emergency surgery.
- Patient scheduled to receive regional (spinal) anesthesia in conjunction with general endotracheal anesthesia.
- Patient scheduled to receive laryngeal mask anesthesia.
- Patient scheduled to receive propofol during the maintenance phase of anesthesia.
- Patient scheduled to receive an intragastric tube in situ postoperatively.
- Patient with vomiting from any organic cause.
- Any drug with a potential anti-emetic effect within 24 hours prior to the administration of anesthesia

Study Treatments: Patients were randomized, with stratification for age group and country, to receive a single IV dose of either 1mcg/kg (up to a maximum of 0.075 mg) or 3 mcg/kg (up to a maximum of 0.25 mg). Study drug was administered IV push within 5 minutes before induction of general endotracheal anesthesia or immediately following placement of an IV line following inhalation anesthesia induction in a blinded fashion. Dose selection was guided by pharmacokinetic results from adult studies in PONV and CINV and from a pediatric study in CINV.

Study Procedures: Informed consent was obtained from the parent(s)/legal guardian(s) of the patient. Assent was obtained from patients aged 7 years and older using an age-appropriate assent form.

Details of the surgery including time of induction and end of anesthesia, type of surgical procedure, all anesthetic medication used, and recovery time (T0) were recorded. Any other rescue medications or postoperative medications were recorded with drug name, dose, route, time, and frequency.

A study nurse recorded emetic episodes through 72 hours post-recovery in a patient diary for all patients. Patients aged 6-16 years completed nausea assessments themselves using a visual analog scale following administration of the scale by a study nurse.

Adverse events and prior and concomitant medications were assessed at all study visits. Additional safety measures included clinical labs, physical examinations, vital

signs, and 12-lead ECG in triplicate assessed at scheduled time. Figure 2 outlines the timing of all study procedures.

A detailed table of the study procedures and their timing are presented in Appendix 1, Section 9.4.1.

Efficacy endpoints: The original primary efficacy endpoint was the proportion of patients with no emetic episodes at the overall time period 0-72 hours post-operatively. An emetic episode was defined a forceful, single vomit or retch, or any number of continuous vomits or retches separated by the absence of both vomiting and retching for at least 3 minutes. In the WR issued after the study was completed, the FDA requested the primary efficacy endpoint of Complete Response (CR) (no vomiting, no retching, and no use of rescue medications) from 0 to 24 hours and this was performed as a post-hoc analysis and included as an addendum to the original study report, with agreement from the FDA at the pre-sNDA meeting.

Secondary endpoints were:

- Proportion of patients with no emetic episodes for the following time periods: 0-6 hours, 6- 24 hours, 24-48 hours, 48-72 hours, 0-24 hours, 0-48 hours and 24-72 hours;
- Severity of nausea (only for patients aged 6 up to 16 years inclusive) for the following time periods: 0-6 hours, 6-24 hours, 24-48 hours, and 48-72 hours; and at the overall time period (0-72 hours);
- Time to first emetic episode;
- Time to first administration and need for rescue medication;
- Time to treatment failure (based on time to the first emetic episode or time to the first administration of rescue medication, whichever occurs earlier);
- Proportion of patients who are not administered a rescue medication during the following time periods: 0-6 hours, 6-24 hours, 24-48 hours, 48-72 hours, 0-24 hours, 0-48 hours, 0-72 hours and 24-72 hours;
- Proportion of patients with CR during the 0-6 hour, 6-24 hour, 24-48 hour, 48-72 hour, 0-24 hour, 0-48 hour, 0-72 hour and 24-72 hour time intervals.

Safety endpoints: Adverse events, physical examination, vital sign measurements, clinical laboratory assessments (hematology, blood chemistry, urinalysis), 12-lead electrocardiogram (ECG) recording.

Statistical Analysis: A sample size of 150 evaluable patients was calculated to provide a power of 78% of observing at least one adverse event with palonosetron with an incidence of 1.0% and a power of 95% of observing at least one adverse event with an incidence of 2.0%.

Two datasets were defined, the Full Analysis Set (FAS) and the Safety Dataset. The FAS included all randomized patients who received the study drug and had general

anesthesia and surgery. The Safety Dataset included all subjects who received study drug. The difference between the Safety Dataset and the FAS is due to one patient who was randomized to the low dose group and treated in the high dose. This patient was included in the low dose group for the efficacy analyses and in the high dose group for safety analyses.

All statistical analyses were descriptive and no statistical tests to detect difference between treatment groups were planned. Descriptive statistics included n (number of observed values), mean, median, standard deviation (SD), minimum and maximum for continuous variable, and frequency counts and percentages for categorical variables. Baseline and demographic variables was summarized by treatment group and overall using descriptive statistics in both study sets. Subgroup analysis was performed by stratification for age and country. Post-hoc subgroup analyses using age groups defined by the WR were performed and presented as an addendum to the original study report.

The efficacy evaluation was conducted on the FAS. The primary efficacy analysis was the proportion of subjects with no emetic episodes during the overall time period 0-72 hours post-operatively. Post-hoc analysis of the WR defined primary efficacy endpoint, CR from 0-24 hours, was performed and presented as an addendum to the original study report. All efficacy analyses were performed according to dose groups; subgroups analysis was performed for the stratification criteria (age group and country). Post-hoc subgroup analyses using age groups defined by the WR were performed and presented as an addendum to the original study report.

All patients who received a dose of palonosetron were included in the safety analysis. Only treatment emergent adverse events (TEAEs) were summarized. The incidence of TEAEs was calculated based upon MedDRA primary SOC (system organ class) and MedDRA preferred term (PT). There was not a control group to compare safety profiles.

5.3.2 Study PALO-10-14

Title: A Multicenter, Double-blind, Double-dummy, Randomized, Parallel Group, Stratified Study to Evaluate the Efficacy and Safety of a Single IV Dose of Palonosetron Compared to a Single IV Dose of Ondansetron to Prevent Postoperative Nausea and Vomiting in Pediatric Patients.

Investigators and Study Centers: A total of 44 sites were initiated in seven countries located in the United States (12), Ukraine (9), Hungary (5), Poland (5), Russia (5), Czech Republic (6) and Argentina (2). Patients were enrolled into the study by 39 out of 44 Investigators: United States (11), Ukraine (7), Hungary (5), Poland (5), Russia (5), Czech Republic (4) and Argentina (2).

Study Period: June 14, 2011-March 27, 2012

Study Objectives: The primary objective of the study was to evaluate the efficacy of a single palonosetron IV dose compared to a single ondansetron IV dose in the prevention of PONV through 24 hours after surgery in children aged from neonates (0-27 days of age) up to less than 17 years undergoing elective surgical procedures requiring general intravenous anesthesia.

The secondary objective was to evaluate the safety and tolerability of IV palonosetron in pediatric patients.

Study Design: This was a multi-center, randomized, active controlled, double-blind, double dummy, stratified, parallel group study that was designed according the requirements of the FDA WR. There were two study groups who received either IV palonosetron or IV ondansetron (standard therapy). The palonosetron dose was 1 mcg/kg (up to a maximum of 0.075 mg based on body weight) and the ondansetron dose was 0.1 mg/kg (up to a maximum dose of 4 mg based on body weight and age) which was administered IV push within 5 minutes before induction of general IV anesthesia. Patients were stratified by age groups and then randomized to one of the two treatment arms. Patients were stratified by the following age groups: <2 years; 2 to <6 years; 6 to <12 years; 12 to <17 years. For each age group, patients were randomized to balance over all study sites rather than for individual sites. The protocol planned to obtain blood samples for PK analysis from neonates (0-27 days of age) at day 1 and at day 2, if enrollment of neonates was possible.

The study was conducted in a blinded fashion. A Data Monitoring Committee (DMC) comprised of three clinicians and one statistician was established for the evaluation of safety data during the study and they were unblinded, as per the charter. Patients were followed for up to 18 days after dosing for scheduled efficacy and safety assessments. The overall trial design is illustrated in Figure 1.

Figure 2: PALO-10-14 Study Schema

Day	-14 to -1 (or -7 to -1 for patients <2 years)	1	2	7 to 10	15 to 18
Visit	1	2	3	4	5
	Screening	Randomization / Treatment/ Surgical Procedure Single dose IV palonosetron and placebo to ondansetron or Single dose IV ondansetron and placebo to palonosetron	Control Visit	Final Visit	Follow-up Telephone Contact

Source: Sponsor's Clinical Study Report for PALO-10-14, Figure 1 (Module 5.3)

Protocol Amendments: Country-specific protocol amendments were made as requested by national regulatory authority or ethics committees in Poland, Russia, Czech Republic, Argentina and the United States. The most common request for protocol amendments was to increase the minimum age of the study subjects (to 1 month in Czech Republic, Poland, and Russia, and to 2 years in Argentina).
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Study Population: The target population for the study was pediatric patients age 0 to <17 years who were undergoing elective surgical procedures requiring general IV anesthesia. Key inclusion and exclusion criteria are summarized below.

Key Inclusion Criteria:

- Male or female patient aged from full term neonates (0-27 days of age) to less than 17 years.
- In-patient or out-patient scheduled to undergo one of the following procedures: ear, nose and throat surgery (e.g., tonsillectomy, adenoidectomy, myringotomy); eye surgery (e.g. strabismus, vitreoretinal, cataract surgery); urological surgery (e.g. orchidopexy, varicocoele); plastic reconstructive surgery (e.g. cleft lip/cleft palate, burn procedures involving the scalp); hernia repair; orthopedic surgery (e.g. foot and ankle deformities, arthroscopic surgeries, ACL (anterior cruciate ligament) surgery; cardiac surgery; neurosurgery.
- Patient scheduled to undergo surgery requiring general intravenous anesthesia.

- Patient scheduled to receive nitrous oxide during the maintenance phase of anesthesia.
- Patient weighed at least 3.2 kg.
- ASA (American Society of Anesthesiologists) physical status I, II or III

Key Exclusion Criteria

- The patient and/or parents/caregivers were expected by the Investigator to be non-compliant with the study procedures.
- Lactating females.
- Patient aged ≤6 years who received any investigational drug within 90 days prior to Day 1, or patient aged >6 years who received any investigational drug within 30 days prior to Day 1 or was expected to receive investigational drugs prior to study completion.
- Patient having participated in any previous trial with palonosetron.
- History of allergy to any components or any other contraindications to the use of any 5-HT_3 receptor antagonists.
- Patient to undergo emergency surgery.
- Patient scheduled to receive regional anesthesia (lumbar, epidural, spinal) alone or in conjunction with general intravenous anesthesia.
- Patient scheduled to receive laryngeal mask anesthesia.
- Patient scheduled to receive propofol during the maintenance phase of anesthesia.
- Patient scheduled to receive intragastric tube in situ postoperatively.
- Patient suffering from any concomitant disease uncontrolled by therapy, which, at the judgment of the Investigator, could have compromised the outcome of surgery.
- Patient with history of gastro-esophageal reflux (except for patients up to 12 months).
- Patient with ongoing vomiting from any organic cause.
- Patient having experienced any vomiting, retching, or nausea within 24 hours prior to the administration of the study drug.
- Use of specified medications with potential anti-emetic effect within 48h prior to surgery

Study Treatments: The dose selection for palonosetron was based on adult and pediatric pharmacokinetic data and metabolism and ontogeny considerations. Dosing of ondansetron was administrated according to the pediatric posology instructions in the ondansetron label.

The study used a double-dummy design where each study patient received two treatments, an active compound and a matching placebo. Palonosetron/matching placebo was given as a single IV push at a 1 mcg/kg (up to a maximum of 0.075 mg based on body weight). The ondansetron/matching placebo dose was 0.1 mg/kg up to a

maximum dose of 4 mg for patients aged 0 to 12 years and 4mg for subjects aged 13 to <17 years by a single IV infusion. Ondansetron/matching placebo was administered first, followed by administration of palonosetron/matching placebo and then by IV general anesthesia. If induction of anesthesia was performed by inhalation, study drugs could be administered immediately after placement of an IV line following the inhalation anesthesia induction.

Study Procedures: Informed consent was obtained from the parent(s)/legal guardian(s) of the patient. Assent was obtained from patients aged 7 years and older using an age-appropriate assent form.

Details of the surgery including time of induction and end of anesthesia, type of surgical procedure, all anesthetic medication used, and recovery time (T0) were recorded. Any other rescue medications or postoperative medications were recorded with drug name, dose, route, time, and frequency.

The patient, the patient's parent(s)/legal guardian(s) or a study nurse recorded emetic episodes through 24 hours post-recovery in a patient diary for all patients. Information on concomitant medications or rescue medications administered was also recorded. Patients aged ≥16 years were asked by the investigator at Visit 3 about their feeling of nausea using a Yes or No question.

Adverse events and prior and concomitant medications were assessed at all study visits. Additional safety measures included clinical labs, physical examinations, vital signs, and 12-lead ECG in triplicate assessed at scheduled time. Table X outlines the timing of all study procedures.

Blood samples were planned to be collected for neonates (0-27 days of age) for PK analysis. However, investigators were unable to enroll neonates into the study so this analysis was not performed.

A detailed table of the study procedures and their timing are presented in Appendix 2, Section 9.4.2.

Efficacy endpoints: The primary efficacy endpoint was the proportion of patients with Complete Response (no vomiting, no retching or use of antiemetic rescue medications) during the first 24 hours after T_0.

Secondary efficacy endpoints (0-24 hours) included:

- Proportion of patients with no vomiting.
- Proportion of patients without emetic episodes (defined as vomiting and/or retching).
- Proportion of patients without antiemetic rescue medication.

- Proportion of patients without nausea (patient aged >6years).
- 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 occurred first).

Safety endpoints: The safety variables included adverse events, physical examination, vital sign measurements, clinical laboratory assessments (hematology, blood chemistry, urinalysis), 12-lead ECG recording in triplicate.

A DMC comprised of three clinicians and one statistician was established for the evaluation of safety data during the study.

Pharmacokinetic endpoints: Blood samples were planned to be collected for neonates (0-27 days of age) for PK analysis. However, investigators were unable to enroll neonates into the study so this analysis was not performed.

Statistical Analysis:
Sample size: The sample size was based on the assumption of a CR rate in the 0-24 hour time interval of 70% in the palonosetron and ondansetron groups. For a non-inferiority test using a type I error equal to 0.025 (one sided), a sample size of 330 evaluable patients per group provides a power of 80% to show that the lower bound of the CI of the difference ($CR_{\text{0-24 hr palonosetron}} - CR_{\text{0-24 hr ondansetron}}$) is superior to the pre-fixed threshold of -10%.

Analysis populations: The Full Analysis Set (FAS) was the primary dataset used for efficacy analysis. The FAS includes all randomized patients who received the active study drug, general anesthesia and surgery (evaluable patients).

Per protocol population (PP): The PP is a subset of the FAS that was determined with a blind review of the data in order to define the violations leading to exclusion from the PP.

As-treated population: The As-Treated population includes all randomized patients who received the active study drug, general anesthesia and surgery (evaluable patients), with each patient being assigned to the treatment actually received. For this study, the As-treated population was the same as the FAS.

Modified FAS: During the course of the study, 12 patients became potentially unblinded to the Sponsor. The Modified FAS is a subset of the FAS that excludes these 12 subjects for sensitivity analysis.

The Safety population (SAF) includes all randomized patients who received active study drug and had at least one post-treatment safety assessment. Patients were assigned to study treatment arms according to the actual treatment received.

Efficacy endpoint: The primary efficacy endpoint was the proportion of patients showing CR during the first 24 hours postoperatively, starting at T0. The objective of the primary efficacy analysis was to demonstrate the non-inferiority of palonosetron compared to ondansetron.

The null hypothesis (H0) was stated as:
H0: $CR_{0\text{-}24\ hr\ palonosetron} - CR_{0\text{-}24\ hr\ ondansetron} < -10\%$

The alternative hypothesis (H1) was stated as:
H1: $CR_{0\text{-}24\ hr\ palonosetron} - CR_{0\text{-}24\ hr\ ondansetron} > -10\%$

Primary efficacy analysis: The stratum adjusted Mantel-Haenszel method was used to compute the Confidence Interval (CI) of the difference in proportion. If the lower bound of the 95% CI of the difference ($CR_{0\text{-}24\ hr\ palonosetron} - CR_{0\text{-}24\ hr\ ondansetron}$) was strictly superior to the Non-inferiority margin (δ=-0.1) then the null hypothesis (H0) was be rejected.

The co-primary efficacy analyses were based on the CI from the stratum adjusted Mantel-Haenszel method with correction of continuity computed on the “as-treated” population and the probability of the χ 2 calculated with the stratum adjusted Miettinen and Nurminen method on the FAS and the “as-treated” population.

In order to provide substantial evidence of efficacy, all the primary (stratum adjusted Mantel-Haenszel performed on the FAS) and co-primary (stratum adjusted Mantel-Haenszel performed on the As-treated population, stratum adjusted Miettinen and Nurminen performed on the FAS and As-Treated populations) efficacy analyses should demonstrate positive results in favor of palonosetron (i.e., the null hypothesis must be rejected).

Patient disposition: Disposition was summarized by treatment arm and age groups using descriptive statistics. Demography and other baseline characteristics were summarized by treatment for the FAS and SAF using descriptive statistics.

Adjustment for covariates: Age was the main factor expected to potentially influence results. This was accounted for by stratification by age with randomization.

Handling of missing data: Conservative approaches were applied. 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 impute the missing values.

For time to event analyses (e.g., time to first vomiting, first emetic episode, first administration of rescue medication, and treatment failure), the value defined as lack of efficacy was used to impute the missing value. Additionally the missing time-to-event was 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 (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 T0+24hours.

6 Review of Efficacy

Efficacy Summary

As PALO-07-29 was essentially a proof-of-concept study with no placebo or active control arm, PALO-10-14 was the primary study reviewed for the efficacy evaluation.

PALO-10-14 was a multi-center, randomized, active controlled, double-blind, double dummy, stratified, parallel group study to evaluate the safety and efficacy of a single dose of IV palonosetron for the prevention of PONV through 24 hours post-surgery in pediatric patients (neonate to <17 years of age) compared to standard therapy. The study enrolled pediatric patients who were scheduled to undergo elective surgical procedures requiring general IV anesthesia and who were scheduled to receive nitrous oxide during the maintenance phase of anesthesia. Patients received a single dose of either IV palonosetron 1mcg/kg or IV ondansetron 0.1mg/kg immediately preceding general anesthesia. The primary efficacy endpoint was CR (no vomiting, no retching and no use of rescue medication) from 0-24 hours. The study used a non-inferiority design to compare palonosetron to ondansetron as standard of care with a non-inferiority margin pre-specified at 10%.

Of 670 patients randomized, 661 patients received treatment with either palonosetron (n=331) or ondansetron (n=330). Patients were stratified by age groups pre-defined in the WR: <2 years (n=46), 2 to <6 years (n=247), 6 to <12 years (n=234), 12 to <17 years (134). There were no neonates enrolled in the study. Subject demographics were well balanced between the two treatment arms.

The proportion of treated patients with CR was 78.2% in the palonosetron group and 82.7% in the ondansetron group. The primary efficacy analysis assessed the non-inferiority of palonosetron to ondansetron based on the stratum adjusted Mantel-Haenszel method for the FAS comparing proportions of patients with CR at 0-24 hours. The difference between treatments was -4.4% (-10.5%, 1.7%). The lower bound of the confidence interval did not meet the pre-specified non-inferiority margin of 10%,

therefore, the null hypothesis was not rejected and non-inferiority of palonosetron to ondansetron was not proven. There were 3 co-primary efficacy analyses and 6 supportive sensitivity analyses performed with the same endpoint that all supported the primary efficacy analysis.

Key secondary endpoints included:

1. No vomiting from 0-24 hours- The stratum adjusted Mantel Haenszel analysis of the proportion of patients with no vomiting from 0-24 hours showed the difference between treatments was -4.5% (-9.9%,1.0%).
2. Use of antiemetic rescue medication- The stratum adjusted Mantel Haenszel analysis of the proportion of patients without use of antiemetic rescue medication showed the difference between treatments was -3.3% (-6.8%,0.3%).
3. Time to rescue- Because of low rates of administration of rescue medications, a meaningful Kaplan-Meier curve could not be generated.
4. Time to first vomiting episode- The Cox Hazard Ratio stratified by age stratum for the time to first vomiting was 1.407 (0.941, 2.106)..

Although a few of the secondary endpoints were within the non-inferiority margin, the non-inferiority of palonosetron to ondansetron was not proven overall.

6.1 Indication

The Sponsor is not requesting an indication for post-operative nausea and vomiting in the pediatric population. The studies submitted for this application are intended to fulfill the WR from the FDA and to support PREA requirements and a pediatric exclusivity determination.

6.1.1 Methods

As PALO-07-29 was essentially a proof-of-concept study with no placebo or active control arm, PALO-10-14 was the primary study reviewed for the efficacy evaluation. A summary of the results of PALO-07-29 can be found in Appendix 3, Section 9.4.3.

The objective of PALO-10-14 was to evaluate the safety and efficacy of a single dose of IV palonosetron for the prevention of PONV through 24 hours post-surgery in pediatric patients (neonate to <17 years of age) compared to standard therapy. PALO-10-14 was designed according the requirements of the FDA WR. This was a multi-center, randomized, active controlled, double blind, double dummy, stratified, parallel group study. The study enrolled pediatric patients who were scheduled to undergo elective surgical procedures requiring general IV anesthesia and who were scheduled to receive nitrous oxide during the maintenance phase of anesthesia. The patients were stratified by age according to age groups defined in the WR and randomized to treatment within each age stratum. Patients received a single dose of either IV palonosetron 1mcg/kg or IV ondansetron 0.1mg/kg immediately preceding general anesthesia. The primary

efficacy endpoint was CR (no vomiting, no retching and no use of rescue medication) from 0-24 hours. The study used a non-inferiority design to compare palonosetron to ondansetron as standard of care. Details of the inclusion and exclusion criteria, study design, and statistical analysis for PALO-10-14 are described in Section 5.3.2.

6.1.2 Demographics

There were 670 patients randomized. Of those randomized, 661 patients received treatment and were included in the FAS. Table 3 summarizes the demographics of the patients included in the FAS. There were more males (60.5%) than females (39.5%) enrolled in the study. The majority of patients were White (94.9%). The highest proportion of subjects was enrolled in the 2 to <6 years and 6 to <12 years age groups. The fewest subjects were in the <2 years of age group due to difficulties with enrollment in this age group that was well-documented by the Sponsor. No neonates were enrolled in the study. The age range of the subjects was from 30 days old to 16.9 years. The demographic profiles were similar between the two treatment groups.

The CSR documents the Sponsor's efforts to enroll patients across different age groups, races and ethnicities. These efforts included newsletters to Investigators to encourage enrollment across ages and minorities, directly advising Investigators via the CRO to encourage enrollment across these groups, and increasing the enrollment caps to top enrolling sites to additional subjects in these groups. The Sponsor tracked the demographics of the study and provided 3 enrollment updates to the FDA during the study.

Table 3: Demographics of the Full Analysis Set

	Palonosetron 1mcg/kg (N=331) n (%)	Ondansetron 0.1mg/kg (N=330) n (%)	Total (N=661) n (%)
Gender			
Male	199 (60.1)	201 (60.9)	400 (60.5)
Female	132 (39.9)	129 (39.2)	261 (39.5)
Age (years)			
Mean (SD)	7.82 (4.44)	7.43 (4.32)	7.63 (4.38)
Median	6.55	6.32	6.44
Age groups			
<2 years	22 (6.6)	24 (7.3)	46 (6.0)
2 to <6 years	124 (37.5)	123 (37.3)	247 (37.4)
6 to <12 years	117 (35.3)	117 (35.5)	234 (35.4)
12 to <17 years	68 (20.5)	66 (20.0)	134 (20.3)
Race			
White	315 (95.2)	312 (94.5)	627 (94.9)
Black	13 (3.9)	12 (3.9)	25 (3.8)
Asian	1(0.3)	1 (0.3)	2 (0.3)
American Indian	0 (0)	1 (0.3)	1 (0.2)
Other	2 (0.6)	4 (1.2)	6 (0.9)
Ethnicity			
Hispanic	24 (7.3)	22 (6.7)	46 (7.0)
Country			
Argentina	7(2.1)	6 (1.8)	13 (2.0)
Czech Republic	7 (2.1)	13 (3.9)	20 (3.0)
Hungary	117 (35.3)	102 (30.9)	219 (33.1)
Poland	28 (8.5)	26 (7.9)	54 (8.2)
Russia	24 (7.3)	46 (13.9)	70 (10.5)
Ukraine	59 (17.8)	66 (20.0)	125 (18.9)
USA	89 (26.9)	71 (21.5)	160 (24.2)

Source: Derived from Sponsor's Clinical Study Report for PALO-10-14, Table 14.1.3.1.1 (Module 5.3)

Surgical procedures: Table 4 provides a summary of the types of surgical procedures that were performed during the study. The majority of patients (71.6%) underwent ear, nose and throat surgery. The types of procedures were fairly well balanced between the two treatment arms.

Table 4: Surgical procedures and duration of anesthesia in PALO-10-14

Surgical Procedure	Palonosetron 1mcg/kg (N=331) n (%)	Ondansetron 0.1mg/kg (N=330) n (%)	Total (N=661) n (%)
Ear, nose and throat surgery	237 (71.6)	236 (71.5)	473 (71.6)
Eye surgery	5 (1.5)	11 (3.3)	16 (2.4)
Hernia repair	21 (6.3)	19 (5.8)	40 (6.1)
Neurosurgery	0 (0.0)	1 (0.3)	1 (0.2)
Orthopedic surgery	34 (10.3)	26 (7.9)	60 (9.1)
Plastic reconstructive surgery	13 (3.9%)	10 (3.0)	23 (3.5)
Urological surgery	21 (6.3)	27 (8.2)	48 (7.3)

Source: Adapted from Sponsor's Clinical Study Report Study PALO-10-14, Table 13 (Module 5.3)

Concomitant Medications: All patients (100%) received intra- or peri-operative medications during the study course. The types of medications that were used were generally well balanced between the treatments groups. A table of the intra- and peri-operative medications is provided in Appendix 4, Section 9.4.4. An analysis of the primary endpoint by selected concomitant medications is provided in Section 6.1.10.

6.1.3 Subject Disposition

There were 670 patients randomized in the study. Of these, 661 patients were administered study drug and were included in the Full Analysis Set (FAS). There were 15 subjects who discontinued the study prematurely. Of the 15 subjects who discontinued the study, 9 subjects did not receive study drug, 1 subject in the ondansetron group discontinued due to an adverse event that occurred pre-treatment, 1 subject withdrew consent, and 4 subjects were lost to follow-up. Table 5 describes the patient disposition. As there was a very low dropout rate and most subjects were lost prior to treatment, it is unlikely that the loss of these subjects influenced the outcome of the study.

Table 5: Patient Disposition (Randomized Population) in PALO-10-14

Patient Disposition	**Palonosetron 1mcg/kg (N=336) n (%)**	**Ondansetron 0.1mg/kg (N=334) n (%)**
Not treated patients	5 (1.5)	4 (1.2)
Treated patients	331 (98.5)	330 (98.8)
Patients completing the study	326 (97)	329 (98.5)
Primary reasons for premature termination		
Not treated	5 (1.5)	4 (1.2)
Lost to follow-up	4 (1.2)	0 (0)
Withdrawal of consent	1 (0.3)	0 (0)
Adverse Event	0 (0)	1 (0.3)

Source: Adapted from Sponsor's Clinical Study Report Study PALO-10-14, Table 5 (Module 5.3)

Protocol Deviations: Major protocol deviations were defined as deviations affecting the primary efficacy endpoint. Decisions regarding inclusion or exclusion of individual patients from the analysis population were made before the study data was unblinded. Major protocol deviations are listed in Table 6. Nine subjects were randomized but did not receive study drug and were excluded from the FAS. As these patients did not receive the study drug, the exclusion of these patients is unlikely to influence the outcome of the study. Twelve patients were potentially unblinded to the sponsor statistician. These subjects were included in the FAS but were not included in the Per-protocol analysis population. A sensitivity analysis was conducted by the Sponsor on the Modified FAS that excluded these subjects and there was no significant change in the study results.

Table 6: Major Protocol Deviations in the Randomized Population in PALO-10-14

Major Deviation	Palonosetron 1 mcg/kg (N=336)	Ondansetron 0.1 mg/kg (N=334)
Patients with Major deviations leading to exclusion from the Full Analysis Set [n (%)]	**5 (1.5%)**	**4 (1.2%)**
Drug not taken	5 (1.5%)	4 (1.2%)
No general anesthesia	5 (1.5%)	4 (1.2%)
Patients not operated	5 (1.5%)	2 (0.6%)
Patients with Major deviation leading to exclusion from the Per- Protocol Population [n (%)]	**16**	**22**
Patient potentially unblinded to sponsor statistician	4 (1.2%)	8 (2.4%)
Patient not treated with nitrous oxide during anesthesia	4 (1.2%)	7 (2.1%)
Treatment received different from treatment assigned	1 (0.3%)	1 (0.3%)
Propofol administration in maintenance phase for a significant duration	2 (0.6%)	0 (0.0%)
No diary	0 (0.0%)	2 (0.6%)
Treated before randomization	0 (0.0%)	1 (0.3%)
History of gastro-esophageal reflux	1 (0.3%)	0 (0.0%)

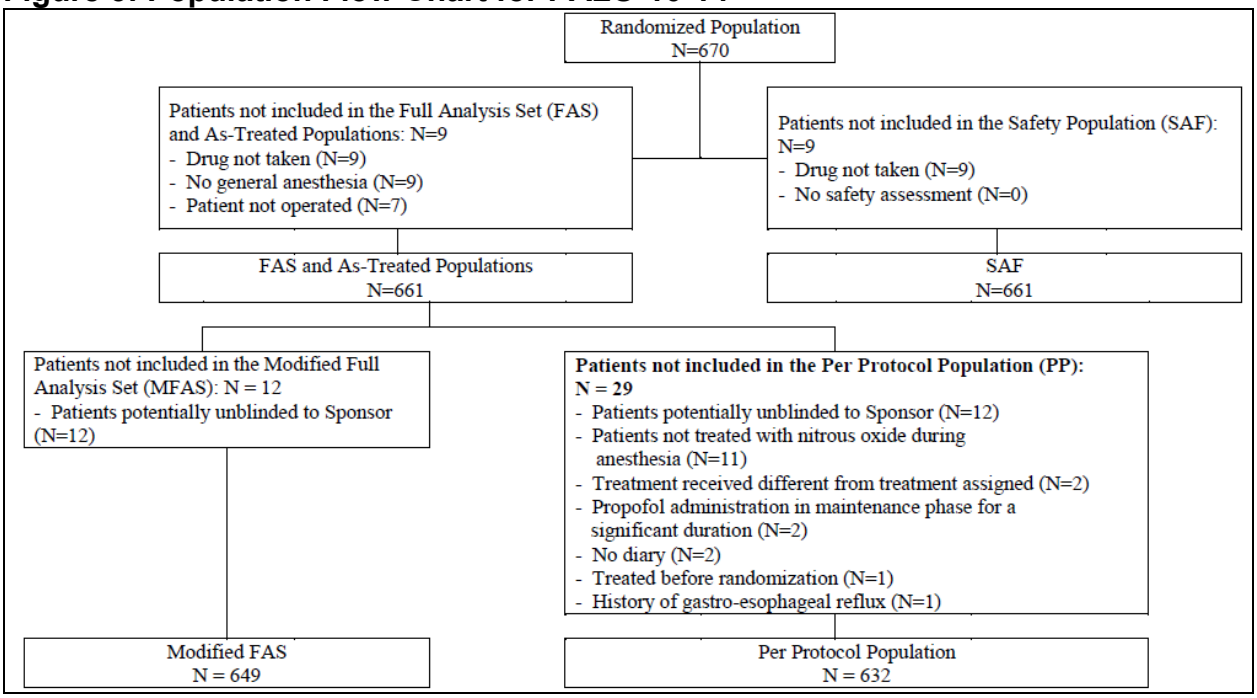
N= Number of patients randomized in treatment arm
n = number of patients with major deviation
% = Percentage of patients with major deviation in treatment arm

Source: Sponsor's Clinical Study Report Study PALO-10-14, Table 8 (Module 5.3)

Analysis Datasets:

There were 661 subjects who received study drug and were included in the FAS. The As-Treated Population and the SAF were identical to the FAS. There were 12 subjects who were potentially unblinded to the Sponsor and were excluded from the Modified FAS. There were 29 subjects with major protocol deviations who were excluded from the PP Population. Figure 3 describes the number of patients in each dataset.

Figure 3: Population Flow Chart for PALO-10-14



Source: Sponsor's Clinical Study Report Study PALO-10-14, Figure 2 (Module 5.3)

6.1.4 Analysis of Primary Endpoint(s)

Consistent by the FDA WR, the primary efficacy endpoint was the proportion of patients showing CR defined as no vomiting, no retching, and no use of rescue medication from 0-24 hours. Time 0 (T0) started as soon as the patient woke up and showed any active reaction.

Table 7 provides a summary of the CR rates overall and by age group. The proportion of treated patients with CR was 78.2% in the palonosetron group and 82.7% in the ondansetron group. There was a higher proportion of patients with CR in the ondansetron dose group in all age stratums except for 2 to <6 years in which palonosetron performed better by a small margin.

Table 7: Proportion of patients with Complete Response in PALO-10-14

	Palonosetron 1 mcg/kg (N=331)	**Ondansetron 0.1 mg/kg (N=330)**
Overall population		
Number of Patients	331	330
Patients with CR	259 (78.2%)	273 (82.7%)
Wilson 95% CI of CR	[73.3%; 82.5%]	[78.1%; 86.6%]
<2 years stratum		
Number of Patients	22	24
Patients with CR	18 (81.8%)	22 (91.7%)
Wilson 95% CI of CR	[59.0%; 94.0%]	[71.5%; 98.5%]
2 to <6 years stratum		
Number of Patients	124	123
Patients with CR	101 (81.5%)	98 (79.7%)
Wilson 95% CI of CR	[73.3%; 87.6%]	[71.3%; 86.2%]
6 to <12 years stratum		
Number of Patients	117	117
Patients with CR	88 (75.2%)	99 (84.6%)
Wilson 95% CI of CR	[66.2%; 82.5%]	[76.5%; 90.4%]
12 to <17 years stratum		
Number of Patients	68	66
Patients with CR	52 (76.5%)	54 (81.8%)
Wilson 95% CI of CR	[64.4%; 85.6%]	[70.0%; 89.9%]

Source: Adapted from Sponsor's Clinical Study Report Study PALO-10-14, Table 17 (Module 5.3)

The primary efficacy analysis assessed the non-inferiority of palonosetron to ondansetron based on the stratum adjusted Mantel-Haenszel method for the FAS comparing proportions of patients with CR at 0-24 hours. The difference between treatments was -4.4% (-10.5%, 1.7%) (Table 8). The lower bound of the confidence interval did not meet the pre-specified non-inferiority margin of 10%, therefore, the null hypothesis was not rejected and non-inferiority of palonosetron to ondansetron was not proven.

Table 8: Primary Efficacy Analysis (Full Analysis Set) for PALO-10-14

Complete response 0-24 hrs Stratum Adjusted Mantel-Haenszel Full Analysis Set (N=661)		
<2 years stratum	Delta CR[1]	-9.9%
2 to <6 years stratum	Delta CR[1]	1.8%
6 to <12 years stratum	Delta CR[1]	-9.4%
12 to <17 years stratum	Delta CR[1]	-5.4%
Overall	**Weighted Sum of Delta CR**	**-4.4%**
	95% CI of the Weighted Sum of Delta CR	[-10.5%; 1.7%]
	P-value[2]	0.0368

[1] Delta CR = Difference of rates of patients showing complete response (CR Palonosetron - CR Ondansetron).
[2] H_0 is rejected if p-value <0.025.
Note: Delta CR per strata is presented in order to provide details of computation.

Source: Sponsor's Clinical Study Report Study PALO-10-14, Table 19 (Module 5.3)

Additionally, there were 3 co-primary efficacy analyses and 6 supportive sensitivity analyses performed with the same endpoint. The 3 co-primary analyses support the conclusions of the primary analysis.

1. A stratum adjusted Mantel-Haenszel method was performed on the As-Treated population. Since the As Treated population was the same as the FAS, the results are the same as the primary analysis.
2. A stratum adjusted Miettinen and Nurminen method was performed on the FAS population with a p-value of 0.0718 (H_0 rejected if p-value <0.05).
3. A stratum adjusted Miettinen and Nurminen was performed on the As-Treated population. Since the As Treated population was the same as the FAS, the results are the same as the second co-primary analysis.

The 6 supportive sensitivity analyses also support the conclusions of the primary analysis. Table 9 provides the results fo the 6 sensitivity analyses.

Table 9: Sensitivity Analyses for Complete Response by Treatment in PALO-10-14

Complete Response 0-24hrs	
Stratum Adjusted Mantel-Haenszel (PP)	
Overall Weighted Sum of Delta CR 95% CI of the Weighted Sum of Delta CR	-4.6% [-10.7%; 1.5%]
Stratum Adjusted Miettinen and Nurminen (Iteration 4)(PP)	
Overall Chi^2	3.1199
Overall P-value	0.0773
11th Method Newcombe (FAS)	
Overall Delta CR 95% CI of Delta CR	-4.5% [-10.7%; 1.8%]
Unconditional Exact Confidence Interval (FAS)	
Overall Delta CR 95% CI of Delta CR	-4.5% [-12.1%; 3.1%]
Stratum Adjusted Mantel-Haenszel (MFAS for sensitivity)	
Overall Weighted Sum of Delta CR 95% CI of the Weighted Sum of Delta CR	-4.0% [-10.1%; 2.2%]
Stratum Adjusted Miettinen and Nurminen (Iteration 3) (MFAS for sensitivity)	
Overall Chi^2	3.7716
Overall P-value	0.0521

Note: Delta CR = Difference of rates of patients showing complete response (CR Palonosetron - CR Ondansetron).

Source: Sponsor's Clinical Study Report Study PALO-10-14, Table 21 (Module 5.3)

The 3 co-primary efficacy analyses and 6 supportive sensitivity analyses are all consistent with the findings of the primary analysis and support the validity of primary analysis.

6.1.5 Analysis of Secondary Endpoints(s)

There were four secondary endpoints specified in the FDA WR:

- No vomiting from 0-24 hours
- Use of antiemetic rescue medication
- Time to rescue
- Time to first vomiting episode

No vomiting from 0-24 hours-The proportion of treated patients with no vomiting from 0-24 hours was 83.1% in the palonosetron group and 87.6% in the ondansetron group. Treatment effects were consistent across all age groups. The stratum adjusted Mantel

Haenszel analysis of the proportion of patients with no vomiting from 0-24 hours showed the difference between treatments was -4.5% (-9.9%, 1.0%).

Use of antiemetic rescue medication- The proportion of treated patients without use of antiemetic rescue medication was 93.1% in the palonosetron group and 96.4% in the ondansetron group. Treatment effects were consistent across all age groups. The stratum adjusted Mantel Haenszel analysis of the proportion of patients without use of antiemetic rescue medication showed the difference between treatments was -3.3% (-6.8%, 0.3%).

Time to rescue- The proportion of patients administered rescue medications was 6.9% in the palonosetron group and 3.6% in the ondansetron group. Because of the low rates of administration of rescue medications, a meaningful Kaplan-Meier analysis of time to rescue could not be performed.

Time to first vomiting- The proportion of patients with vomiting was 16.9% in the palonosetron group and 12.4% in the ondansetron group. The Kaplan-Meier curves showed an initial separation at 1 hour and then a consistent separation after 4 hours with a lower probability of vomiting in the ondansetron group. The Cox Hazard Ratio stratified by age stratum for the time to first vomiting was 1.407 (0.941, 2.106).

6.1.6 Other Endpoints

The Sponsor analyzed the following additional secondary endpoints:

- Proportion of patients with no emetic episodes
- Proportion of patients without nausea
- Time to treatment failure
- Time to first emetic episode

Proportion of patients with no emetic episodes- The proportion of treated patients with no emetic episodes was 80.1% in the palonosetron group and 83.9% in the ondansetron group. The stratum adjusted Mantel Haenszel analysis of the proportion of patients with no emetic episodes showed the difference between treatments was -3.9% (-9.8%, 2.1%).

Proportion of patients without nausea- The proportion of treated patients without nausea was 83.2% in the palonosetron group and 82.0% in the ondansetron group. The stratum adjusted Mantel Haenszel analysis of the proportion of patients without nausea showed the difference between treatments was 1.3% (-6.5%, 9.1%).

Time to treatment failure- Treatment failure was defined as time to first emetic episode or time to first administration of rescue medication, whichever occurred first. The proportion of patients with treatment failure was 21.8% in the palonosetron group and

17.3% in the ondansetron group. The Kaplan-Meier curves showed a consistent separation after 5 hours with a lower probability of failure in the ondansetron group. The Cox Hazard Ratio stratified by age stratum for the time to treatment failure was 1.284 (0.907, 1.817).

Time to first emetic episode- The proportion of patients with at least one episode of emesis was 19.9% in the palonosetron group and 16.1% in the ondansetron group. The Kaplan-Meier curves showed an initial separation at 2 hours and a consistent separation after 5 hours with a lower probability of failure in the ondansetron group. The Cox Hazard Ratio stratified by age stratum for the time to first emetic episode was 1.226 (0.882, 1.818).

6.1.7 Subpopulations

Age: All efficacy analyses were presented overall and by age group. In general, ondansetron performed better than palonosetron across age groups. Although there was a slightly better response to palonosetron in the age 2 to <6 years, the difference was small and does not appear to be clinically meaningful.

Gender: Men showed higher rates of CR than women across treatment groups (Table 10). Ondansetron performed better than palonosetron regardless of gender.

Table 10: Complete Response Rates by Gender in PALO-10-14

Gender	Palonosetron1 mcg/kg (N=331) % CR	Ondansetron 0.1 mg/kg (N=330) % CR
Men	80.9%	85.1%
Women	74.2%	79.1%

Source: Clinical reviewer's analysis of ISS data. Module 5.3.5.3

Race/Ethnicity: The study population was 94.9% White and 7% Hispanic. The homogeneity of the population does not allow for meaningful interpretation of the efficacy data by race and ethnicity.

Geographic Region: Table 11 shows CR rates by country. The Czech Republic and the US had the largest difference in CR rates between the palonosetron and ondansetron treatment groups was in Czech Republic and USA. The sample size was small in the Czech Republic so it is difficult to interpret the significance of these findings. In US, the discrepancy appears to come from a single site that enrolled 65 subjects and had a CR rate of 51.6% in palonosetron and 64.7% in ondansetron.

CR rates were markedly higher in Russia and Ukraine and lower in Czech Republic than in other countries. In general, ondansetron performed better palonosetron in most

countries so it is unlikely that these discrepancies in country reporting rates significantly influenced the results of the study.

Table 11: Complete Response Rates by Country in PALO-10-14

Country	Palonosetron1 mcg/kg (N=331) % CR	Ondansetron 0.1 mg/kg (N=330) %CR
Argentina (n=13)	71.4%	83.3%
Czech Republic (n=20)	42.9%	61.5%
Hungary (n=119)	82.1%	79.4%
Poland (n=54)	75.0%	76.9%
Russia (n=70)	91.7%	91.3%
Ukraine (n=125)	94.9%	97.0%
US (n=160)	62.9%	74.6%

Source: Clinical reviewer's analysis of ISS data. Module 5.3.5.3

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Efficacy was not proven in the pediatric population for PONV; therefore, there are no dosing recommendations.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This study tested a single dose of study drug and efficacy was not proven. Persistence of efficacy or tolerance effects cannot be determined in this study.

6.1.10 Additional Efficacy Issues/Analyses

Although the use of intra- and peri-operative medications was generally well balanced across the treatment groups, a request was sent to the Sponsor to perform additional exploratory analyses of the effect of concomitant medications on the primary endpoint of CR at 0-24 hours. The Sponsor identified agents that were active in the CNS and therefore, reasonably likely to affect CR rates, and that also showed a >3.5% difference in use between the treatment arms. A table of the intra- and peri-operative medications is provided in Appendix 4, Section 9.4.4.

Based on these criteria, the Sponsor identified the following medications:

- Halogenated hydrocarbons with 254/331 (76.7%) and 239/330 (72.4%) patients in the palonosetron and ondansetron arms, respectively (difference 4.3%).
- Benzodiazepine derivatives: 242/331 (73.1%) and 218/330 (66.1%) patients in the palonosetron and ondansetron arm (difference 7.0%).
- Natural opium alkaloids: 34/331 (10.3%) and 22/330 (6.7%) patients in the palonosetron and ondansetron arms (difference 3.6%).

The Sponsor then identified rates of CR for each of the medications in Table 12.

Table 12: Complete Response rates for selected intra- and peri-operative medications in PALO-10-14

	Complete Response 0 to 24 Hours	
	Palonosetron 1 mcg/kg n/N (%)	Ondansetron 0.1 mg/kg n/N (%)
Overall population (FAS)	259/331 (78.2%)	273/330 (82.7%)
Halogenated hydrocarbons	191/254 (75.2%)	188/239 (78.7%)
Benzodiazepine derivatives	185/242 (76.4%)	168/218 (77.1%)
Natural opium alkaloids	19/34 (55.9%)	15/22 (68.2%)

Source: Sponsor's IND Addendum, Annex 2

CR rates for halogenated hydrocarbons and benzodiazepine derivatives were slightly lower but generally comparable to the overall population. CR rates for patients who received natural opium alkaloids were lower for both treatment groups than the overall population. CR rates were also lower for the palonosetron group that had a greater number of patients exposed to natural opium alkaloids than in ondansetron. An analysis of subjects who were non-responders showed that there were 15/72 patients (20.8%) in the palonosetron arm and 7/57 (12.3%) in the ondansetron arm that were administered natural opium alkaloids and were non-responders.

The Sponsor performed the primary efficacy analysis excluding all subjects who received natural opium alkaloids. These results are provided in Table 13. In this post-hoc analysis, the difference between treatments was -2.9% (-9.1%, 3.3%). The lower limit of the confidence interval was within the 10% non-inferiority margin and supported the non-inferiority of palonosetron to ondansetron.

Table 13: Post-hoc efficacy analysis excluding patients who received natural opium alkaloids in PALO-10-14

Complete response 0-24 hrs Stratum Adjusted Mantel-Haenszel (N=605)		
<2 years stratum	Delta CR	-11.7%
2 to <6 years stratum	Delta CR	1.8%
6 to <12 years stratum	Delta CR	-5.1%
12 to <17 years stratum	Delta CR	-4.7%
Overall	**Weighted Sum of Delta CR**	**-2.9%**
	95% CI of the Weighted Sum of Delta CR	[-9.1%; 3.3%]

Delta CR = Difference of rates of patients showing complete response (CR Palonosetron - CR Ondansetron)

Source: Sponsor's Addendum, Annex 4

This is a post-hoc exploratory analysis of the effect of selected concomitant medications on CR rates. While the findings of this analysis are interesting and it is certainly possible that the administration of natural opium alkaloids contributed to the negative study, it is likely not the only factor. The small sample size and the highly selective nature of this analysis make it difficult to interpret. However, it is worth considering the use of natural opium alkaloids in the design of future studies of PONV.

7 Review of Safety

Safety Summary

Aloxi has been available for the use in adults for CINV since 2003 and for PONV since 2008. The safety profile of the drug for PONV in the pediatric trials was generally similar to the safety profile in adults that is currently in the drug label.

Safety analyses were performed on an integrated safety database that included data from 811 patients pooled from two pediatric PONV studies PALO-07-29 (n=150) and PALO-10-14 (n=661). The safety population included all randomized patients who received study drug (PALO-07-29) and had at least one post-study drug safety assessment (PALO-10-14). It should be noted that there was a marked difference in adverse event (AE) reporting rates between the PALO-07-29 (AE reporting rate of 40.7%) and PALO-10-14 studies (AE reporting rate of 70.0%). To minimize the disparities in the adverse event reporting rates, the studies were pooled together to form an integrated safety database for analysis.

There were no deaths during the study. All reported serious adverse events (SAEs) and severe AEs appeared to be related to the surgical procedure and were not assessed as causally related to the study drug. There were no drop-outs in the palonosetron group

due to AEs. 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).

The most common treatment-emergent adverse events (TEAEs) were related to the surgical procedure, such as procedural pain, oropharyngeal pain, and pyrexia. Of TEAEs that were assessed as causally related to palonosetron, the most common were QT prolongation on ECG (6/481 (1.3%)), t wave inversion on ECG (2/481 (0.4%)) and headache (2/481 (0.4%)). The drug-related TEAEs are comparable between the palonosetron 1mcg/kg and ondansetron groups. All drug-related TEAEs occurred at a low incidence rate of <2% and are generally consistent with the adverse drug reactions in the current Aloxi label for PONV in the adult population. No new safety signals were identified. With respect to adverse events (AEs), there was no clear or consistent dose-response trend or trend in specific subgroups such as age, gender, or race/ethnicity.

The effects of palonosetron on cardiac conduction were previously studied in an adult thorough QT study. There was no significant effect of palonosetron on the QT interval detected in that study. Given that the heart rate (HR) increase and QT prolongation may be associated with the surgery or medications given intra-operatively, the ECG changes seen in these studies do not appear to be clinically significant.

In summary, review of the safety database from the pediatric PONV studies demonstrated no clear safety signals. The safety profile was generally consistent with that of the adult PONV safety profile in the current Aloxi label.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety analysis was performed on data from two studies for PONV in the pediatric population, PALO-07-29 and PALO-10-14. The safety population included all randomized patients who received study drug (PALO-07-29) and had at least one post-study drug safety assessment (PALO-10-14). Section 5 contains a detailed description of studies PALO-07-29 and PALO-10-14. It should be noted that there was no placebo control group in these studies; however, PALO-10-14 included an active comparator arm.

7.1.2 Categorization of Adverse Events

The Sponsor defined an adverse event (AE) as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. The AE

could be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

A treatment emergent adverse event (TEAE) was defined as an adverse event that starts or worsens in intensity after the start of the administration of the study drug (or on the same day if the start time of the adverse event is not available) and before Day 15 for a non-serious adverse event or before Day 30 for an SAE.

Signs and symptoms considered as lack of efficacy (nausea and vomiting) occurring up to 24 hours (in Study PALO-10-14) or up to 72 hours (in PALO-07-29) in the postoperative observation period were not considered as an AE, unless in the Investigator's opinion the sign or symptom was to be considered as an AE.

Serious adverse events were defined as any events, whether or not considered drug-related that result in the following outcomes:

- Death
- Life-threatening event, including any AE during which the subject is, in the view of the Investigator, at immediate risk of death from the event as it occurs. This definition does not include events that may cause death if they had occurred in a more severe form.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability or incapacity.
- A congenital anomaly or birth defect.
- Other medical events that based upon appropriate medical judgment were thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining a Serious Adverse Event.

The investigator categorized AEs as mild, moderate or severe in intensity. Relationship to study drug was assessed as definite, probable, possible, unlikely, not related or unassessable.

Adverse events were coded using the MedDRA dictionary (version 14.0). The coding of verbatim terms was reviewed and felt to be adequate; therefore, the Sponsor's coding is used for the safety analyses in this clinical review.

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

The integrated safety database included data from 811 patients pooled from two pediatric PONV studies PALO-07-29 (n=150) and PALO-10-14 (n=661). Study PALO-07-29 had two arms for palonosetron of 1mcg/kg (n=74) and 3mcg/kg (n=76) with no placebo or active comparator arms. Study PALO-10-14 had a 1mcg/kg palonosetron arm (n=331) and an active comparator arm receiving 0.1mg/kg ondansetron (n=330).

Therefore, the palonosetron 1mcg/kg group includes subjects from both PALO-07-29 and PALO-10-14 while the palonosetron 3mcg/kg group includes subjects only from PALO-07-29.

There was a marked difference in adverse event reporting rates between the PALO-07-29 and PALO-10-14 studies. In PALO-07-29, a total of 92 TEAEs were experienced by 61 (40.7%) patients: 38 events occurred in 29 out of 74 (39.2%) patients in the palonosetron 1 mcg/kg group and 54 events occurred in 32 out of 76 (42.1%) patients in the palonosetron 3 mcg/kg group. In PALO-10-14, 736 adverse events were reported by 463 (70.0%) patients. There were 344 adverse events reported by 235 (71.0%) patients in the palonosetron 1mcg/kg group and 392 events were reported by 228 (69.1%) patients. To minimize the disparities in the adverse event reporting rates, the studies are being pooled together to form an integrated safety database for analysis.

7.2 Adequacy of Safety Assessments

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

A total of 481 pediatric patients were exposed to a single dose of palonosetron in studies PALO-07-29 and PALO-10-14. There were 405 subjects exposed to 1mcg/kg up to a maximum dose of 0.075 mg and 76 subjects exposed to 3mcg/kg up to a maximum of 0.25 mg.

The demographics of the pediatric subjects exposed to palonosetron are summarized in Table 14 below. Most subjects were between the ages of 2-12 years and few subjects were <2 years of age. There were more males than females, although this was evenly distributed across the treatment groups. The subjects were predominantly white and not Hispanic. Ethnicity was not collected in study PALO-07-29. Ukraine contributed the largest number of subjects to the studies. The potential impact of demographic discrepancies on the safety profile are discussed in Section 7.5.3 below.

Table 14: Demographics of the safety population from the ISS

	Palonosetron 1 mcg/kg (N=405) n(%)	Palonosetron 3 mcg/kg (N=76) n(%)	Palonosetron all doses (N=481) n(%)	Ondansetron 0.1 mg/kg (N=330) n(%)
Age				
< 2 years	25 (6.2)	4 (5.3)	29 (6.0)	24 (7.3)
2 to < 6 years	141 (34.8)	17 (22.4)	158 (32.8)	123 (37.3)
6 to < 12 years	146 (36.0)	33 (43.4)	179 (37.2)	117 (35.5)
12 to < 18 years	93 (23.0)	22 (28.9)	115 (23.9)	66 (20.0)
Gender				
Male	245 (60.5)	47 (61.8)	292 (60.7)	200 (60.6)
Female	160 (39.5)	29 (38.2)	189 (39.3)	130 (39.4).
Race				
White	389 (96.0)	76 (100)	465 (96.7)	312 (94.5)
Black	13 (3.2)	0 (0)	13 (2.7)	12 (3.6)
Asian	1 (0.2)	0 (0)	1 (0.2)	1 (0.3)
American Indian Native	0 (0)	0 (0)	0 (0)	1 (0.3)
Other	2 (0.4)	0 (0)	2 (0.4)	4 (1.2)
Ethnicity				
Hispanic	24 (5.9)	0 (0)	24 (5.0)	22 (6.7)
Missing ethnicity	74 (18.2)	76 (100)	150 (31.2)	0 (0)
Country				
Argentina	7 (1.7)	0 (0)	7 (1.5)	6 (1.8)
Czech Republic	7 (1.7)	0 (0)	7 (1.5)	13 (3.9)
Hungary	117 (28.9)	0 (0)	117 (24.3)	102 (30.9)
Poland	28 (6.9)	0 (0)	28 (5.8)	26 (7.9)
Russia	51 (12.6)	26 (34.2)	77 (16.0)	46 (13.9)
Ukraine	106 (26.2)	50 (65.8)	156 (32.4)	66 (20.0)
USA	89 (22.0)	0 (0)	89 (18.5)	71 (21.5)

Source: Clinical reviewer's analysis of ISS data. Module 5.3.5.3

7.2.2 Explorations for Dose Response

Dose response for PONV in the pediatric population was assessed in the proof-of-concept dose-finding study PALO-07-29. The study compared the efficacy and safety of palonosetron at doses of 1mcg/kg and 3mcg/kg. Efficacy and safety were found to be comparable between the two dose groups and no dose response was observed.

7.2.3 Special Animal and/or In Vitro Testing

There was no special animal or In Vitro Testing submitted for this supplemental NDA application.

7.2.4 Routine Clinical Testing

The clinical testing in PALO-07-29 and PALO-10-14 appeared adequate to assess safety. Safety assessments included physical examination, vital sign measurements, 12-lead ECG evaluations, clinical laboratory tests (hematology, blood chemistry, and urinalysis) and evaluation of adverse events. The timing of the clinical assessments was specified in each study protocol. Additional details of the clinical testing are provided in Section 5.

7.2.5 Metabolic, Clearance, and Interaction Workup

There were no additional metabolic, clearance or interaction workups submitted for this application.

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

Labels for $5HT_3$ antagonists identify hypersensitivity reactions, QT prolongation and masking of ileus/distention as potential adverse events for this drug class. Hypersensitivity reactions and masking of ileus/distention are included in the label for Aloxi. Aloxi has previously performed a thorough QT study and found no evidence of QT prolongation and this warning was removed from the label for Aloxi. The Sponsor provided adequate safety monitoring and there were no new or unexpected events identified for $5HT_3$ antagonists in the PONV clinical trials.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths during the studies or in the 30 day period following study drug administration. .

7.3.2 Nonfatal Serious Adverse Events

There were no SAEs reported in study 07-29; therefore, there are no SAEs reported in the palonosetron 3 mcg/kg group. All SAEs were reported in the Palonosetron 1 mcg/kg and ondansetron groups. There were 15 subjects who reported a total of 31 SAEs. Of these, 30 were considered treatment-emergent SAEs. There were 4 subjects in the palonosetron 1mcg/kg group and 11 subjects in the ondansetron 0.1 mcg/kg group who experienced SAEs. There were no subjects who discontinued from the study due to

SAEs. The narratives and CRFs for the subjects who experienced SAEs were reviewed and the SAEs appeared to be related to the surgical procedures and not to the study drug. The SAEs are described in Table 15 below.

Table 15: Serious Adverse Events listing from ISS

Subject	Age (years)	Sex	Treatment	Study Day	Preferred Term	Disposition
1002	6.5	F	Palonosetron	1	Abdominal pain	Hospitalized/Recovered
				-1	Neutrophil count increased	Hospitalization/Recovered
				8	Pulpitis dental	Tooth extraction/Recovered
				2	Pyrexia	Hospitalized/Recovered
				3	Urinary tract infection	Hospitalized/Recovered
				1	Vomiting	Hospitalized/Recovered
1635	5.3	F	Palonosetron	7	Post procedural haemorrhage	Surgery/Recovered
1655	0.7	F	Palonosetron	5	Apnoea	Hospitalized/Recovered
				6	Dehydration	Hospitalized/Recovered
				9	Gastroenteritis viral	Hospitalized/Recovered
1692	0.3	M	Palonosetron	8	Hernial eventration	Surgery/Recovered
				1	Ileus	Surgery/Recovered
1022	16.6	F	Ondansetron	8	Post procedural haemorrhage	Hospitalized/Recovered
1048	4.4	M	Ondansetron	1	Palatal oedema	Hospitalized/Recovered
				1	Post procedural haemorrhage	Hospitalized/Recovered
1068	14.1	F	Ondansetron	8	Haemoptysis	Hospitalized/Recovered
				8	Wound haemorrhage	Hospitalized/Recovered
1074	6	F	Ondansetron	1	Post procedural haemorrhage	Surgery/Recovered
1102	4.1	F	Ondansetron	3	Post procedural haemorrhage	Hospitalized/Recovered
1143	6	M	Ondansetron	3	Dehydration	Hospitalized/Recovered
				3	Hypovolaemia	Hospitalized/Recovered
1232	7	M	Ondansetron	11	Nausea	Action not reported/Recovered
				11	Post procedural haemorrhage	Hospitalized/Recovered
				11	Post procedural haemorrhage	Hospitalized/Recovered
1234	7.2	M	Ondansetron	12	Bronchitis	Hospitalized/Recovered
1335	12.4	F	Ondansetron	7	Circulatory collapse	Hospitalized/Recovered
				2	Dehydration	Action not reported/Recovered
				14	Dehydration	Hospitalized/Recovered
				2	Vomiting	Hospitalized/Recovered
1619	1.4	F	Ondansetron	10	Glioma	Hospitalized/Recovered
1707	13.9	M	Ondansetron	12	Ureteric anastomosis complication	Surgery/Recovered with Sequelae

Source: Clinical reviewer's analysis of ISS data and CRF. Modules 5.3.5.3 and 5.3.5.1.

7.3.3 Dropouts and/or Discontinuations

Of the 881 patients who received study drug, there were 6 (0.7%) subjects who did not complete the study. The majority were lost to follow-up. One patient (Subject ID 1130) in the ondansetron group was discontinued due to an adverse event of "hepatic enzyme increased." The subject had elevated liver enzymes at baseline prior to study drug administration and was transferred to another hospital for a pre-planned liver biopsy. There was no worsening of the patient's condition reported and the transfer reportedly occurred for logistical reasons. There did not appear to be a relationship between the study drug and drop-outs. A summary of the reasons for premature termination are outlined in Table 16 below.

Table 16: Reasons for premature termination

	Palonosetron 1mcg/kg (N=405) n (%)	**Palonosetron 3mcg/kg (N=76) n (%)**	**Palonosetron ALL (N=481) n (%)**	**Ondansetron 0.1 mg/kg (N=330) n (%)**
Adverse Event	0 (0)	0 (0)	0 (0)	1 (0.3)
Lack of Efficacy	0 (0)	0 (0)	0 (0)	0 (0)
Withdrawal of consent	1 (0.2)	0 (0)	1 (0.2)	0 (0)
Lost to follow-up	4 (1.0)	0 (0)	4 (0.8)	0 (0)
Total Drop-outs	5 (1.2)	0 (0)	5 (1.0)	1 (0.3)

Source: Clinical reviewer's analysis of ISS data. Module 5.3.5.3.

7.3.4 Significant Adverse Events

Twelve severe adverse events occurred in 10 patients (Table 17). There were no severe adverse events in study PALO-07-29; therefore, all severe adverse events occurred in study PALO-10-14. There were 3 severe AEs in the palonosetron 1mcg/kg group and 9 severe AEs in the ondansetron 0.1mcg/kg group. All severe AEs appear to be related to the surgical procedure and not to the study drug.

Table 17: Listing of Severe Adverse Events from ISS

Severe Adverse Event	Palonosetron 1 mcg/kg (N=405) n	Ondansetron 0.1mg/kg (N=330) n
Bronchitis	0	2
Dehydration	0	1
Hernial eventration	1	0
Ileus	1	0
Laryngotracheal oedema	1	0
Nausea	0	1
Neutrophil count decreased	0	1
Palatal oedema	0	1
Post procedural haemorrhage	0	1
Procedural pain	0	1
Ureteric anastomosis complication	0	1
Total	3	9

Source: Clinical reviewer's analysis of ISS data. Module 5.3.5.3

7.3.5 Submission Specific Primary Safety Concerns

The FDA WR noted that palonosetron undergoes renal and hepatic elimination and requested careful monitoring for infusion reactions. Routine clinical laboratories included renal and liver function testing. There were no infusion reactions reported as adverse events in either pediatric PONV study. Monitoring for these safety concerns appeared to be adequate.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Patients were to be monitored for the occurrence of AEs by a member of the clinical staff during the administration of the study drug and anesthetic agents until patients were discharged to the ward after the surgery. At each subsequent visit and during follow up telephone contact, patients were to be questioned about the occurrence of new AEs and about the outcome of any AEs recorded previously. This monitoring is consistent with standard AE collection procedures and appears to be adequate.

As previously described in Section 7.1.3, there was a difference in AE reporting rates between the PALO-07-29 and PALO-10-14 studies. In PALO-07-29, a total of 92 TEAEs were experienced by 61 (40.7%) patients. In PALO-10-14, 736 adverse events were reported by 463 (70.0%) patients. A summary of AE incidence rates for each study are described in Table 18 below.

Table 18: Incidence of Adverse Events in each pediatric PONV study

PALO-07-29	**Palonosetron 1 mcg/kg (N=74) n (%)**	**Palonosetron 3 mcg/kg (N=76) n (%)**
At least one TEAE	29 (39.2)	32 (42.1)
At least one drug-related TEAE	0 (0)	0 (0)
At least one serious TEAE	0 (0)	0 (0)
At least one severe TEAE	0 (0)	0 (0)
Deaths	0 (0)	0 (0)
PALO-10-14	**Palonosetron 1 mcg/kg (n=331)**	**Ondansetron 0.1 mg/kg (n=330)**
At least one TEAE	235 (71.0)	228 (69.1)
At least one drug-related TEAE	16 (4.8)	15 (4.5)
At least one serious TEAE	4 (1.2)	11 (3.3)
At least one severe TEAE	2 (0.6)	8 (2.4)
Deaths	0 (0)	0 (0)

Source: Clinical reviewer's analysis of individual study data. Module 5.3.5.1.

Of the 811 subjects treated with study drug in the two PONV studies, there were 524 (64.6%) patients who experienced 829 adverse events. Table 19 provides a summary of the AE incidence across the pooled safety dataset. There appears to be a lower AE rate in the palonosetron 3mcg/kg dose group; however, all subjects in this dose group came from PALO-07-29 that had a lower AE event rate reported overall. The AE incidence is generally comparable between the palonosetron 1mcg/kg and ondansetron 0.1 mg/kg groups.

Table 19: AE incidence rate in ISS

	Palonosetron 1 mcg/kg (N=405) n (%) E*	**Palonosetron 3 mcg/kg (N=76) n (%) E**	**Palonosetron all doses (N=481) n (%) E**	**Ondansetron 0.1 mg/kg (N=330) n (%) E**
At least one TEAE	264 (65.2) 382	32 (42.1) 54	296 (61.5) 436	228 (69.1) 393
At least one drug-related TEAE	16 (4.0) 20	0	16 (3.3) 20	15 (4.5) 18
At least one serious TEAE	4 (1.0) 11	0 (0.0) 0	4 (0.8) 11	11 (3.3) 19
At least one drug-related serious TEAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
At least one severe TEAE	2 (0.5) 3	0 (0.0) 0	2 (0.4) 3	8 (2.4) 9
Withdrawn due to TEAE	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
Deaths	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0

*n=number of patients with ADs, E=number of AEs
Source: Clinical reviewer's analysis of ISS data. Module 5.3.5.3

Common Adverse Events. Table 20 provides the most common adverse events reported in ≥1% of subjects receiving palonosetron across the two studies. Most adverse events appeared to be related to the surgical procedure. There were a few AEs that were reported more commonly in the palonosetron 3mc/kg group than the palonosetron 1 mcg/kg group or the ondansetron group (vomiting, rhinalgia, asthenia, and nausea), but the significance of this is difficult to interpret given the much smaller sample size in this group. AE rates in the palonosetron 1 mcg/kg group and in the combined palonosetron groups were generally comparable to the ondansetron group.

Table 20: Common Adverse Events in ≥1% of all subjects exposed to palonosetron

	Palonosetron 1mcg/kg (N=405) n (%)	Palonosetron 3mcg/kg (N=76) n (%)	Palonosetron ALL (N=481) n (%)	Ondansetron 0.1 mg/kg (N=330) n (%)
Procedural pain	167 (41)	19 (25)	186 (39)	123 (37)
Oropharyngeal pain	32 (7.9)	2 (2.6)	34 (7.1)	37 (11)
Pyrexia	23 (5.7)	2 (2.6)	25 (5.2)	25 (7.6)
Pain	15 (3.7)	0 (0)	15 (3.1)	15 (4.5)
Vomiting	6 (1.5)	5 (6.6)	11 (2.3)	10 (3)
Cough	7 (1.7)	0 (0)	7 (1.5)	5 (1.5)
Scar	7 (1.7)	0 (0)	7 (1.5)	4 (1.2)
Rhinalgia	3 (0.7)	4 (5.3)	7 (1.5)	4 (1.2)
Abdominal pain	6 (1.5)	0 (0)	6 (1.2)	4 (1.2)
Ear pain	6 (1.5)	0 (0)	6(1.2)	9 (2.7)
Electrocardiogram QT prolonged	6 (1.5)	0 (0)	6 (1.2)	5 (1.5)
Headache	5 (1.2)	0 (0)	5 (1)	10 (3)
Asthenia	2 (0.5)	3 (3.9)	5 (1)	2 (0.6)
Nausea	1 (0.2)	4 (5.3)	5 (1)	5 (1.5)

Source: Clinical reviewer's analysis of ISS data. Module 5.3.5.3

Sponsor-assessed causality. In PALO-07-29, there were no AEs that were assessed as related to study drug. Therefore, all drug-related AEs are from study PALO-10-14. The drug-related TEAEs are comparable between the palonosetron 1mcg/kg and ondansetron groups (Table 21). All drug-related TEAEs occurred at a low incidence rate of <2% and are generally consistent with the ADRs in the current Aloxi label for PONV in the adult population. No new safety signals were identified.

Table 21: Drug-related TEAEs occurring in > 1 patient across dose groups

	Palonosetron 1mcg/kg (N=405) n (%)	Palonosetron 3mcg/kg (N=76) n (%)	Palonosetron ALL (N=481) n (%)	Ondansetron 0.1 mg/kg (N=330) n (%)
Electrocardiogram QT prolonged	6 (1.5)	0 (0)	6 (1.3)	5 (1.5)
Electrocardiogram T wave inversion	2 (0.5)	0 (0)	2 (0.4)	2 (0.6)
Headache	2 (0.5)	0 (0)	2 (0.4)	3 (0.9)
Abdominal pain	1 (0.3)	0 (0)	1 (0.2)	2 (0.6)
Vomiting	1 (0.3)	0 (0)	1 (0.2)	1 (0.3)

Source: Clinical reviewer's analysis of ISS data. Module 5.3.5.3

7.4.2 Laboratory Findings

Routine hematology and chemistry evaluations and urinalysis were performed at screening and at the final study visit (Study days 7-10). Lab values were reviewed in aggregate using summary statistics and shifts from baseline. Although there were isolated lab abnormalities, no trends were identified. Clinically significant outliers were reported as AEs.

Patients received only a single dose of study drug and significant changes in labs are not expected. Interpretation of lab changes are limited by physiologic shifts that may occur in the peri-operative period as a result of the procedure and the administration of IV fluids and concomitant medications that may be given during that time.

7.4.3 Vital Signs

Vital signs measurements (pulse rate, systolic blood pressure, and diastolic blood pressure) were measured at the screening, Study Day 1, and at the final visit. Vital signs were reviewed in aggregate using summary statistics and shifts from baseline. Although there were isolated vital sign abnormalities, no trends were identified. Clinically significant outliers were reported as AEs.

As patients received only a single dose of study drug, significant changes in vital signs are not expected. Interpretation of vital signs are limited by physiologic changes that may occur in the peri-operative period with post-procedural pain and administration of concomitant medications.

7.4.4 Electrocardiograms (ECGs)

A 12-lead ECG in triplicate was performed at screening, within 3 to 6 hours after study drug administration on Day 1, and at the final study visit (PALO-10-14 only). ECGs were evaluated by a central blinded cardiologist.

QT prolongation was reported as AEs in both palonosetron and ondansetron groups but rates were comparable between the two groups. The most common ECG abnormalities that occurred in >2% of all patients are summarized in Table 22 below. These abnormalities occurred across treatment groups and there was a lower frequency in the palonosetron groups than the ondansetron treatment groups.

Table 22: ECG Abnormalities occurring in >2% of treated patients

ECG Abnormality	Palonosetron 1mcg/kg (N=405) n (%)	Palonosetron 3mcg/kg (N=76) n (%)	Palonosetron ALL (N=481) n (%)	Ondansetron 0.1 mg/kg (N=330) n (%)
HR increase ≥ 25% from baseline and HR>100 beat/min	44 (10.9)	5 (6.6)	49 (10.2)	48 (14.5)
QTcB post-baseline value >450msec and baseline values ≤ 450msec	45 (11.1)	4 (5.3)	49 (10.2)	40 (12.1)
QTcB change from baseline >30 and ≤60 msec	30 (7.4)	0 (0)	30 (6.2)	33 (10)
QTcF change from baseline >60 msec	10 (2.5)	1 (1.3)	11 (2.3)	15 (4.5)

Adapted from Sponsor's ISS Tables 2.36A and 2.36B; Module 5.3.5.3

The effects of palonosetron on cardiac conduction were previously studied in an adult thorough QT study, PALO-03-11. There was no significant effect of palonosetron on the QT interval detected in that study. Given that the heart rate (HR) increase and QT prolongation may be associated with the surgery or medications given intra-operatively, the ECG changes seen in the PONV studies do not appear to be clinically significant.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies performed.

7.4.6 Immunogenicity

There were no immunogenicity measures in this study.

7.5 Other Safety Explorations

None.

7.5.1 Dose Dependency for Adverse Events

There were 405 subjects exposed to a single dose of palonosetron 1mcg/kg and 76 subjects exposed to 3mcg/kg. There were a few AEs that were reported more commonly in the palonosetron 3mc/kg group than the palonosetron 1 mcg/kg group or the ondansetron group (vomiting, rhinalgia, asthenia, and nausea), but this is difficult to interpret given the much smaller sample size in this group. Overall, there was a lower incidence of TEAEs reported in the 3mcg/kg dose group than in the 1mcg/kg pooled dose group. However, the 3mcg/kg dose group was drawn solely from study PALO-07-29 which had a markedly lower adverse event reporting rate than study PALO-10-14. With this caveat in mind, there does not appear to be a dose dependent relationship to adverse events in the PONV studies.

7.5.2 Time Dependency for Adverse Events

The majority of AEs were reported within the first day following the administration of study drug and most appeared to be related to the surgical procedure.

7.5.3 Drug-Demographic Interactions

Age: There was no substantial difference across the age groups in overall TEAE rates for the combined palonosetron doses. In the combined palonosetron dose group, TEAEs occurred in 65.5% of patients <2 years, 63.3% of patients 2 to <6 years; 59.2% of patients 6 to <12 years; and 61.7% of patients 12 to <18 years in patients taking all doses of palonosetron. In the ondansetron group, TEAEs occurred in 54.2% of patients <2 years, 66.7% of patients 2 to <6 years; 65.8% of patients 6 to <12 years; and 84.8% of patients 12 to <18 years (Source: Table 2.4B ISS Module 5.3.5.3). With the exception of the <2 year old group, TEAE rates, SAEs, and severe AEs were lower than the ondansetron group. As there were only 53 patients <2 years of age, it is difficult to determine if this finding is clinically meaningful.

Gender: TEAEs occurred in 66.1% of women and 58.6% of men in the combined palonosetron dose group and in 74.6% of women and 65.5% of men in the ondansetron dose group (Source: Table 2.5B ISS Module 5.3.5.3). Since there was a higher rate of AEs for women in both palonosetron and ondansetron arms, this does not suggest a relationship between gender and safety with palonosetron.

Race/ethnicity: The study population was 95.8% White and ethnicity was 72.4% Non-Hispanic, 4.9% Hispanic, and 18.5% unknown (Source: Table 2.6B ISS Module 5.3.5.3).

The homogeneity of the population does not allow for meaningful interpretation of the adverse event data by race and ethnicity.

Region: Across all drug doses, there was a substantial difference in AE reporting between Russia and Ukraine and all other countries. TEAEs were reported by 50.7% of patients in Russia and Ukraine, 70% of patients in the US, 76.9% of patients in Latin America, and 77.5% of patients in Europe (Source: Table 2.7B ISS Module 5.3.5.3). This is largely accounted for by study PALO-07-29 which was conducted only in Russia and Ukraine and was previously noted in the review (Section 7.1.3) to have markedly lower AE reporting rates than study PALO-10-14. There was no marked difference in the quality or characteristic of the AEs reported between the two studies, only the frequency of the AE reporting. Therefore, it is unlikely that the safety profile differs significantly by region but merely reflects a difference between studies.

7.5.4 Drug-Disease Interactions

There are no significant drug-disease interactions.

7.5.5 Drug-Drug Interactions

No specific drug-drug interactions were assessed in this study. Palonosetron is eliminated by renal excretion and hepatic metabolism. It is not an inhibitor or inducer of the major CYP enzymes. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low.

7.6 Additional Safety Evaluations

No additional safety evaluations are indicated.

7.6.1 Human Carcinogenicity

N/A

7.6.2 Human Reproduction and Pregnancy Data

There were no pregnant or breast-feeding patients in this study. Aloxi is labelled as Category B for teratogenic effects. There have been no adequate and well-controlled studies in pregnant women.

7.6.3 Pediatrics and Assessment of Effects on Growth

Since patients only received acute administration of a single dose of palonosetron, no assessments of growth were performed in the PONV studies.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdoses occurred in the study. Palonosetron is not known to have any concerns for drug abuse potential, withdrawal and rebound.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Palonosetron received marketing authorization in the US on July 25, 2003 for CINV in adults and on Februay 29, 2008 for PONV in adults. Oral and IV formulations of Aloxi and have been approved for these indication in over 70 countries for adults only. There are currently no approved indications for the pediatric population.

The Sponsor has regularly submitted Periodic Safety Update Reports (PSUR) to the FDA and other regulatory authorities. The last Aloxi PSUR reported to the FDA is PSUR no. 16 which covered the period July 25, 2003 to July 24, 2013.

The Written Request stated that the following data should be submitted with the sNDA: "Under section 505A(d)(2)(B)of the Act, when you submit the study reports, you must submit all post-marketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient."

Additional clarification was requested by the Sponsor and the Agency provided the following Written Response on January 16, 2013: "You have submitted post-market safety data for Aloxi I.V. (0.25mg and 0.075mg) and oral (0.5mg) formulations to the Agency for the time period of 25-July-2003 through 24-July-2012. You should re-submit the pediatric reports and additional post-market safety data not represented in the current labeling." Consistent with this request, the Sponsor has provided all pediatric reports and all safety reports not currently reflected in the label.

As of the time of this submission, there are 4 non-serious post-market reports in the pediatric population (ages 7-17 years) from off-label use for CINV. These were previously reported in PSUR no. 16. There were two reports of lack of efficacy. There was one report of a pediatric patient who received an inappropriate dose of 0.75mg IV with no associated adverse effects. The fourth patient was a 17 year-old patient with B-lymphobastic lymphoma receiving recurrent chemotherapy with thiotepa and concomitant furosemide who developed hyponatremia, muscle spasm and tremor. These four reports do not appear to present any new safety signals for the use of Aloxi in the pediatric population. There were no reports of use for PONV.

There are 35 post-marketing reports in adults treated for CINV that are not currently in the Aloxi label. One report was from a literature article and the remaining cases were spontaneously reported.

The most common post-market reports related to *inappropriate schedule of drug administration* or *medication error* that occurred in Japan. There were 16 individual cases in Japan where subjects received palonosetron for two or more consecutive days, which is not consistent with the dosing regmin approved in Japan. There were no adverse events reported with these cases.

There were 8 non-serious cases with the PT *Off-label*.

- There were 7 non-serious reports of hiccups that all occurred at the same cancer center in the US. Palonosetron was administered by IV bolus instead of over a 30 second push.
- There was one case where a patient received palonosetron for CINV and experienced dissociative fugue, speech disorder, and headache.

There were four reports where there was a drug administration error or incorrect route of drug administration: intra-arterial administration, intra-muscular administration, infusion into a peritoneal port, and an intravenous injection that went paravenous. There were no adverse effects reported with these administrations.

There were 4 reports of *accidental overdose* or *incorrect dose administered* where patients received doses between 0.5mg daily and 0.75 mg bid. There was one case of *intentional drug misuse* where a patient intentionally took palonosetron with another 5HT-3 antagonist. There were no adverse events associated

There were two serious post-market reports:

- A female patient in her 50's with esophageal cancer who received an unspecified dose of palonosetron for two days and developed *increased blood pressure, heart rate increased, hyperhidrosis, unresponsive to stimuli* and *inappropriate schedule of drug administration* (serious). Concomitant medications included 5-FU, cisplatin, and dexamethasone.
- A female patient (age unknown) was treated with palonosetron experienced *nausea* and *electrocardiogram QT prolongation*, and *off-label drug use* (serious). Concomitant medications included fluconazole and arsenic trioxide.

Overall, these post-market reports for the adult and pediatric patients do not suggest any new safety signals for Aloxi.

9 Appendices

9.1 Literature Review/References

1. Rose J and Watcha M. Postoperative nausea and vomiting in paediatric patients. Br j Anaesth 1999; 83: 104-17

2. Kovac A. Management of Postoperative Nausea and Vomiting in Children. Pediatr Drugs 2007; 9: 47-69.

3. Gan TJ, Meyer T, Apfel C, et al. Consensus Guidelines for Managing Postoperative Nausea and Vomiting. Anesth Analg 2003;97:62–71.

4. Patel R, Davis P, Orr R, et al. Single dose ondansetron prevents postoperative vomiting in pediatric outpatients. Anesth Analg 1997; 85:538-45.

5. Aloxi® [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2013

9.2 Labeling Recommendations

In general, the Sponsor's proposed labelling for PONV appeared adequate with only minor changes necessary. The Sponsor is not seeking an indication for PONV in the pediatric population so information on the PONV studies is contained only in Section 8.4. This section contains a general description of the studies and safety findings.

Following are recommendations for the Sponsor-proposed label:

- The study description of PALO-07-29 should be more concise.
- A comment should be added to the PALO-07-29 description that no dose response was seen.
- In the description of PALO-10-14, the age range should be changed to >30 days to <17 years since no neonates were enrolled in the study.
- Remove the statement about analysis of opium alkaloids as this was an exploratory analysis and should not be included in the label.
- Remove rates of adverse drug reactions.

9.3 Advisory Committee Meeting

N/A

9.4 Supporting Information

9.4.1 Appendix 1. PALO-07-29 Study Procedures

Appendix 1: PALO-07-29 Study Procedures

Visit	1	2[7]	3		4	5	Follow up[11]
Timepoint (Day)	Day –7 to Day 0	1	2	3	4	7-10	15 days post dose
Assessments	Screening/ Baseline	Randomization/ Treatment/ Surgical Procedure	Control Visit		Control Visit	Final Visit	
Informed Consent	X						
Inclusion/Exclusion Criteria[1]	X	X					
Demography	X						
ASA status	X						
Medical history	X						
Prior and concomitant medication recording	X	X	X	X	X	X	X
Hematology[2]	X					X	
Serum chemistry[2]	X					X	
Urinalysis[2]	X					X	
Pregnancy test (urine)[3]	X	X					
Physical examination	X				X[10]	X	
Vital signs	X	X				X	
12-lead ECG[4]	X	X[8]					
Randomization		X					
Study drug administration[5]		X					
Surgical operation		X					
Record time of recovery (T0)		X					
Record efficacy parameters		Recording up to 72 hours after T0 at scheduled timepoint[9]					
Patient Diary	Instruction	Filled in daily up to 72 hours after T0			Collection		
Adverse event recording	X[6]	X	X	X	X	X	X
Time of earliest hospital discharge					X		

1 Eligibility criteria should be checked prior to randomization.
2 Blood samples will be sent to the central laboratory.
3 For female patients of childbearing potential prior to study drug administration.
4 12-lead ECG will be recorded in triplicate and evaluated in the central laboratory.
5 Study drug will be administered immediately (no more than 5 minutes) before the induction of general endotracheal anesthesia, or immediately after placement of IV line following an inhalation anesthesia induction.
6 Pre-treatment adverse events recording.
7 If a patient is eligible at Visit 1 and the study medication administration and the surgical procedure can be done on that day, Visit 1 and Visit 2 procedures including screening, randomization, study drug administration and surgical procedure can be accomplished on the same day.
8 Within 3 to 6 hours after study drug administration.
9 At 6, 24, 48 and 72 hours after T0.
10 Limited physical examination (i.e., cardiovascular and respiratory systems, others).
11 Follow up Visit or Telephone Contact (15 ± 3 days, if Day 15 is a holiday or a weekend day).

Source: Sponsor's Clinical Study Report for PALO-07-29, Table 9.3 (Module 5.3)

9.4.2 Appendix 2. PALO-10-14 Study Procedures

Appendix 2: PALO-10-14 Study Procedures

Visit	1	2[7]	3[10]	4	5[11]
Timepoint (Day)	-14 to -1; -7 to -1 (for patients aged <2 years	1	2	7 to 10	15 to 18
Assessments	Screening/ Baseline	Randomization/ Treatment/ Surgical Procedure	Control Visit	Final Visit	Follow-up Telephone Contact
Informed Consent / Assent	X				
Inclusion/Exclusion Criteria[1]	X	X			
Demography	X				
ASA status	X				
Medical history	X				
Prior and concomitant medication recording	X	X	X	X	X
Hematology, Serum chemistry [2]	X			X	
Urinalysis[2]	X			X	
Pregnancy test (urine)[3]	X	X			
Physical examination	X			X	
Vital signs	X			X	
Height/length measurement	X				
Weight measurement		X			
12-lead ECG[4]	X	X[8]		X	
Randomization		X			
Study drug administration[5]		X			
Surgical operation		X			
Record time of recovery (T_0)		X			
PK for neonates (0-27 days of age)[6]		X	X		
Record efficacy parameters		Recording up to 24h after T_0 (Day2)			
Patient Diary	Instruction	Fill in up to 24h after T_0 (Day 2)	Collection[12]		
Adverse event recording		X[9]	X	X	X

1 Eligibility criteria were checked prior to randomization.
2 Blood and urine samples were sent to the central laboratory.
3 For female patients who have attained menarche.
4 Triplicate 12-lead ECGs were recorded and evaluated in the central ECG reading.
5 Study drugs were administered in double dummy fashion: ondansetron/matching placebo first and palonosetron/matching placebo second immediately (no more than 5 minutes) before the induction of general intravenous anesthesia.
6 Blood samples were drawn immediately after the palonosetron/matching placebo dose, 4 hours post palonosetron/placebo dose and 24 hours post palonosetron/placebo dose.
7 If a patient was eligible at Visit 1, and the study medication administration and the surgical procedure could be done on that day, Visit 1 and Visit 2 procedures including screening, randomization, study drug administration and surgical procedure could be accomplished on the same day.
8 Within 3 to 6 hours after study drug administration.
9 Pre-treatment adverse events recording.
10 Visit 3 to be performed 24 to 27 hours after T_0.
11 Follow up Telephone Contact (15 to 18 days after study drug administration).
12 For out-patients not able to reach the site for the visit and if no study personnel could visit the patient at his/her home, for patients not included in the PK part of the study, this visit could be performed by phone. In this case the diary was to be collected during following days at the hospital, but at the latest during Visit 4 (Day 7 to 10).

Source: Sponsor's Clinical Study Report Study PALO-10-14, Table 3 (Module 5.3)

9.4.3. Appendix 3: Summary of efficacy for PALO-07-29

PALO-07-29 was a multicenter, double-blind, randomized, stratified, parallel group, phase 3 study involving 2 study groups each receiving one of two doses of palonosetron administered as a 10-second IV push immediately (within 5 minutes) before induction of general endotracheal anesthesia, or immediately after placement of IV line following an inhalation anesthesia induction (Study Day 1). The low dose was 1 mcg/kg up to a maximum of 0.075 mg, and the high dose was 3 mcg/kg up to a maximum of 0.25 mg.

PALO-07-29 was completed in 2008, 2 years prior to the issuance of the FDA WR. Age groups and the primary endpoint specified in the WR are different than those presented in the original study report. The original data was reanalyzed post-hoc according the age groups and primary endpoint specified in the FDA WR and presented as an Addendum to the original study report, as agreed upon by the FDA at the pre-sNDA meeting. The data presented in this summary are drawn from the study report Addendum and are consistent with the WR.

A total of 150 patients were enrolled across 12 sites in Russia and Ukraine. All subjects were treated and completed the study. Patient demographics are describe in Table 23 below.

Table 23: Demographics for PALO-07-29

	Palonosetron 1mcg/kg (N=75) n (%)	**Palonosetron 3mcg/kg (N=75) n (%)**	**Total (N=150) n(%)**
Age Group			
<2 years	3 (4.0)	4 (5.3)	7(4.7)
2 to <6 years	18 (24.0)	16 (21.3)	34 (22.7)
6 to <12 years	29 (38.7)	33 (44.0)	62 (41.3)
12 to <17 years	25 (33.3)	22 (29.3)	47 (31.3)
Gender			
Female	29 (38.7)	29 (38.7)	58 (38.7)
Male	46 (61.3)	46 (61.3)	92 (61.3)
Race			
White	75 (100)	75 (100)	150 (100)

Source: Adapted from Sponsor's Clinical Study Report Addendum (Module 5.3).

The study enrolled subjects aged 1 month to < 17 years. The patient population was divided into four age groups: < 2 years; 2 to < 6 years; 6 to < 12 years ; 12 to < 17 years. Most of the subjects were 6 years of age or older and there were more men than women in the study. The age and gender distributions were comparable across the

dose groups. Since the study was conducted in Russia and Ukraine where most people are Caucasian, all patients enrolled in the study were white.

The efficacy endpoint of Complete Response (defined as no vomiting, no retching, and no use of rescue medication) from 0 to 24 hours was not the pre-specified primary endpoint of the original PALO-07-29 study; however, it was a secondary endpoint. This endpoint was required as a primary efficacy endpoint in the WR and is presented here.

All statistical analyses are descriptive and no statistical tests to detect difference between treatment groups were planned. Descriptive statistics include n (number of observed values), mean, median, standard deviation (SD), minimum and maximum for continuous variable, and frequency counts and percentages for categorical variables. Baseline and demographic variables are summarized by treatment group and overall using descriptive statistics in both study sets. Subgroup analysis is performed by stratification for age and country. CR rates are presented as frequency counts and percentages together with the 95% Confidence Interval according to the Wilson method with correction of continuity and the Clopper-Pearson exact confidence interval.

Overall, the CR rate was 88.0% [78.0%-94.0%] in the palonosetron 1 mcg/kg dose group and 84% [73.3%-91.1%] in the palonosetron 3mcg/kg dose group. Complete response rates by age group are provided in Table 24. Results were comparable between treatment arms.

Table 24: Complete Response Rates in PALO-07-29

Complete Response 0-24 hours		
Full Analysis Set	Palonosetron 1 mcg/kg (N= 75)	Palonosetron 3 mcg/kg (N= 75)
Age Group		
<2 years		
Patients with CR/n (%)[1]	3/3 (100.0%)	4/4 (100.0%)
Wilson* 95% CI of CR	[31.0%-100.0%]	[39.6%-100.0%]
2 to <6 years		
Patients with CR/n (%)[1]	15/18 (83.3%)	14/16 (87.5%)
Wilson* 95% CI of CR	[57.7%-95.6%]	[60.4%-97.8%]
6 to <12 years		
Patients with CR/n (%)[1]	23/29 (79.3%)	26/33 (78.8%)
Wilson* 95% CI of CR	[59.7%-91.3%]	[60.6%-90.4%]
12 to <17 years		
Patients with CR/n (%)[1]	25/25 (100%)	19/22 (86.4%)
Wilson* 95% CI of CR	[83.4%-100.0%]	[64.0%-96.4%]
Overall		
Patients with CR/n (%)[1]	66/75 (88.0%)	63/75 (84.0%)
Wilson* 95% CI of CR	[78.0%-94.0%]	[73.3%-91.1%]

Source: Sponsor's Clinical Study Report Addendum (Module 5.3).

As there was no evidence of dose response, this study supported the selection of palonosetron 1mcg/kg in the pivotal study, PALO-10-14.

9.4.4 Appendix 4. Intra- and Peri-operative medication administered in ≥10 patients PALO-10-14

Appendix 4: Intra- and Peri-operative medication administered in ≥10 patients PALO-10-14

ATC Classification Level 1 ATC Classification Level 4	Palonosetron 1 mcg/kg (N=331) n (%) E	Ondansetron 0.1 mg/kg (N=330) n (%) E	Safety Population (N=661) n (%) E
Number of patients treated with peri- and intra-operative medication	331 (100%) 3515	330 (100%) 3453	661 (100%) 6968
Nervous system	**331 (100%) 1998**	**330 (100%) 1939**	**661 (100%) 3937**
Other general anesthetics	330 (99.7%) 647	329 (99.7%) 647	659 (99.7%) 1294
Halogenated hydrocarbons	254 (76.7%) 386	239 (72.4%) 369	493 (74.6%) 755
Benzodiazepine derivatives	242 (73.1%) 265	218 (66.1%) 246	460 (69.6%) 511
Opioid anesthetics	214 (64.7%) 311	219 (66.4%) 325	433 (65.5%) 636
Other hypnotics and sedatives	51 (15.4%) 55	57 (17.3%) 58	108 (16.3%) 113
Anilides	54 (16.3%) 57	44 (13.3%) 47	98 (14.8%) 104
Amides	50 (15.1%) 63	42 (12.7%) 56	92 (13.9%) 119
Pyrazolones	42 (12.7%) 44	40 (12.1%) 41	82 (12.4%) 85
Barbiturates, plain	38 (11.5%) 45	34 (10.3%) 41	72 (10.9%) 86
Morphinan derivatives	30 (9.1%) 30	31 (9.4%) 31	61 (9.2%) 61
Natural opium alkaloids	34 (10.3%) 36	22 (6.7%) 24	56 (8.5%) 60
Anticholinesterases	20 (6.0%) 20	16 (4.8%) 16	36 (5.4%) 36
Phenylpiperidine derivatives	20 (6.0%) 22	15 (4.5%) 17	35 (5.3%) 39
Esters of aminobenzoic acid	8 (2.4%) 8	10 (3.0%) 11	18 (2.7%) 19
Blood and blood forming organs	**278 (84.0%) 626**	**280 (84.8%) 631**	**558 (84.4%) 1257**
Salt solutions	219 (66.2%) 380	230 (69.7%) 385	449 (67.9%) 765
Solutions affecting the electrolyte balance	104 (31.4%) 105	86 (26.1%) 91	190 (28.7%) 196
Other systemic hemostatics	35 (10.6%) 36	55 (16.7%) 59	90 (13.6%) 95
Local hemostatics	37 (11.2%) 38	36 (10.9%) 36	73 (11.0%) 74
Solutions for parenteral nutrition	16 (4.8%) 16	22 (6.7%) 2	38 (5.7%) 38
Amino acids	15 (4.5%) 20	16 (4.8%) 17	31 (4.7%) 37
IV Solution additives	15 (4.5%) 18	10 (3.0%) 11	25 (3.8%) 29
Musculo-skeletal system	**244 (73.7%) 329**	**238 (72.1%) 334**	**482 (72.9%) 663**
Other quaternary ammonium compounds	167 (50.5%) 176	170 (51.5%) 179	337 (51.0%) 355
Choline derivatives	56 (16.9%) 75	57 (17.3%) 92	113 (17.1%) 167
Acetic acid derivatives and related substances	52 (15.7%) 53	48 (14.5%) 48	100 (15.1%) 101
Propionic acid derivatives	25 (7.6%) 25	14 (4.2%) 15	39 (5.9%) 40

Appendix 4 (cont)

ATC Classification Level 1 ATC Classification Level 4	Palonosetron 1 mcg/kg (N=331) n (%) E	Ondansetron 0.1 mg/kg (N=330) n (%) E	Safety Population (N=661) n (%) E
Various	**172 (52.0%) 245**	**153 (46.4%) 240**	**325 (49.2%) 485**
Medical gases	153 (46.2%) 218	146 (44.2%) 228	299 (45.2%) 446
Antidotes	17 (5.1%) 23	9 (2.7%) 9	26 (3.9%) 32
Cardiovascular system	**131 (39.6%) 141**	**139 (42.1%) 143**	**270 (40.8%) 284**
Antiarrhythmics, class I and III	98 (29.6%) 102	110 (33.3%) 112	208 (31.5%) 214
Antiarrhythmics, class IA	30 (9.1%) 31	28 (8.5%) 28	58 (8.8%) 59
Antiinfectives for systemic use	**52 (15.7%) 56**	**58 (17.6%) 59**	**110 (16.6%) 115**
First-generation cephalosporins	27 (8.2%) 28	25 (7.6%) 25	52 (7.9%) 53
Third-generation cephalosporins	5 (1.5%) 5	15 (4.5%) 15	20 (3.0%) 20
Respiratory system	**52 (15.7%) 55**	**47 (14.2%) 54**	**99 (15.0%) 109**
Antiseptics	22 (6.6%) 22	19 (5.8%) 19	41 (6.2%) 41
Sympathomimetics, plain	13 (3.9%) 14	8 (2.4%) 8	21 (3.2%) 22
Alimentary tract and metabolism	**29 (8.8%) 35**	**21 (6.4%) 27**	**50 (7.6%) 62**
Synthetic anticholinergics, quaternary ammonium compounds	16 (4.8%) 17	13 (3.9%) 14	29 (4.4%) 31
H2-receptor antagonists	11 (3.3%) 11	8 (2.4%) 8	19 (2.9%) 19
Sensory organs	**19 (5.7%) 19**	**12 (3.6%) 12**	**31 (4.7%) 31**
Systemic hormonal preparations, excl. Sex hormones	**7 (2.1%) 7**	**9 (2.7%) 9**	**16 (2.4%) 16**
Antiparasitic products, insecticides and repellent	**3 (0.9%) 3**	**1 (0.3%) 1**	**4 (0.6%) 4**
Dermatologicals	-	**4 (1.2%) 4**	**4 (0.6%) 4**
Genito urinary system and sex hormones	**1 (0.3%) 1**	-	**1 (0.2%) 1**

Source: Sponsor's Clinical Study Report for PALO-10-14, Table 15. (Module 5.3)

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/s/

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05/05/2014

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05/05/2014