22 January 2015
EMA/CHMP/138512/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aloxi

International non-proprietary name: palonosetron

Procedure No. EMEA/H/C/000563/II/0038

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

© European Medicines Agency, 2015. Reproduction is authorised provided the source is acknowledged.

Table of contents

List of abbreviations

AE	adverse event
ASA	American Society of Anesthesiologists
BPCA	Best Pharmaceuticals for Children Act (BPCA)
CI	confidence interval(s)
CINV	chemotherapy-induced nausea and vomiting
CR	complete response
CSR	clinical study report
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
FAS	full analysis set
FDA	Food and Drug Administration
FPI	full prescribing information
GCP	Good Clinical Practice
HCl	hydrochloride
HR	heart rate
5-HT	5-hydroxytryptamine, serotonin
5-HT3	5-hydroxytryptamine, subreceptor 3
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISU	International System of Units
IV	intravenous(ly)
MH	Mantel Haenszel
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
PALO	palonosetron
PD	pharmacodynamic
PK	pharmacokinetic(s)
PONV	postoperative nausea and vomiting
PP	per protocol population
PPSR	Proposed Paediatric Study Request(s)
PREA	Paediatric Research Equity Act (PREA)
PT	preferred term
QTc	corrected QT interval
QTcB	corrected QT interval, Bazett formula
QTcF	corrected QT Interval, Fridericia formula
SCE	Summary of Clinical Efficacy
sNDA	supplemental New Drug Application
SOC	system organ class
TEAE	treatment-emergent adverse event(s)
US, USA	United States of America
WR	Written Request from US Food and Drug Administration

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Helsinn Birex Pharmaceuticals Ltd. submitted to the European Medicines Agency on 12 June 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name**
Aloxi	palonosetron

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

The Marketing authorisation holder (MAH) applied for an extension of the therapeutic indication for the IV formulation for paediatric patients 1 month of age and older for the prevention of nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy for the IV formulation, based on the paediatric studies PALO-10-14 and PALO-10-20. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.8, 4.9, 5.1, and 5.2 of the SmPC. Sections 5.1 and 5.2 of the SmPC of the Aloxi Oral formulation were updated to reflect those studies. The MAH took the opportunity of this variation to update the Aloxi product information annexes in line with Version 9 of the QRD template.

The Package Leaflet was proposed to be updated in accordance.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet

Information on paediatric requirements

Not applicable.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Patrick Salmon Co-Rapporteur: Arantxa Sancho-Lopez

Timetable	Actual dates
Submission date	12 June 2014
Start of procedure:	27 June 2014
CXMP CoRapporteur Assessment Report	6 August 2014
CXMP Rapporteur Assessment Report	20 August 2014
PRAC Rapporteur Assessment Report	20 August 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	11 September 2014
Rapporteur Revised Assessment Report	22 September 2014
Request for supplementary information (RSI)	25 September 2014
PRAC Rapporteur Assessment Report on responses	14 November 2014
CXMP Rapporteur Assessment Report on responses	24 November 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	4 December 2014
Rapporteur Revised Assessment Report on responses	12 December 2014
2nd Request for supplementary information (RSI)	18 December 2014
Rapporteurs' Joint Assessment Report on 2nd round of responses	8 January 2015
CHMP Opinion	22 January 2015

2. Scientific discussion

2.1. Introduction

Palonosetron hydrochloride is a potent and selective serotonin (5 hydroxytryptamine or 5-HT) receptor antagonist, which has a high affinity for 5-HT3 receptors in a variety of experimental models. It is structurally unrelated to other currently available 5-HT3 receptor antagonists. Nausea and vomiting are triggered by release of 5-HT in a cascade of neuronal events involving both the central nervous system and the gastrointestinal tract. The 5-HT3 receptor has been demonstrated to selectively participate in the emetic response, thus providing a physiological explanation for the antiemetic effects of 5-HT3 receptor antagonists.

Palonosetron 250 mcg solution for injection (Aloxi EU/1/04/306/001) was approved in Europe via the Centralised Procedure on the 22nd of March 2005 and it is indicated for the prevention of acute chemotherapy-induced nausea and vomiting (CINV) associated with HEC and for prevention of CINV associated with MEC. Palonosetron 500 mcg oral soft capsules were approved as a line extension application on the 5th of May 2010 for the prevention of CINV associated with MEC (Aloxi EU/1/04/306/002-003).

The claimed additional indication is as follows:

Aloxi is indicated in paediatric patients 1 month of age and older for

- the prevention of nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy

In support of this application the results of two Phase 3 studies (PALO-10-20 conducted in paediatric patients for the prevention of chemotherapy induced nausea and vomiting (CINV) and PALO-10-14 conducted in

paediatric patients to investigate the prevention of post-operative nausea and vomiting (PONV)) are provided but only an indication in CINV is being sought.

The entire clinical development of Aloxi for paediatric use is based on four paediatric clinical trials: CINV trials PALO-10-20 and PALO-99-07 and PONV trials PALO-10-14 and PALO-07-29. The data and analyses for PALO-99-07 (CINV) and PALO-07-29 (PONV) CSRs were assessed and included into the SmPC in 2010 (Variation EMEA/H/C/000563/II/0025).

2.2. Non-clinical aspects

No new clinical data except environmental risk assessment have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

An environmental risk assessment (ERA) has been submitted to support a Type II variation for Aloxi 250 micrograms solution for injection to include an indication for use in paediatric patients. The ERA has been prepared in accordance with CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 1; EMA, 2006) and further guidance obtained in Questions and Answers on Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMA/CHMP/SWP/44609/2010; EMA,2011).

The environmental risk of palonosetron was assessed as part of the initial MA application for Aloxi 250 mcg solution for injection (as indicated in adults), and more recently, during the line extension application for Aloxi 500 mcg soft capsules. In both cases, the dose of palonosetron was sufficiently low that it passed the Phase I screening level ERA. Therefore, this simplified ERA for palonosetron for paediatric use refers to the approved ERA for Aloxi 500 mcg soft capsules. The Environmental Risk Assessment for Palonosetron in Aloxi 500 mcg soft capsules can be summarised as follows:

Phase I assessment

Persistence, bioaccumulation and toxicity

The octanol/water partition coefficient of palonosetron has been determined using the HPLC method at neutral pH and pH 11.5 and using test solutions of Palonosetron.HCl. This assay has been performed according to OECD Guidelines for the Testing of Chemicals no. 117: "Partition Coefficient (n-octanol/water), High Performance Liquid Chromatography (HPLC) Method", April 13, 2004 and European Community (EC), EC no. 440/2008, Part A: Methods for the Determination of Physico-Chemical Properties, Guideline A.8: “Partition Coefficient”, Official Journal of the European Union no. L142, May 31, 2008.

The Pow and log Pow values of Palonosetron are:

Neutral pH		pH 11.5	
Pow	log Pow	Pow	log Pow
< 2.0	< 0.3	9.9×10^2	3.0

Calculation of the predicted environmental concentration (PEC)
The predicted environmental concentration in surface water ($PEC_{SURFACEWATER}$) has been calculated following the formula required by the current CHMP guidance document as follows.

$$PEC_{SURFACEWATER} = \frac{DOSEai * Fpen}{WASTEWinhab * DILUTION}$$

where:
DOSEai: Maximum daily dose of active ingredient consumed per inhabitant
Fpen: Percentage of market penetration
WASTEWinhab: Volume of waste water per inhabitant per day
DILUTION: Factor of dilution for wastewater into surface water

Thus, the values chosen for parameters were
DOSEai = 0.5mg, the maximum daily dose.
Fpen = 0.01, the recommended default value.
WASTEWinhab = 200 litres/inhabitant/day, the recommended default value.
DILUTION = 10, the recommended default value.

The justification for the values used is the following: Although the guidance indicates that DOSEai is 'per inhabitant', implying adjustment for the proportion of patients in the population, it also states that the highest recommended dose should be used. Adjustment of this value for population is not permitted as this is already computed into the default Fpen value. The maximum daily oral dose, 0.5mg (500mcg), is therefore used as the DOSEai.

Accordingly, the $PEC_{SURFACEWATER}$ in the worst case scenario is:

$$\frac{0.5mg \times 0.01}{200L \times 10} = 0.0000025mg/L \text{ or } 0.0025\mu g/L$$

The worst case calculation of $PEC_{SURFACEWATER}$ for palonosetron hydrochloride is 0.0025µg/L, and is less than the specified action limit of 0.01µg/L. It is therefore assumed that palonosetron does not represent a risk for the environment.
On this basis it is concluded that a Phase II assessment of palonosetron hydrochloride is not required.

2.2.2. Discussion on non-clinical aspects

No new nonclinical pharmacology, pharmacokinetics and toxicology data have been submitted in this application, which was considered acceptable by the CHMP.
An environmental risk assessment (ERA) has been submitted to support a Type II variation for Aloxi 250 micrograms solution for injection to include an indication for use in paediatric patients. In this way, the results of the log KOW of palonosetron is <4.5. Therefore, according the CHMP Guideline on the Environmental Risk Assessment, a persistence, bioaccumulation and toxicity assessment is not required.
On other hand, as the PECSURFACEWATER for palonosetron hydrochloride is 0.0025µg/L, i.e, it is less than the specified action limit of 0.01µg/L, and no other environmental concern are apparent, it is assumed that palonosetron is unlikely to represent a risk for the environment and a phase II environmental assessment is not required for this medicinal product.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of palonosetron.

Considering the above data, palonosetron is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Overview of Palonosetron Paediatric Clinical Studies Design in CINV

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

[a]: in PALO-99-07 study, palonosetron was given as a single IV push administered 30 minutes before the start of MEC or HEC. In PALO-10-20 study palonosetron and ondansetron were given as a 15 minutes IV infusion of, 30 minutes prior to start of MEC or HEC and ondansetron was re-administered 4 hours and 8 hours after the first study drug administration. [b]: CC defined as CR and no more than mild nausea. [c]: assessed at the end of the first 24 hours after the start of chemotherapy. Note; study doses are expressed doses are expressed as µg/kg according to ISU.

Table 2: Overview of Palonosetron Paediatric Clinical Study Designs in PONV

Study Number Study Dates Study Sites	Objective Study Design Study Target Population	Mean Age (Range) Gender M/F Treatment[a]; No. Treated (FAS)	Primary Efficacy Endpoint Other Efficacy Endpoints
PALO-07-29 August 2008 – December 2008 4 sites in Russia and 8 sites in Ukraine	Safety and Efficacy Randomised, double-blind, parallel group, stratified by age group and by country Paediatric patients undergoing surgical elective procedures requiring general endotracheal inhalation anesthesia and receiving nitrous oxide during the maintenance phase of anesthesia,	9.2 y (0.7 - 16.7) 92M/58F **Palonosetron IV:** 1 mcg/kg, max 0.075 mg > 28 d to 23 m; n = 3 2 to 11 y ; n = 47 12 to 16 y ; n = 25 3 mcg/kg, max 0.25 mg > 28 d to 23 m; n = 4 2 to 11 y ; n = 49 12 to 16 y ; n = 22	No emetic episodes from 0 to 72 h postoperatively No emetic episodes at additional time intervals; Severity of nausea; Time to first emetic episode, administration or need of rescue medication, treatment failure; Patients without rescue medication by time interval; Complete response[b] by time interval
PALO-10-14 June 2011 – March 2012 44 sites in the US, Europe (Hungary, Poland, Czech Republic), Ukraine, Russia and South America (Argentina)	Efficacy and Safety Randomised, active-controlled, double-blind, double-dummy, parallel group, stratified by age group Paediatric patients undergoing surgical elective procedures requiring general IV anesthesia and receiving nitrous oxide during the maintenance phase of anesthesia	7.63 y (0.08 - 16.97) 400M/261F **Palonosetron IV:** 1 mcg/kg, max 0.075 mg < 2 y; n = 22 2 to < 6 y; n = 124 6 to < 12 y; n = 117 12 to < 17 ; n = 68 **Ondansetron IV:** 0.1 mg/kg, max 4 mg < 2 y; n = 24 2 to < 6 y; n = 123 6 to < 12 y; n = 117 12 to < 17 y; n = 66	Complete response[c] from 0 to 24 h postoperatively Patients without vomiting, emetic episode, antiemetic rescue medication, nausea (patients aged ≥ 6 years) from 0 to 24 h; Time to first vomiting, emetic episode, rescue medication, treatment failure from 0 to 24 h

[a]: In study PALO-07-29, palonosetron was given as a single IV push over about 10 seconds immediately before start anesthesia induction, or immediately after placement of IV line following inhalation anesthesia induction In study PALO-10-14, palonosetron/matching placebo was given as a single IV push over about 10 seconds, administered no more than 2 minutes after administration of ondansetron/matching placebo and no more than 5 minutes before the start of general anesthesia.
[b]: Defined as no emesis and/or retching and no rescue medication.
[c]: Defined as no vomiting, no retching, and no use of antiemetic rescue medication

2.3.2. Pharmacokinetics

This application only concerns the intravenous route of administration; no bioavailability or bioequivalence studies are required. Two LC-MS/MS methods were used for the analytical determination of palonosetron in the pharmacokinetic studies carried out in paediatrics. Both methods were validated and met standard criteria.

The PK objectives of study PALO-10-20 included the evaluation of palonosetron concentration at the end of the 15-minute infusion (CT) in all patients, and a PK sub-study in a subset of patients who underwent PK sampling at multiple time points. The PK of palonosetron and its metabolite M9, administered by IV bolus over 30 seconds, have been characterised in paediatric CINV patients receiving HEC or MEC in the first clinical study PALO-99-07. Palonosetron plasma concentrations from PALO-10-20 were pooled with those from PALO-99-07 to provide a population PK analysis (PALO-10-35) across all paediatric CINV patients. Lastly, a population PK/PD analysis (PALO-11-20) to evaluate exposure/response with data deriving only from PALO-10-20 was also conducted.

Study PALO-10-20 PK part

The primary objective of this study was to evaluate the efficacy of 2 different doses of IV palonosetron in the prevention of CINV in paediatric patients receiving MEC or HEC through 120 hours after start of chemotherapy in single and repeated chemotherapy cycles. The secondary objectives were to evaluate the safety and tolerability of IV palonosetron in paediatric patients and to evaluate the PK of IV palonosetron in a subset of paediatric patients receiving MEC or HEC.

During the first study cycle, a single PK sample was obtained at TT (end of infusion) from all patients, if clinically feasible. In addition, a subgroup of patients was selected for a PK sub-study. Patients selected for

the PK sub-study had PK samplings at each regular visit and had 1 additional visit specific for the collection of PK samples. The number of PK samples for each patient depended upon the patient's weight and the number and volume of blood samples. Patients weighing 7.5 kg or more were randomised to 1 of 2 different groups (Group A, Group B), for collection of PK samples at up to 8 predefined time points. For patients weighing <7.5 kg, predefined PK samples were eliminated, with more samples omitted as body weight decreased so the total volume of blood collected did not exceed 3% of the total blood volume. Non-compartmental methods were used to calculate the PK parameters for palonosetron.

Results

PK Population

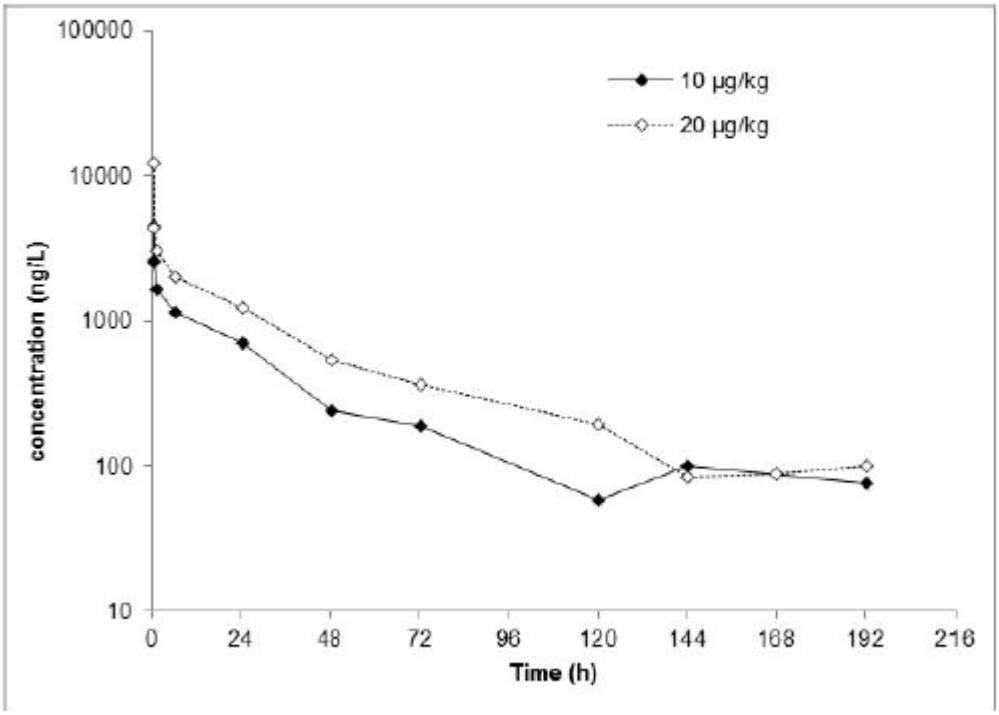
The PK population was comprised of 281 patients for whom at least one evaluable palonosetron sample was available: 144 patients in the palonosetron 10 mcg/kg group and 137 patients in the palonosetron 20 mcg/kg group. The PK sub study population was comprised of 61 patients 32 in the palonosetron 10 mcg/kg group and 29 patients in the palonosetron 20 mcg/kg group

Table 2-5 Demographic Characteristics of PK Sub-study Population

	Palonosetron 10 mcg/kg (N=32)	Palonosetron 20 mcg/kg (N=29)
Gender		
Male	17 (53.1%)	14 (48.3%)
Female	15 (46.9%)	15 (51.7%)
Age at randomization (years)		
<2 years	4 (12.5%)	3 (10.3%)
2 to <6 years	10 (31.3%)	8 (27.6%)
6 to <12 years	6 (18.8%)	8 (27.6%)
12 to <17 years	12 (37.5%)	10 (34.5%)
Race/Ethnicity		
White / Not Hispanic	30 (93.8%)	28 (96.6%)
White / Hispanic	1 (3.1%)	1 (3.4%)
Asian / Not Hispanic	1 (3.1%)	–

The percentage of female patients contributing samples to the PK sub-study was slightly higher in the palonosetron 20 mcg/kg group than in the palonosetron 10 mcg/kg group (51.7% vs. 46.9%). Distribution of patients by age group was similar between treatment arms for three of the four age groups, with about 30% of patients in the 2 to <6 years and 12 to <17 years age groups and about 10% of patients in the <2 years age group. The proportion of patients in the 6 to <12 years age group was higher in the palonosetron 20 mcg/kg group than in the palonosetron 10 mcg/kg group (27.6% vs. 18.8%). The majority of patients were White and not Hispanic.

Figure 2-1 Median Palonosetron Plasma Concentration vs. Time Profiles – Overall – PK Sub-study Population (Log-Linear Scale)



N=32 for the 10 mcg/kg group and N=29 for the 20 mcg/kg

The median PK profiles for the palonosetron 10 mcg/kg and 20 mcg/kg doses followed the same pattern with the maximum palonosetron concentration corresponding to the end of infusion. A bi-exponential decrease of plasma palonosetron concentrations with a short distribution phase and a slow elimination phase was evident. The decrease was roughly parallel for the two profiles suggesting that T½ is comparable among dose levels. For 12 individual PK profiles, Cmax was observed 15 to 60 minutes after the end of infusion.

When comparing the median PK profiles by both dose levels and age ranges, no differences between the overall concentration versus time pattern were evident except for the youngest patients (aged <2 years) receiving the lowest dose level (10 mcg/kg). Because the <2 years age group included only 4 patients, and the absolute dose delivered in this group was very low, one can assume that the palonosetron elimination phase in the concentration-time profile was not shown because the plasma concentrations in this age group were below the lower limit of quantification.

Overall and by age groups, the GM of nominal dose-normalised AUCs were quite close for the 10 and 20 mcg/kg doses with inter-individual variability ranging from 26.7% (AUC0-t in the 20 mcg /kg group in patients aged 12 to <17 years) to 81.3% (AUC0-t in the 10 mcg /kg group in patients aged 2 to <6 years). Similar results were observed when total dose-adjusted AUC values were compared. These results demonstrate that AUC increased with increasing dose across the four age groups. Moreover, a trend toward increased AUC values with increasing age was observed, with statistical significance assessed by ANOVA for the nominal dose-normalised AUC0-∞ ($p = 0.0027$).

Overall, the GM of total dose-normalised Cmax was about 1.41-fold higher in the 20 mcg/kg group. The opposite trend was observed for Cmax in the individual age groups. A possible explanation for the differences in results could be the high inter-individual variability, as expressed by CV%, that was 100% or higher in nearly all cases. The wide distribution of palonosetron plasma concentrations at the end of infusion could be explained by fluctuations in the rate of infusion, the real PK blood sampling time, or possibly

unreported deviations from the protocol instructions aimed at avoiding sample contamination during collections obtained immediately after dosing.

Median Tmax values correspond as expected to the end of infusion although, as previously mentioned, some individual Cmax values were observed up to 1 h after the end of infusion.

Median T½ values were around 20 to 30 h, and were generally comparable between the two dose levels with the exception of results obtained for the youngest patients administered palonosetron 10 mcg/kg. As previously described, for this small group of patients, no terminal phase was observed in the PK profiles and thus determination of corresponding T½ is likely underestimated. Nonetheless, an apparent slight trend towards a T½ increase with age is evident when single patient data are plotted.

Population PK Analyses

PALO-10-35 was a pooled population PK analysis, conducted on palonosetron plasma concentration data from PALO-99-07 and PALO-10-20 clinical studies.

The primary objective was to assess the PK parameters in the full range of paediatric ages, for the 3 palonosetron doses administered during the 2 paediatric trials performed in the CINV indication.

Methods

Population PK models were built using a nonlinear mixed effects modelling technique with NONMEM® software (double precision, version VII, level 7.20), NM-TRAN version III level 1.0, and PREDPP version IV level 1.0 or greater (ICON Development Solutions) and PDx-Pop software. The first order conditional estimation (FOCE) method with interaction was used for model development. The potential significant covariates were screened using exploratory graphical techniques within the Xpose 4 software package.

Various covariate models were compared and assessed. A step-wise forward additional procedure was used to evaluate the covariates. The following criteria were used for assessing significance of covariates in each adding-on step:

- Decrease in objective function value of at least 6.64 ($\Delta 6.64$, $\chi 2<0.01$) points using FOCE or 10.83 ($\Delta 10.83$, $\chi 2<0.001$) points using FO;
- Decrease in the inter-individual variability and residual error;
- Decrease in the standard error of the model parameter estimates;
- Randomness of the individual weighted residual plots (stratified by the covariate values);
- Correlation between the observed concentrations versus individual predicted concentrations (stratified by the covariate values).

The model selection was based on both the objective function and the qualitative evaluation of all the other above mentioned criteria.

After the full model was defined, the significance of each covariate was tested individually by removing one at a time from the full model. The least non-significant covariate was excluded from the model first and the elimination steps were repeated until all non-significant covariates were excluded.

The final model with non-correlated random effects (the diagonal OMEGA matrix) was refined by testing correlations between random effects.

A visual predictive check was performed and the original data was compared to the median (50th percentile), 10th, and 90th percentiles for the pooled, simulated data and the observations outside 90% CI

were calculated. This was used to provide evidence of whether the derived model and associated parameters are consistent with the data.

A proportional plus additive residual error model was used to describe the residual error and values were estimated to be 25.9% (proportional) and the fixed 50 ng/L (SD, additive error that was approximately equivalent to the lowest measurable concentration of 48ng/L). The proportional error was estimated with good precision as the relative standard error was low (%RSE=6.38). During the base model development, it was noted that if the additive error parameter was estimated, it resulted in significant model instability. Therefore, the additive error was fixed to a value of SD=50 and this enabled improved model stability. This model instability may be related to the difference between the very high concentrations at the early time points (0.25 to 0.32 hours), where a cluster of concentrations were greater than 10-fold the median of the concentrations during this time period.

Following covariate evaluation the final model (Run# 096a) was determined to include: WT on CL; WT on V1; WT on V2; and WT on Q.

Results

The final model (Model 096a) resulted in a reduction of 271 points in the OFV when compared with that of base model (Model 004). Inter-subject variability of the estimated PK parameters decreased by 15.7% for CL, by 25% for Q, and by 51.8% for V2. The final model was found to have a slightly increased IIV for V1, by 4%.

The final model for palonosetron was evaluated by performing a predictive check (PPC). The PPC estimated 5.24% of the observed concentrations fell outside the 90% PIs for palonosetron. This confirms that the final PK model provides a good description of the observed data.

The palonosetron PK parameters CL, V1 and V2 increased with increasing age and were comparable across the dose groups. However, since palonosetron was dosed on a weight basis and since the weights across the age groups overlapped, weight normalised PK parameters were also determined.

These parameters show a similar range across the different age groups and demonstrate that once patient body weight is taken into consideration, palonosetron clearance and volume of distribution (CL, V1, and V2) across the age groups are comparable. Although there is a slight decreasing trend of palonosetron CL with increasing patient age, this analysis demonstrates that no further adjustment of dosing beyond dosing palonosetron on a body weight basis, is required for paediatric patients.

Study PALO-10-35 PK data showed consistent pharmacokinetic results with those previously reported for palonosetron in adult patients: there were no significant effects of BMI, age, race, gender, ALT, AST, alkaline phosphatase, bilirubin, creatinine clearance and concurrently administered medications, including CYP2D6 inducers or inhibitors, CYP3A4 inducers or inhibitors, cyclophosphamide, dexamethasone, cytarabine, doxorubicin, fluconazole, or ranitidine, on the disposition of palonosetron. These results are consistent with what has previously been reported for palonosetron for adult patients.

The analysis of model independent parameters (T½, Cmax, Tmax, AUC0-last, AUC0-∞, dose-normalized Cmax, dose-normalised AUC0-last, and dose-normalised AUC0-∞) demonstrated that maximum palonosetron concentrations and exposures increased with increasing dose. A consistent trend when comparing AUCs across age groups was not evident, although it appears that dose-normalised AUCs may increase with age.

Palonosetron half-life appeared to be independent of dose. Patient age also does not impact palonosetron half-life despite a slight increase with age. In general palonosetron median Cmax estimates increased with increasing dose for each study, despite variability likely due to the small sample size by age group.

Pharmacokinetics in children across phase III studies

After single-dose IV administration of palonosetron (3, 10 and 20 mcg/kg), PK profiles across both studies (PALO-99-07 and PALO-10-20) were widely comparable for all age groups and dose levels. Peak concentrations were generally achieved after the IV bolus in PALO-99-07 and at the end of the infusion for PALO-10-20. Main PK parameters appear to be consistent between the two studies, providing an overall understanding of PK results across all doses and age groups. Increases in systemic exposure (AUC values) were clearly related to palonosetron dose across the three dose levels tested. The exposure of palonosetron was similar across age groups after the single dose, although a slight trend toward increased AUC values with age was observed in study PALO-10-20.

A direct comparison of Cmax between the two studies was not feasible due to the different methods of administration used (30-second IV bolus vs. 15-minute IV infusion). However, across the three dose levels, peak exposure as reported by Cmax or CT showed a relationship to palonosetron dose in the range of 3 to 20 mcg/kg.

Terminal elimination half-life (T½) values from the two studies appeared to be independent of the dose administered, ranging between 12 and 34 hours. A slight trend toward longer half-life for older patients was observed, consistent with half-life values of approximately 40 hours reported in adults. In both PALO-99-07 and PALO-10-20 studies, clearance and volume of distribution appeared to increase with age. These increases are essentially due to the fact that palonosetron dose was adjusted based on the individual body weight. When Vss is expressed as L/kg, there are no apparent differences across the four age groups and among the three dose levels evaluated. When normalised for body weight, CL ranged between 0.14 and 0.32 L/h/kg and appeared to be independent of the dose administered. A slight trend toward reduced clearance values in older patients was observed, particularly at the two higher doses tested, consistent with lower CL values of approximately 0.16 L/h/kg reported in adults. In both studies, no relevant differences were observed in any of the PK parameters between genders or types of chemotherapy.

PALO-99-07 and PALO-07-29 were reviewed previously within a type II variation.

The CHMP conclusions on **PALO-07-29** in November 2010 were as follows:

The report on this study performed in Russia and the Ukraine, in 7 patients aged over 28 days and up to 23 months, 96 patients between 2 years and 11 years, and 47 patients between the ages of 12 and 16 years, suggests no safety issue and also suggests efficacy up to 72 hours post operatively.

The CHMP conclusions on **PALO-99-07**, also in November 2010, were as follows:

This study suggests better efficacy in treatment with palonosetron 10.0 µg/kg compared to palonosetron 3.0 µg/kg. There was also higher efficacy in open-label, than in randomised patients (2 to 17 year olds).

Efficacy was not assessed for delayed onset nausea and vomiting and comparative efficacy in multiple cycles was not demonstrated.

Exposure to palonosetron was generally dose proportional, for the 3.0 µg/kg and 10.0 µg/kg dose levels, across all age groups evaluated. Both clearance and volume of distribution appear to increase with increasing age. These increases are largely due to the expected increase in body weight among the three age groups. Mean terminal elimination half-life values ranged from 21-37 hours across the three age groups and did not change with dose or age. There was no effect of gender on clearance, volume of distribution or half-life. M9 metabolite concentrations increased with increasing dose. There were no differences in exposure observed between age groups. Exposure to the metabolite M9 was less than 10% of the palonosetron exposure. There was no correlation between palonosetron concentrations and ECG findings.

The PK data along with safety and efficacy data obtained in this study indicate that, as for most paediatric dosing regimens, palonosetron dosing will need to be weight -based up to a maximum total dose of 0.75 mg.

At that time CHMP agreed that the following information, based on these studies be included in the SmPC, section 5.1

Paediatric population

Prevention of Chemotherapy Induced Nausea and Vomiting (CINV):

The safety and efficacy of Palonosetron i.v at single doses of 3µg/kg and 10µg/kg was investigated in a clinical study in 72 patients in the following age groups, >28 days to 23 months (12 patients), 2 to 11 years (31 patients), and 12 to 17 years of age (29 patients), receiving highly or moderately emetogenic chemotherapy. No safety concerns were raised at either dose level. The primary efficacy variable was the proportion of patients with a complete response (CR, defined as no emetic episode and no rescue medication) during the first 24 hours after the start of chemotherapy administration. Efficacy after palonosetron 10 µg/kg compared to palonosetron 3µg/kg was 54.1% and 37.1% respectively. Pharmacokinetic information is provided in section 5.2.

Prevention of Post Operative Nausea and Vomiting (PONV):
The safety and efficacy of Palonosetron i.v at single doses of 1µg/kg and 3µg/kg was compared in a clinical study in 150 patients in the following age groups, >28 days to 23 months (7 patients), 2 to 11 years (96 patients), and 12 to 16 years of age (47 patients) undergoing elective surgery. No safety concerns were raised in either treatment group. The proportion of patients without emesis during 0-72 hours post-operatively was similar after palonosetron 1 µg/kg or 3 µg/kg (88% vs 84%).

And in section 5.2

Paediatric patients

Across all age groups, (>28 days to 23 months (11 patients), 2 to 11 years (30 patients), and 12 to 17 years of age (29 patients)) of CINV paediatric patients, exposure to palonosetron was generally dose proportional for the 3µg/kg and 10µg/kg dose levels. Both clearance and volume of distribution appear to increase with increasing age largely due to the expected increase in body weight among the age groups. Mean terminal elimination half-life values ranged from 21-37 hours and did not change with dose or age. There was no effect of gender on clearance, volume of distribution or half-life. Please see section 4.2 for information on paediatric use.

2.3.3. Pharmacodynamics

Mechanism of action

Nausea and vomiting are triggered by release of 5-HT in a cascade of neuronal events involving both the central nervous system and the gastrointestinal tract. The 5-HT3 receptor has been demonstrated to selectively participate in the emetic response. Palonosetron is a selective high-affinity receptor antagonist of the 5HT3 receptor.

Primary and secondary pharmacology

A PK/PD analysis using data from PALO-10-20 was undertaken to assess the possible relationship between plasma exposure parameters versus response.

The primary objective was to correlate exposure metrics including Cmax, CT and AUCs with the complete response (CR) outcome.

Methods

A logistic regression analysis was used to link exposure metrics (Cmax, CT, AUC0-t and AUC0-∞) to response (CR in the acute, 0-24 hours post-dose, or delayed, >24-120 hours post-dose, phases.

This analysis also explored other covariates besides exposure that may have had an effect (predictors) of response. These covariates included the following:

• Patient demographics (age, weight, gender)

• HEC or MEC treatment

• Total palonosetron dose administered

Results

A total of 279 subjects from Study PALO-10-20 were available for this analysis. This dataset includes all patients analysed in Study PALO-10-20 as part of the PK sub-study analyses and/or of statistics on end-of-infusion palonosetron (TT) concentrations, and with available CR data.

Displays of PK endpoints versus PD endpoints were prepared to evaluate the relationship between exposure and response. The box plots of complete response in the acute phase (CRA) and complete response in the delayed phase (CRD) versus PK parameters showing the 10th, 25th, 50th, 75th and 90th percentiles and outliers and the scatterplots revealed the distribution of the PK parameters by clinical response (CRA and CRD). From visual inspection, the PK parameters are similar between responders and non-responders, indicating that drug response was independent of drug exposure.

Selected palonosetron PK parameters, i.e., Cmax, CT, AUC0-last and AUC0-inf, were used as predictors for the response variables of CRA and CRD. The PK parameters were log-transformed as they were found, upon visual inspection of the plots, not to be normally distributed. In addition, selected covariates (demographic factors, HEC or MEC treatment, and the palonosetron total dose) were incorporated into the model to test their impact on the estimates of the probability of response.

The base model started with one PK parameter (Cmax, CT, AUC0-last or AUC0-inf) at a time used as a predictor to estimate the probability of response (CRA or CRD). The models show that the slopes of the regression lines were very small, indicating no real change over the exposure parameters, for both CRA and CRD. This indicated that no correlation between the PK parameters and response was evident.

Several covariates were tested to determine if they would have a potential further impact on the regression. Patient age, weight, gender, chemotherapy regimen (HEC or MEC) and palonosetron dose were evaluated. The objective function (OFV) of each of the full models was compared with that from each of the corresponding base models. If the decrease in OFV of the full model was >15.1 (p=0.01, df=5), then the model was found to be statistically different from the base model.

For the logistic regression models of Cmax, CT, AUC0-last and AUC0-inf, versus CRA, the OFV of the full models were slightly decreased when compared to their respective base models (PALO-11-20,). None of the OFV for the full models reached the statistically significant value of >15.1 for the change in the OFV (p=0.01, df=5), therefore indicating that none of the covariates had a significant impact on the models tested. Therefore, for Cmax, CT, AUC0-last and AUC0-inf, versus CRA, the base model was retained as the final model.

For the logistic regression models of Cmax, CT, AUC0-last and AUC0-inf, versus CRD, the OFV of the full models were slightly decreased when compared to their respective base models (PALO-11-20). None of the OFV for the full models reached the statistically significant value of >15.1 for the change in the OFV (p=0.01, df=5), therefore indicating that none of the covariates had a significant impact on the models tested. Therefore, also for Cmax, CT, AUC0-last and AUC0-inf, versus CRD, the base model was retained as the final model. In addition, the 95% CI for the OR included 1, indicating that there is no relationship between the palonosetron PK parameters and response.

2.3.4. Discussion on clinical pharmacology

Single-dose i.v. Aloxi pharmacokinetic data was obtained from a subset of paediatric cancer patients (n=280) that received 10 µg/kg or 20 µg/kg. After a 15 min infusion, palonosetron PK profiles appear widely comparable for all age groups and both dose levels, with a peak generally reported immediately at the end of infusion, followed by a first rapid palonosetron concentration decrease and a much slower elimination phase, with a terminal elimination T½ of about 20 to 30 h.

AUC values, as well as concentrations at the end of infusion, were clearly related to the palonosetron dose level. Relation of Cmax values with dose levels could not be clearly shown. For 12 individual PK profiles, Cmax was observed 15 to 60 minutes after the end of infusion. The high intra- and inter-subject variability observed could explain in part the delay in these 12 subjects. Fluctuations in the rate of infusion and in the sampling time could have contributed to some extent as well.

Both, clearance and volume of distribution appear to increase with increasing age; however, no apparent differences in the distribution of individual patient values across the age groups and between the two dose levels could be detected following normalisation by body weight. No clinically relevant differences were observed in any of the PK parameters reported between genders or types of chemotherapy.

The data do not indicate that the pharmacokinetics of palonosetron is strictly dependent on patient age. Whereas a few slight trends were reported for some PK parameters (including T½ and CL) among age groups and peak plasma concentrations (CT) reported at the end of the 15 minute infusion were highly variable in all age groups and tended to be lower in patients < 6 years ranges remained within the parameter variability observed and were mostly overlapping between age groups. No further adjustment of dosing, beyond dosing palonosetron on an individual patient weight basis, is required for paediatric patients.

As labelled in the product information the number of children under the age of 2 is small. However, the efficacy data from study PALO-10-20 does not indicate a lesser effect of palonosetron in this younger patient subgroup and supports the proposed dose of 20mcg/kg.

Acknowledging that different dose levels and modes of administration pose several limitations to perform a direct comparison, the observed PK results are in line with what has been previously reported for palonosetron in adult patients. Useful information for the prescribing physician on comparability in terms of dose-normalised AUC0-∞, CL, T½ and Vss between adult cancer patients and paediatric cancer patients were included in section 5.2. of the SPC.

The logistic regression analysis of CR in the acute phase and CR in the delayed phase, using measures of palonosetron exposure as predictors of response, indicated that no clear relationship was evident between drug exposure and response in paediatric patients. None of the patient factors tested, including body weight, age, gender, chemotherapy regimen, or total dose administered, had an impact on the response variables, CR in the acute phase or CR in the delayed phase.

2.3.5. Conclusions on clinical pharmacology

The Pharmacology of palonosetron for the proposed dose of 20mcg/kg is considered to be sufficiently characterized.

2.4. Clinical efficacy

The applicant has provided results from four studies in support of this application.

PALO-07-29 (PONV) and PALO-99-07 (CINV) were early trials and both are considered pilot (proof-of-concept) studies. As the designated paediatric age groups in these pilot studies were different from those subsequently specified by the FDA, addenda to these study reports were prepared and are provided. Since the data and analyses for PALO-99-07 (CINV) and PALO-07-29 (PONV) CSRs were submitted and assessed by the EMA in 2010, in this application only the above mentioned study report addenda are included. Two larger studies PALO-10-14 (PONV) and PALO-10-20 (CINV) are provided. As the MAH is only seeking an indication in CINV, efficacy assessment concentrates on PALO-10-20.

PALO-99-07 and PALO-10-20 were conducted to investigate the efficacy of palonosetron IV in the prevention of CINV in paediatric cancer patients. A total of 585 paediatric patients were enrolled or randomised in the 2 Phase 3 studies of IV palonosetron for the prevention of CINV. The studies were conducted in paediatric cancer patients receiving MEC or HEC chemotherapy. Of the 585 patients, 577 were randomised/assigned to treatment and 565 were part of the evaluable population for efficacy during the first cycle (patients treated by HEC/MEC chemotherapy and by study drug). A total of 403 patients were assigned/randomised to palonosetron (35 to the 3 mcg/kg dose, 203 to the 10 mcg/kg dose, and 165 to the 20 mcg/kg dose) and 162 were randomised to ondansetron (0.15 mg/kg 3 times every 4 hours) as standard therapy.

2.4.1. Dose response study(ies)

No specific dose finding study was performed in the paediatric population.

The MAH indicates that the dose selection of palonosetron to be administered to paediatric patients in this study was based on:

- Clinical and PK data for palonosetron in paediatric oncology patients
- Clinical and PK data for palonosetron in adult oncology patients
- Metabolism and ontogeny considerations (including CYP 450 enzymes involved in the disposition of palonosetron)

A study (**PALO-99-07**) in preventing CINV in paediatric patients receiving moderately or highly emetogenic chemotherapy demonstrated that the proportion of patients with complete response was higher in patients treated with palonosetron 10 mcg/kg than in patients treated with palonosetron 3 mcg/kg. The PK portion of the study demonstrated that paediatric patients require higher weight-based (mcg/kg) doses than adult patients due to greater clearance in children than in adults.

The efficacy of palonosetron in preventing CINV in adult oncology patients was demonstrated by three Phase 3 studies (PALO-99-03, PALO-99-04, and PALO-99-95) with IV palonosetron at doses of 0.25 mg and 0.75 mg (corresponding to 3 mcg/kg and 10 mcg/kg) in patient populations receiving MEC or HEC. These studies demonstrated that the 0.25 mg dose was the lowest effective dose, with no significant difference in safety profile between the doses.

In adults, approximately 50% of a dose of palonosetron is eliminated by hepatic metabolism, primarily by CYP2D6 (with minor contribution of other CYP enzymes) and 40% via renal clearance. Therefore, ontogenic factors were to be considered for both routes of elimination.

It appears that renal clearance (based on glomerular filtration rate [GFR]) of palonosetron may be close to adult levels after 1 year of age, when normalised for body surface area.

Literature sources suggest that hepatic metabolism of palonosetron between 1 and 5 years, primarily driven by CYP2D6, would be expected to be close to adult capacity.

In addition, PK evidence from Study PALO-99-07 indicates that clearance of palonosetron in paediatric CINV patients (age >1 month) is higher compared to adults, but no age changes are shown when clearance is adjusted for weight. Therefore after one month of age, an adult dose (adjusted for weight) appeared to be appropriate.

2.4.2. Main study

PALO-10-20

A Multicenter, Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Two Different Doses of Palonosetron Compared to Ondansetron in the Prevention of CINV in Pediatric Patients Undergoing Single and Repeated Cycles of MEC or HEC

Methods

Study participants

Diagnosis and Main Criteria for Inclusion: The target population was paediatric patients aged from full-term neonates to <17 years scheduled to receive at least one moderately or highly emetogenic chemotherapeutic agent for histologically or cytologically confirmed malignant disease. For patients aged ≥10 years ECOG PS ≤2 was requested.

Main exclusion criteria The main exclusion criteria were patients suffering from ongoing vomiting from any organic aetiology (including patients with history of gastric outlet obstruction or intestinal obstruction due to adhesions or volvulus) or patients with hydrocephalus; patients who experienced any vomiting, retching, or nausea within 24 hours prior to the administration of the study drug; patients who received any drug with potential antiemetic effect within 24 hours prior to administration of study treatment; patients who had received total body irradiation, upper abdomen radiotherapy, radiotherapy of the cranium, craniospinal regions or the pelvis within 1 week prior to study entry (screening) or were expected to receive any of these treatments less than 24 hours after study drug administration; patients with baseline prolongation of QTc interval (>460ms); patients with known allergies to components or contraindications to 5-HT3 receptor antagonists; patients with active infection or uncontrolled medical condition.

Overall, the inclusion and exclusion criteria were similar between the two Phase 3 PALO-99-07 and PALO-10-20 studies and the ITT and FAS populations were similar in terms of age, gender, and ethnic origin. The ages of patients were well balanced across treatment groups in both studies; the mean age of patients in each treatment group in both studies ranged between 8 and 9 years old. The distribution of genders was well balanced across treatment groups in PALO-99-07 with approximately 60% enrolment of male patients compared with approximately 40% enrolment of female patients. There were some minor differences in gender between treatment groups in PALO-10-20 with the overall distribution of about 53% male and 46% female patients. The majority of patients in both studies were White and of Hispanic or non-Hispanic origin.

The 2 studies differed with regard to the emetogenicity of the chemotherapeutic agents received by most patients. In study PALO-99-07, the majority of patients in both treatment groups received HEC (68.0%) whereas in study PALO-10-20, the majority of patients in all 3 treatment groups received MEC (69.2%). Within each study, the distribution of patients by emetogenicity of the chemotherapy they received was well balanced across treatment groups.

Treatments

A double-dummy design was adopted for this study i.e., each patient received two different medications: an active compound and a placebo for the other treatment. Study drugs were administered only to patients who participated in the study.

Palonosetron/matching placebo was administered as either 10 mcg/kg up to a maximum total dose of 0.75 mg in the lower dose group or 20 mcg/kg up to a maximum total dose of 1.50 mg in the higher dose. In the neonate sub-study, sequential cohorts of 3 patients each were to be given palonosetron doses of 3 mcg/kg, 10 mcg/kg, and 20 mcg/kg, respectively, after the DMC had determined that the preceding dose was safe and well tolerated. Open-label palonosetron diluted in isotonic saline was the only study drug to be administered to patients in the neonate sub-study.

All patients randomized to ondansetron/matching placebo received three doses of 0.15 mg/kg up to a maximum total dose of 32 mg.

Palonosetron was administered 30±5 minutes prior to start of chemotherapy as an IV infusion of 15 minutes.

Study drug was administered on Day 1 for up to four study cycles. The planned duration of the study was a maximum of 32 days for the first study cycle, which included screening up to 14 days before randomisation (up to 7 days for patients aged <2 years), the day of randomisation, administration of study drug and chemotherapy (Study Day 1), and the control visits (Study Days 2 to 6). The final Visit was between Day 7 and Day 10, and a follow up telephone contact between Day 15 and Day 18. The maximum duration of each of the subsequent cycles was 21 days. For patients undergoing multiple cycles the total study duration could be up to 16.5 weeks.

The active **comparator** in study PALO-10-20 was selected to be ondansetron (Zofran®), since it is considered to be the current standard of care in the US for the prevention of CINV in paediatric cancer patients.

Medications for Prevention of Nausea and Vomiting

Medication for the prevention of nausea and vomiting or any other medication with potential antiemetic properties within the 24 hours prior to the start of chemotherapy or during the 120 hours after T0 was prohibited. Any medication with potential antiemetic properties taken during the 120 hours after start of chemotherapy was considered as a rescue medication. Use of metoclopramide as rescue medication was not permitted.

If a specific chemotherapy regimen also required MEC or HEC on Days 2 to 6, antiemetic therapy could be given on these days as per standard of care. Antiemetic treatment was prohibited until 24 hours after start of chemotherapy on Day 1.

Medication for the prevention or treatment of nausea and vomiting used in the 14 days preceding Day 1 was to be recorded. Systemic corticosteroid therapy at any dose within 24 hours prior to Day 1 was permitted only if part of the chemotherapy to reduce intracranial pressure or in case of topical and inhaled corticosteroids with dose of ≤10 mg of prednisone daily or its equivalent.

Medication for Treatment of Nausea and Vomiting (Antiemetic Rescue Medication)

Rescue medication was administered to alleviate established, refractory or persistent nausea or vomiting and was permitted on an as-needed basis, not as prevention or to increase the expected antiemetic effects of the study medication.

Rescue medication was defined as any drug taken for nausea or vomiting symptoms at any time during the 120-hours after administration of chemotherapy. The choice of antiemetic rescue medication was at the discretion of the Investigator and was made available to patients whenever needed.

Antiemetics considered as rescue medication included, but were not limited to, the following:

5-HT3 receptor antagonists (e.g. ondansetron);

- Benzamides (alizapride);
- Phenothiazine antiemetics (e.g., promethazine, prochlorperazine, thiethylperazine and perphenazine);
- Dimenhydrinate;
- Corticosteroids;
- Over the counter (OTC) antiemetics;
- Non-pharmacologic methods (e.g., Relief Band, P6 Acupressure).

Objectives

The primary objective of this study was to evaluate the efficacy of two different doses of intravenous (IV) palonosetron, compared to ondansetron, in the prevention of chemotherapy induced nausea and vomiting (CINV) in paediatric patients receiving moderately emetogenic (MEC) or highly emetogenic (HEC) chemotherapy through 120 hours after start of chemotherapy in single and repeated chemotherapy cycles.

The secondary objectives of this study were to evaluate the safety and tolerability of IV palonosetron in paediatric patients and to evaluate the pharmacokinetics of IV palonosetron in a subset of paediatric patients receiving MEC or HEC.

Outcomes/endpoints

The primary efficacy parameter was the proportion of patients showing CR from 0 to 24 hours (acute phase) after the first chemotherapy dose was administered in the first chemotherapy cycle. The efficacy evaluation was based on the comparison between palonosetron and ondansetron according to a non-inferiority test.

The key secondary efficacy endpoint was the proportion of patients with CR from > 24 to 120 hours (delayed phase) during the first cycle of chemotherapy. Moreover CR from 0 to 120 hours (overall period) was evaluated. In addition these secondary efficacy parameters were analysed for each period (acute, delayed, and overall): proportion of patients without vomiting; proportion of patients without emetic episodes; proportion of patients without antiemetic rescue medication; proportion of patients without nausea (patients aged ≥ 6 years). Finally, time to first vomiting, time to first emetic episode, time to first administration of rescue medication and the time to treatment failure (either the time to first emetic episode or the time to first administration of rescue medication, whichever occurred first) were also analysed. Supplementary exploratory sensitivity analyses were added to the analysis plan after the protocol completed in order to evaluate the impact on the CR of prophylactic antiemetic medication given for further administration of HEC or MEC on Days 2-6.

For Cycles 2, 3 and 4 the following secondary efficacy parameters were defined for each period (acute, delayed, and overall): proportion of patients showing CR; proportion of patients without vomiting; proportion of patients without emetic episodes; proportion of patients without antiemetic rescue medication and proportion of patients without nausea (patients aged ≥ 6 years).

The FAS including all randomised patients who have received the active study drug and highly or moderately emetogenic chemotherapy was the primary population for efficacy analyses. All efficacy assessments were summarised for the first 24 hours after T0 (time of start of administration of the most emetogenic agent on day 1 of each cycle) for all patients and for subgroups based on age stratification criteria. For the primary efficacy analysis, the CI was built on the FAS using the stratum adjusted Mantel-Haenszel (MH) method with correction of continuity and was compared to the non-inferiority margin. The co-primary efficacy analyses were based on the CI from the stratum adjusted MH method with correction of continuity computed on the "as-treated" population and the probability of the chi-square calculated with the stratum adjusted Miettinen and Nurminen method on the FAS and the "as-treated" population. Additional sensitivity analyses were conducted to assess the robustness of the conclusion. Secondary efficacy analyses were performed for the FAS, and subgroup analyses were performed for the stratification criteria.

Sample size

PALO-10-20 (planned and analysed): The protocol planned to enrol 492 evaluable patients (i.e. 164 patients/group) undergoing MEC or HEC in the double-blind portion of the study. Eligible patients were randomised to one of three treatment groups, stratified by emetogenicity (HEC/MEC) and by age (<2 years, 2 to <6 years, 6 to <12 years, and 12 to <17 years). The study also planned to include a small sample of neonates (full term [≥37 weeks gestation] infants <28 days old) in a preliminary open-label sub-study, to assess exposure and tolerability of palonosetron in these patients. Despite reasonable and diligent efforts, the Investigators were unable to enrol neonates.

The sample size of 492 evaluable patients (164 per treatment arm) was based on the assumption of a CR rate in the time interval 0-24 hours of 60% in the palonosetron and ondansetron arms. For a non-inferiority test using a type I error equal to 0.05 (two- sided), a sample size of 164 evaluable patients per treatment arm provided a power of 80% to show that the lower bound of the CI of the difference (CR0-24 hr palonosetron - CR0-24 hr comparator) is superior to the pre-fixed threshold of -15%.

Randomisation

Patients meeting all inclusion and none of the exclusion criteria were randomised to one of the three treatment groups using the IWRS, which assigned patients to treatment using a computer-generated randomisation schedule stratified by emetogenicity (HEC, MEC) and age groups (<2 years; 2 years up to <6 years; 6 years up to <12 years; 12 years up to <17 years) through static central permuted blocks.

The study was conducted in a double-blind, double-dummy manner except for the open-label neonate sub-study. Each study kit contained either ondansetron and placebo to palonosetron, or palonosetron and placebo to ondansetron.

Blinding (masking)

The study was conducted in a double-blind, double-dummy manner except for the open-label neonate sub-study. Each study kit contained either ondansetron and placebo to palonosetron, or palonosetron and placebo to ondansetron.

Statistical methods

Analysis Populations: The **Full Analysis Set (FAS)** was based on the subset of patients evaluable for the efficacy. The **Per Protocol (PP)** Population included all patients in the FAS that did not have major protocol deviations, i.e. deviations that interfered with assessments of the primary efficacy endpoint. The **Safety Population (SAF)** included all randomized patients receiving at least one study treatment and having at least one post-treatment safety assessment. For analysis, patients were assigned to study treatment groups according to the randomised treatment for the FAS and PP populations, and according to the actual treatment received for the SAF and the As-treated population (the latter corresponding to the FAS but analysed according to the actual treatment received).

Analysis of Primary Efficacy Endpoint:

The primary efficacy endpoint was to demonstrate the non-inferiority of palonosetron compared to ondansetron in terms of proportion of patients reporting CR in the time interval 0-24 hours after the start of chemotherapy (T0) in the first study cycle.

Analysis of Secondary Efficacy Endpoints:

The key secondary efficacy endpoint was the CR from 24 to 120 hours (Delayed period) after T0 during the first cycle. The difference in CR for the Delayed period between treatment groups was analyzed using the Mantel-Haenszel method and the Miettinen and Nurminen method on the FAS population and the As-treated population at a type I error of 5% (accepted type I error for non-primary analyses) and at a type I error of 2.5% (for informative purpose to be consistent with the primary efficacy analysis).

Safety Analysis:

Safety assessments were summarized descriptively for the SAF. The incidence of AEs was summarized by treatment, MedDRA (v. 14.0) primary System Organ Class and MedDRA Preferred Term for all TEAEs, drug related TEAEs, serious TEAEs, drug related serious TEAEs, TEAEs leading to discontinuation, and drug related TEAEs leading to discontinuation. All TEAEs were summarized by maximum intensity, maximum severity, and most conservative degree of relationship to study drug. Drug related TEAEs were also summarized by maximum intensity.

Haematology and blood chemistry parameters were categorised with respect to normal ranges (low, normal, high, missing). Urinalysis parameters were categorised as negative, positive or missing. Shift tables summarised changes from baseline with respect to normal ranges to the final visit of each cycle and the last study visit.

Vital signs, ECGs, and physical examinations were summarised descriptively for continuous and categorical variables.

Efficacy and safety assessments were performed for the overall study population as well as for subgroups of patients based on emetogenicity (MEC, HEC), age group (<2 years, 2 to <6 years, 6 to <12 years, 12 to <17 years), gender, race, ethnicity, and sponsor-defined geographic regions (US, Russia and Ukraine, Europe, Latin America).

Pharmacokinetic Analysis:

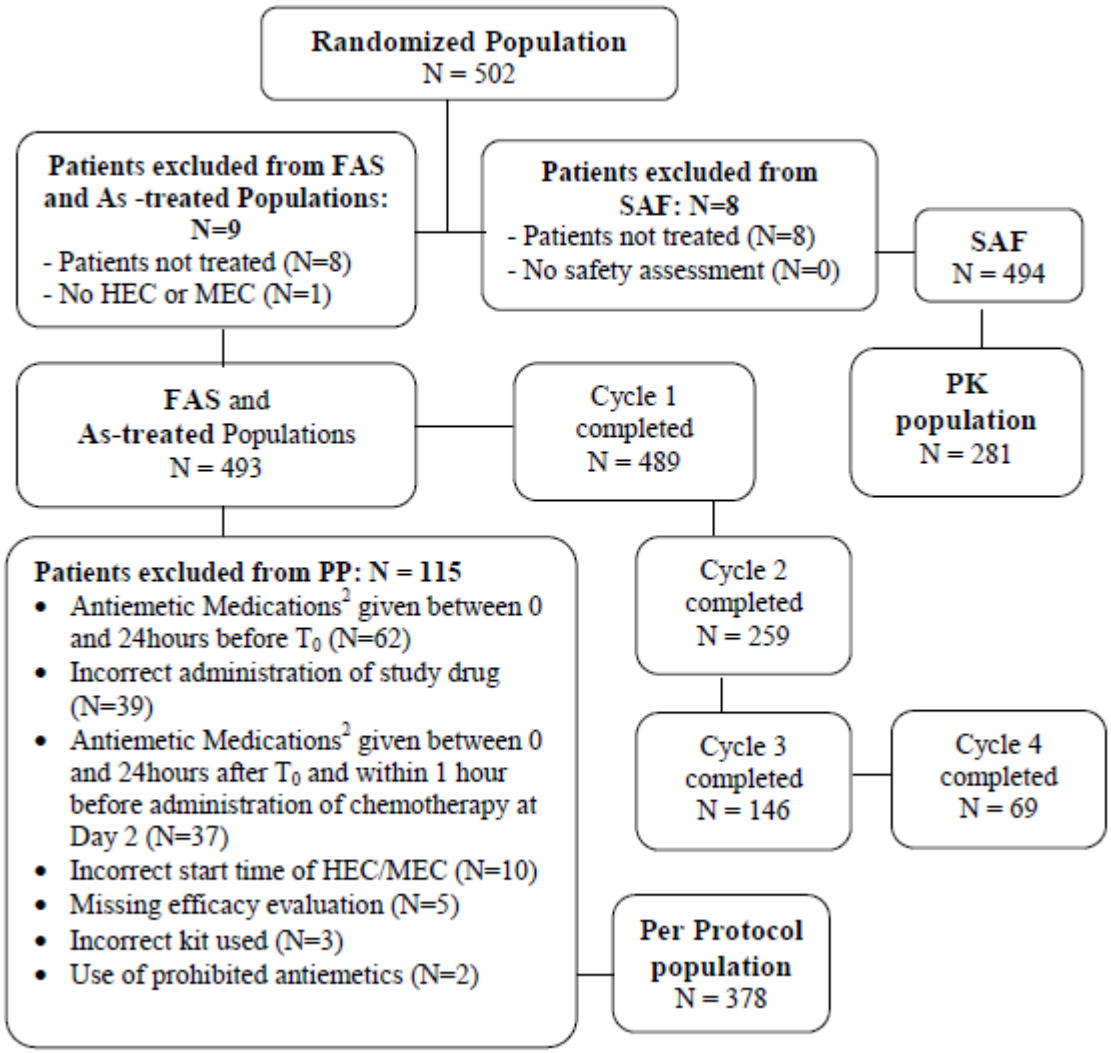
The following PK parameters were determined for each palonosetron dose and for each age group within dose: CT (concentration at the end of infusion of palonosetron), Cmax, Tmax.

Results

Participant flow

The percentage of randomised patients completing at least one study cycle was 98.2% for palonosetron 10 mcg/kg, 96.4% for palonosetron 20 mcg/kg and 97.6% for ondansetron. Death was the reason for study discontinuation in 1 patient in the palonosetron 20 mcg/kg group and 1 in the ondansetron group. Treatment-emergent adverse events (TEAEs) led to discontinuation of 3 patients in the palonosetron 20 mcg/kg group and 2 patients in the ondansetron group (1 in each group was not treated with study drug). The Investigators considered the relationship to study drug unlikely or not related for all AEs that led to premature discontinuation or had fatal outcomes. Consent was withdrawn for 1 patient in the ondansetron group.

Figure 2 Population Flow Chart



Recruitment

The study was performed at 59 sites, including 11 sites in the United States, 7 in Russia and 5 in Poland, 4 sites each in Chile, Czech Republic, Romania and Ukraine, 3 sites each in Bulgaria, France, Hungary, and Peru, and 2 sites each in Argentina, Austria, and Serbia as well as 1 site in Estonia and Germany.

Date of First Patient Enrollment: 12 September 2011

Date of Last Patient Completed: 26 October 2012

Conduct of the study

Country-specific modifications to the protocol were implemented at the request of Competent Authorities and/or Ethics Committees. As the SAP was finalised after the protocol, some analyses not originally foreseen in the protocol were added. These analyses are additional descriptive analyses by age group, gender, race and ethnicity.

Many **paediatric chemotherapy protocols** foresee multiday chemotherapy with HEC or MEC. The protocol allowed such regimens and also the intake of antiemetic medications for prevention of CINV during Days 2-6, as long as they were administered >24 hours after T0. In the analysis of CR in the Delayed phase (which was defined as a key secondary endpoint in this study) these patients were accounted as failures since they received antiemetic medication. Two additional analyses were performed, in order to study the impact of the study medication on CR:

- A sensitivity analysis was performed by creating a new endpoint (Sensitivity CR). The **Sensitivity CR** is defined as the CR except that the intake of an antiemetic medication during the 60 minutes before intake of a HEC/MEC chemotherapy was not accounted as use of an antiemetic rescue medication.
- A further sensitivity analysis was performed on patients receiving HEC/MEC only on Day 1 and excluding all patients receiving HEC/MEC on Days 2-6.

Protocol Deviations

Overall, 124/502 (24.7%) randomised patients had at least one major protocol deviation and were excluded from the PP population. The percentage of patients with major protocol deviations ranged from 23.1% in the palonosetron 10 mcg/kg group to 26.6% in the palonosetron 20 mcg/kg group, with 24.4% in the ondansetron group. **The most frequent major deviations were antiemetic medications given less than 24 hours before T0** (Exclusion criterion #11 - 62 patients), incorrect administration of study drug (39 patients) and antiemetic medication given between 0 and 24 hours after T0 and within 1 hour prior to chemotherapy on Day 2.

Incorrect administration of study drug was mostly due to incorrect duration of infusion (<12 minutes or > 18 minutes) or to incorrect timing of administration in respect to start of chemotherapy. All patients received the foreseen dose of study drug as described in the protocol.

Minor protocol deviations were recorded at every cycle for the randomised population. **A total of 106 (21.1%) patients had at least one minor deviation.** Minor deviations occurring for >10 patients (2% of the overall study population) were incorrect assignment of emetogenicity (38 patients), incorrect administration of study drug (duration of infusion or start time not correct – 29 patients), date of treatment different from date of randomisation (18 patients), and marked prolongation of the QTc interval at baseline (exclusion criterion #8 - 13 patients). The percentage of patients with minor deviations was comparable across treatments.

Three patients did not receive study treatment as randomised during Cycle 1 and were therefore considered as major deviations.

Table 14 Major Protocol Deviations (Randomized Population)

Major Deviation[1]	Palonosetron 10 mcg/kg (N=169)	Palonosetron 20 mcg/kg (N=169)	Ondansetron 3x0.15 mg/kg (N=164)
Number of patients with at least one major deviation	39 (23.1%)	45 (26.6%)	40 (24.4%)
Major deviation leading to exclusion from the Full Analysis Set			
Patient not treated with study treatment	2 (1.2%)	4 (2.4%)	2 (1.2%)
Patient not treated with HEC or MEC chemotherapy	1 (0.6%)	–	–
Major deviation leading to exclusion from the Per Protocol Population			
Antiemetic Medications[2] given between 0 and 24hours before T_0	20 (11.8%)	23 (13.6%)	19 (11.6%)
Incorrect administration of study drug	14 (8.3%)	8 (4.7%)	17 (10.4%)
Antiemetic Medications[2] given between 0 and 24hours after T_0 and within 1 hour before administration of chemotherapy at Day 2	14 (8.3%)	16 (9.5%)	7 (4.3%)
Incorrect start time of HEC/MEC	1 (0.6%)	4 (2.4%)	5 (3.0%)
Missing efficacy evaluation	2 (1.2%)	–	3 (1.8%)
Incorrect kit used	1 (0.6%)	2 (1.2%)	–
Use of prohibited antiemetics	–	1 (0.6%)	1 (0.6%)

[1] Major protocol deviations are the deviations affecting the primary efficacy endpoint.
[2] Any medication with an antiemetic effect given after T_0 was considered as a rescue medication.

Baseline data

A total of 502 patients were enrolled and randomly assigned to treatment at 59 sites. Of the 494 patients that received study drug, 167 were included in the palonosetron 10 mcg/kg group, 165 in the palonosetron 20 mcg/kg group and 162 in the ondansetron group. Study drug was not administered to 8 (1.6%) randomised patients due to vomiting (4 patients: A patient was considered to have completed the study if he/she completed Visit 8 of the last initiated cycle. A total of 485 patients completed all initiated study cycles, while 17 patients terminated the study during one of the cycles.

Overall, at randomisation the age ranged from 64 days to 16.9 years. The FAS included 53.1% of males and 46.9% of females. Most patients were White/not Hispanic (86.2%). Other patients were White/ Hispanic (8.9%), Mixed: White and native Indian/ Hispanic (3.9%), Asian/ not Hispanic (0.4%), Black or African American/ not Hispanic (0.4%) and Latino /Hispanic (0.2%).

The most frequent diagnoses were Acute lymphocytic leukaemia (12.6%), Nephroblastoma (7.9%), Rhabdomyosarcoma (7.7%), Neuroblastoma (6.9%), Medulloblastoma (6.7%), B precursor type acute leukaemia (6.3%) and Ewing's sarcoma (5.1%). While the individual diagnoses were not evenly distributed across the three treatment groups, the combined diagnoses accounted for 50.3% to 56.9% of patients in each treatment group.

Overall, **78.5% of patients were non-naïve to chemotherapy** (76.0% in the palonosetron 10 mcg/kg group, 78.5% in palonosetron 20 mcg/kg group and 81.1% in ondansetron group). In each of the three groups, **51.5% to 55.1% of patients experienced nausea in previous chemotherapy, and 50.3% to 54.5% of patients experienced vomiting/retching in previous chemotherapy**.

Numbers analysed

Overall, 502 patients were randomised in the study, with 169 in the palonosetron 10 mcg/kg group, 169 in the palonosetron 20 mcg/kg group and 164 in the ondansetron group.

Of the 502 randomized patients, 8 patients (2 palonosetron 10 mcg/kg, 4 palonosetron 20 mcg/kg and 2 ondansetron) did not receive the study drug and, therefore, were excluded from the FAS and the SAF. One additional patient (623/5311; palonosetron 10 mcg/kg) received study drug but received neither HEC nor MEC (the patient was treated with Low Emetogenic Chemotherapy [LEC]) and was excluded from the FAS, but was included in the SAF (and in the PK population). Therefore, the FAS included 493 patients, and the SAF included 494 patients.

Table 15 Number of Patients in Each Analysis Population (Cycle 1)

Analysis Population	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3x0.15 mg/kg	Total
Randomized Population	169	169	164	502
Full Analysis Set (FAS)	166	165	162	493
As-treated Population	166	163	164	493
Per Protocol Population (PP)	130	124	124	378
Safety Population (SAF)	167	163	164	494
PK Population	144	137	0	281
PK Sub-Study Population	32	29	0	61

One hundred and twenty-four (124) patients had major protocol deviations and were excluded from the PP population. The PP population consisted of 378 patients: 130 in the palonosetron 10 mcg/kg group, 124 in the palonosetron 20 mcg/kg group and 124 in the ondansetron group. These patients are those from the FAS who did not experience any major protocol deviations.

Patients who did not receive study treatment as randomised were included with the randomised treatment in the FAS and with the actual treatment for the SAF, the As-treated population and the PK population. The As-treated population has the same number of patients as the FAS (493 patients). The patient who received study drug but did not receive HEC or MEC was excluded from the FAS, and thus from the As-treated population.

A total of 281 patients were included in the PK Population. For 280 of these patients the plasma concentration value at TT was available, while 61 patients were included into the PK sub-study.

Outcomes and estimation

The analysis of the efficacy endpoint of CR (no vomiting, no retching, and no use of rescue medication) is presented for PALO-10-20 study followed by subgroup analyses of CR by age group, gender and emetogenicity. Selected analyses include no vomiting, no emetic episodes, no use of rescue medication and no nausea (patients aged ≥ 6 years).

Complete Response (Cycle 1)

The primary efficacy population of the pivotal phase 3 HEC/MEC study PALO-10-20 was the FAS population and was comprised of 493 paediatric evaluable patients. Demographics and baselines characteristics were representative of subjects undergoing HEC and MEC, all treatments and age groups were well balanced. The proportions of patients with CR in the acute, delayed and overall phases during Cycle 1 in study PALO-10-20 are summarised below.

Table 3: Complete Response during Cycle 1 in study PALO-10-20 (FAS)

Complete Response	Treatment Group		
	Palonosetron 10 mcg/kg N = 166	Palonosetron 20 mcg/kg N = 165	Ondansetron 3x0.15 mg/kg N= 162
Acute (0-24 hrs), n (%)	90 (54.2%)	98 (59.4%)	95 (58.6%)
Wilson 95% CI of CR	[46.3%; 61.9%]	[51.5%; 66.9%]	[50.6%; 66.2%]
Delayed (24-120 hrs), n (%)	48 (28.9%)	64 (38.8%)	46 (28.4%)
Wilson 95% CI of CR	[22.3% - 36.5%]	[31.4% - 46.7%]	[21.7% - 36.1%]
Overall (0-120 hrs), n (%)	39 (23.5%)	54 (32.7%)	39 (24.1%)
Wilson 95% CI of CR	[17.4% - 30.8%]	[25.8% - 40.5%]	[17.9% - 31.5%]

CI = confidence interval; N = number of patients.

In the acute phase, a lower number of patients in the palonosetron 10 mcg/kg group reported CR compared with the ondansetron control group (54.2% versus 58.6%) and a similar number of patients had CR in the palonosetron 20 mcg/kg group compared with ondansetron (59.4% versus 58.6%). The stratum adjusted MH primary efficacy analyses used to evaluate the difference in proportions of patients with CR in the acute, delayed and overall phases during Cycle 1 for the FAS is summarised in Table 4.

Table 4: Proportion of Patients with Complete Response during Cycle 1 in Study PALO-10-20: Difference between Treatments (FAS)

Complete Response- First Cycle		
Stratum Adjusted Mantel-Haenszel	**Delta Palonosetron 10 mcg/kg minus Ondansetron 3x0.15 mg/kg (N=328)**	**Delta Palonosetron 20 mcg/kg minus Ondansetron 3x0.15 mg/kg (N=327)**
Acute (0-24 hrs)		
Weighted Sum of Delta CR	-4.41%	0.36%
97.5% CI of the Weighted Sum of Delta CR	[-16.4%; 7.6%]	[-11.7; 12.4]
Delayed (24-120 hrs)		
Weighted Sum of Delta CR	0.42%	10.17%
95% CI of the Weighted Sum of Delta CR	[-9.4%; 10.3%]	[-0.1%; 20.4%]
Overall (0-120 hrs)		
Weighted Sum of Delta CR	-0.60%	8.25%
95% CI of the Weighted Sum of Delta CR	[-10.0%; 8.8%]	[-1.6%; 18.1%]

N = number of patients; Delta CR = Difference of rates of patients showing complete response (CR palonosetron - CR ondansetron). Source Module 2.7.3 CINV Table 2-18, Table 2-22 and Table 2-24.

As noted above, CR was reported for 54.2% of patients treated with palonosetron 10 mcg/kg, 59.4% of patients treated with palonosetron 20 mcg/kg and 58.6% of patients treated with ondansetron. Similar results were obtained in the As-treated and PP populations, with the latter showing a numerically higher, but still comparable, effect of palonosetron 20 mcg/kg compared to that of the other treatment groups (see tables 24 and 27 on the next pages).

The primary statistical analysis of MH (stratum adjusted Mantel-Haenszel test) on the FAS indicated that the 97.5% CI of the difference in CR between palonosetron and ondansetron was of [-16.4; 7.6] and [-11.7; 12.4] for patients treated with palonosetron 10 mcg/kg and palonosetron 20 mcg/kg, respectively. The null

hypothesis (H0) was composite, therefore two separate tests were conducted comparing these intervals with the non-inferiority margin of δ =-15%. As the H0 10 mcg/kg was not rejected, while H0 20 mcg/kg was rejected**, the null hypothesis was rejected but the non-inferiority was achieved only for the dose of palonosetron 20 mcg/kg.**

Table 24 Proportion of Patients with Complete Response in Acute Phase during First Cycle: Confidence Interval of Proportions for Analysis Populations

	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3x0.15 mg/kg
FAS population			
Number of Patients	166	165	162
Patients with CR	90 (54.2%)	98 (59.4%)	95 (58.6%)
Wilson 95% CI of CR	[46.3% - 61.9%]	[51.5% - 66.9%]	[50.6% - 66.2%]
As-treated population			
Number of Patients	166	163	164
Patients with CR	90 (54.2%)	98 (60.1%)	95 (57.9%)
Wilson 95% CI of CR rate	[46.3% - 61.9%]	[52.1% - 67.6%]	[50.0% - 65.5%]
PP population			
Number of Patients	130	124	124
Patients with CR	78 (60.0%)	85 (68.5%)	79 (63.7%)
Wilson 95% CI of CR rate	[51.0% - 68.4%]	[59.5% - 76.4%]	[54.5% - 72.0%]

CR = Complete Response; CI = Confidence Interval

Table 27 Supportive Sensitivity Analyses: Difference Between Treatments in the Proportion of Patients with Complete Response in Acute Phase during First Cycle: Difference between Treatments

		Delta palonosetron 10 mcg/kg minus ondansetron 3x0.15 mg/kg	Delta palonosetron 20 mcg/kg minus ondansetron 3x0.15 mg/kg
Stratum Adjusted Mantel-Haenszel (Per Protocol population)			
Overall Weighted Sum of Delta CR		-4.15%	4.43%
97.5% CI of the Weighted Sum of Delta CR		[-17.7%; 9.4%]	[-9.1%; 18.0%]
P-value		0.0365	0.0006
Note: H_0 is rejected if one of the p-value <0.0125			
Stratum Adjusted Miettinen and Nurminen (Per Protocol population)			
Overall Chi-2		3.4234	10.740
Overall p-value		0.0643	0.0010
Note: H_0 is rejected if one of the p-value <0.025			
Newcombe 11th method (FAS)			
Overall	Delta CR	-4.43%	0.75%
	97.5% CI of Delta CR	[-16.8%; 8.2%]	[-11.7 %; 13.2 %]
Unconditional Exact Confidence Interval (FAS)			
Overall	Delta CR	-4.43%	0.75%
	97.5% CI of Delta CR	[-16.8%; 7.9%]	[-11.8%; 13.0%]

CR in the Acute Phase during the First Cycle by Age Group

Analysis of CR rates by age group revealed different rates for the overall population among treatment arms. Whereas CR rates in the ondansetron group remained around 60% in the four age groups, rates after palonosetron administration ranged between 41.3% and 74.1%, with palonosetron 20 mcg/kg always showing numerically higher CR rates compared to palonosetron 10 mcg/kg.

Nevertheless, the 95% CIs were broadly overlapping, showing no significant differences.

Table 28 Proportion of Patients with Complete Response in the Acute Phase during First Cycle by Age Group - FAS

	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3x0.15 mg/kg
Age <2 years			
Number of Patients	15	15	15
Patients with CR	7 (46.7%)	9 (60.0%)	8 (53.3%)
Wilson 95% CI of CR rate	[22.2% - 72.6%]	[32.9% - 82.5%]	[27.4% - 77.7%]
Age 2 up to <6 years			
Number of Patients	54	54	54
Patients with CR	38 (70.4%)	40 (74.1%)	32 (59.3%)
Wilson 95% CI of CR rate	[56.2% - 81.6%]	[60.1% - 84.6%]	[45.1% - 72.1%]
Age 6 up to <12 years			
Number of Patients	46	46	44
Patients with CR	19 (41.3%)	23 (50.0%)	26 (59.1%)
Wilson 95% CI of CR rate	[27.3% - 56.7%]	[35.1% - 64.9%]	[43.3% - 73.3%]
Age 12 up to <17 years			
Number of Patients	51	50	49
Patients with CR	26 (51.0%)	26 (52.0%)	29 (59.2%)
Wilson 95% CI of CR rate	[36.8% - 65.0%]	[37.6% - 66.1%]	[44.3% - 72.7%]

CR = Complete Response

CR in the Acute Phase during the First Cycle by Emetogenicity

Patients were randomised by the Investigators to HEC or MEC at study entry according to instructions given in the study protocol. Nonetheless, it appeared that some Investigators assigned an incorrect emetogenicity. In order to standardise the emetogenicity, the sponsor re-assigned the emetogenicity group based on the actual chemotherapy received during Day 1.

In patients receiving HEC, 42.6% of patients treated with palonosetron 10 mcg/kg, 51.0% of patients treated with palonosetron 20 mcg/kg and 41.2% of patients treated with ondansetron showed CR in the Acute phase of the first cycle. These results indicated an effect of palonosetron 10 mcg/kg that was similar to that of ondansetron and an effect of palonosetron 20 mcg/kg that was numerically higher to that of ondansetron.

In patients receiving MEC, 59.8% of patients treated with palonosetron 10 mcg/kg, 62.9% of patients treated with palonosetron 20 mcg/kg and 66.7% of patients treated with ondansetron showed CR in the Acute phase of the first cycle. These results indicated that the effect of both palonosetron 10 mcg/kg and palonosetron 20 mcg/kg was numerically lower but comparable to that of ondansetron.

Table 29 Proportion of Patients with Complete Response in the Acute Phase during First Cycle by Emetogenicity - FAS

	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3x0.15 mg/kg
HEC			
Number of Patients	54	49	51
Patients with CR	23 (42.6%)	25 (51.0%)	21 (41.2%)
Wilson 95% CI of CR rate	[29.5% - 56.7%]	[36.5% - 65.4%]	[27.9% - 55.8%]
MEC			
Number of Patients	112	116	111
Patients with CR	67 (59.8%)	73 (62.9%)	74 (66.7%)
Wilson 95% CI of CR rate	[50.1% - 68.8%]	[53.4% - 71.6%]	[57.0% - 75.2%]

Key Secondary Endpoint: CR in the Delayed Phase during the First Cycle

The key secondary endpoint of this study was CR in the Delayed phase (>24-120 hours after T0) of the first cycle, and was achieved by 28.9 % of patients in the palonosetron 10 mcg/kg group, 38.8% in the palonosetron 20 mcg/kg group and 28.4% in the ondansetron group. These results indicated an effect of palonosetron 10 mcg/kg that was comparable to that of ondansetron. The proportion of patients with CR in the Delayed phase was numerically higher in the palonosetron 20 mcg/kg group than in the other two groups by approximately 10%.

In the age strata, the CR rate in the Delayed phase was much higher in the palonosetron 20 mcg/kg group than in the ondansetron group in patients <2 years old (40.0% vs. 13.3%, respectively) and in patients of 12 to <17 years (40.0% vs. 16.3%, respectively). CR rate in the Delayed phase in palonosetron 20 mcg/kg group was slightly higher than in ondansetron group (46.3% vs. 37.0%) in the 2 to <6 years group, and slightly lower (28.3% vs. 36.4%) in the 6 to <12 years age group.

For patients receiving HEC, the CR rate in the Delayed phase was notably higher in the palonosetron 20 mcg/kg group (44.9%) than in the palonosetron 10 mcg/kg group (20.4%) or the ondansetron group (19.6%), while for patients receiving MEC, the CR rates were comparable across treatment groups, ranging from 32.4% to 36.2%.

Table 34 Proportion of Patients with Complete Response in the Delayed Phase of the First Cycle - FAS

	Palonosetron 10 mcg/kg	Palonosetron 20 mcg/kg	Ondansetron 3x0.15 mg/kg
Overall			
Number of Patients	166	165	162
Patients with CR	48 (28.9%)	64 (38.8%)	46 (28.4%)
Wilson 95% CI of CR	[22.3% - 36.5%]	[31.4% - 46.7%]	[21.7% - 36.1%]
Age <2 years			
Number of Patients	15	15	15
Patients with CR	1 (6.7%)	6 (40.0%)	2 (13.3%)
Wilson 95% CI of CR rate	[0.3% - 34.0%]	[17.5% - 67.1%]	[2.3% - 41.6%]
Age 2 to <6 years			
Number of Patients	54	54	54
Patients with CR	19 (35.2%)	25 (46.3%)	20 (37.0%)
Wilson 95% CI of CR rate	[23.0% - 49.4%]	[32.8% - 60.3%]	[24.6% - 51.3%]
Age 6 to <12 years			
Number of Patients	46	46	44
Patients with CR	11 (23.9%)	13 (28.3%)	16 (36.4%)
Wilson 95% CI of CR rate	[13.1% - 39.1%]	[16.5% - 43.7%]	[22.8% - 52.3%]
Age 12 to <17 years			
Number of Patients	51	50	49
Patients with CR	17 (33.3%)	20 (40.0%)	8 (16.3%)
Wilson 95% CI of CR rate	[21.1% - 48.0%]	[26.7% - 54.8%]	[7.8% - 30.2%]
HEC			
Number of Patients	54	49	51
Patients with CR	11 (20.4%)	22 (44.9%)	10 (19.6%)
Wilson 95% CI of CR rate	[11.1% - 33.9%]	[30.9% - 59.7%]	[10.3% - 33.5%]
MEC			
Number of Patients	112	116	111
Patients with CR	37 (33.0 %)	42 (36.2%)	36 (32.4%)
Wilson 95% CI of CR rate	[24.6% - 42.6%]	[27.6% - 45.7%]	[24.0% - 42.1%]

Complete Response in the Overall Phase during the First Cycle

Results in the Overall phase (0-120 hours after T0) of the first cycle were similar to those obtained in the Delayed phase with numeric values of CR slightly lower than the ones in the Delayed phase. CR was observed in the Overall phase (0-120 hours) during the first cycle in 23.5% of patients treated with palonosetron 10 mcg/kg, 32.7% of patients treated with palonosetron 20 mcg/kg and 24.1% of patients treated with ondansetron. These results indicated that the treatment effect of both palonosetron 10 mcg/kg and palonosetron 20 mcg/kg was comparable to that of ondansetron, with numerical superiority of palonosetron 20 mcg/kg in the Overall phase. With respect to emetogenicity subgroups, the CR rate in the Overall phase in patients receiving HEC was higher in the palonosetron 20 mcg/kg group (32.7%) than in the other two treatment groups (13.0% and 13.7%), whereas it was comparable across treatments for patients receiving MEC (28.6% to 32.8%).

During Cycle 1, the proportion of patients reporting no vomiting, or no emetic episode was constantly higher in the palonosetron 20 mcg/kg group compared to the two other groups. Analysis of 95% CI for the MH (not

powered, not adjusted for multiplicity) showed superiority of palonosetron 20 mcg/kg versus ondansetron in all phases.

Table 38 Proportion of Patients without Vomiting during First Cycle - FAS

	Palonosetron 10 mcg/kg (N=166)	Palonosetron 20 mcg/kg (N=165)	Ondansetron 3x0.15 mg/kg (N=162)
Acute phase			
Patients with No Vomiting	133 (80.1%)	138 (83.6%)	119 (73.5%)
Wilson 95% CI	[73.1% - 85.7%]	[76.9% - 88.8%]	[65.8% - 79.9%]
Delayed phase			
Patients with No Vomiting	113 (68.1%)	122 (73.9%)	94 (58.0%)
Wilson 95% CI	[60.3% - 75.0%]	[66.4% - 80.3%]	[50.0% - 65.6%]
Overall phase			
Patients with No Vomiting	98 (59.0%)	114 (69.1%)	83 (51.2%)
Wilson 95% CI	[51.1% - 66.5%]	[61.4% - 75.9%]	[43.3% - 59.1%]

Use of antiemetic rescue medication during Cycle 1 showed numerical differences in rates but the CIs were overlapping and similarly MH did not show statistical differences.

Assessment of nausea was only performed on patients aged 6 years or more. During Cycle 1, the frequency of absence of nausea in palonosetron 20 mcg/kg group was consistently numerically higher than ondansetron across all phases. This was supported for the Delayed and Overall phases by 95% CI for the MH (not powered, not adjusted for multiplicity) showing superiority, despite a reduced population due to selection of a subset of FAS based on age.

In line with results observed at Cycle 1, throughout study Cycles 2 to 4, and across all phases, palonosetron 20 mcg/kg treatment group most of the time reported the highest CR

To establish the impact of concomitant antiemetic medications during the 0-120 hrs period, the two secondary efficacy parameters of Emesis and Nausea were analysed in the delayed phase for the group of patients with or without rescue medication.

The results are presented in Table 1 and Table 2 below.

Table 1: Proportion of Patients without Emetic Episodes and without Nausea in the Delayed Phase during the First Cycle in PALO-10-20 Study - Patients treated with rescue medication

Delayed Phase >24-120hrs - First Cycle Unconditional Exact Method Patients treated with rescue medication		
	Delta Ratio Palo 10mcg/kg-Ond	Delta Ratio Palo 20mcg/kg-Ond
No Emetic episode		
N	214	204
Delta No Emetic episode	14.90%	17.48%
97.5% CI of Delta No Emetic episode	[-0.7%; 29.9%]	[1.7%; 32.6%]
No Nausea		
N	126	125
Delta No Nausea	14.01%	23.00%
97.5% CI of Delta No Nausea	[-6.4%; 33.1%]	[2.6%; 41.8%]

Table 2: Proportion of Patients without Emetic Episodes and without Nausea in the Delayed Phase during the First Cycle in PALO-10-20 Study - Patients not treated with rescue medication

Delayed Phase >24-120hrs - First Cycle Unconditional Exact Method Patients not treated with rescue medication		
	Delta Ratio Palo 10mcg/kg-Ond	Delta Ratio Palo 20mcg/kg-Ond
No Emetic episode		
N	114	123
Delta No Emetic episode	-6.30%	4.43%
97.5% CI of Delta No Emetic episode	[-26.9%; 14.8%]	[-15.9%; 24.5%]
No Nausea		
N	64	64
Delta No Nausea	-14.78%	-6.21%
97.5% CI of Delta No Nausea	[-41.3%; 13.3%]	[-33.5%; 21.6%]

These analyses are based on the Unconditional Exact Method (non-stratified) test, as for some values the stratum adjusted test could not be computed due to low number of patients in strata. Nausea was assessed only in patients aged 6 years or more, leading to a smaller sample size.

Comparing these results to those for the full analysis set (FAS) population reported in PALO-10-20 CSR Table 41 and Table 45, it appears that in the sub-population of patients treated with rescue medication the outcome is in favour of palonosetron, while in the subpopulation not treated with antiemetics, comparison is more frequently in favour of ondansetron. As expected, results on the overall phase reported in Tables 3 and Table 4 below are similar to those of the delayed phase.

Table 3: Proportion of Patients without Emetic Episodes and without Nausea in the Overall Phase during the First Cycle in PALO-10-20 Study - Patients treated with rescue medication

Overall Phase 0-120 hrs - First Cycle Unconditional Exact Method Patients treated with rescue medication		
	Delta Ratio Palo 10mcg/kg-Ond	Delta Ratio Palo 20mcg/kg-Ond
No Emetic episode		
N	214	204
Delta No Emetic episode	12.88%	20.72% [5.0%;
97.5% CI of Delta No Emetic episode	[-2.7%; 27.5%]	35.7%]
No Nausea		
N	126	125
Delta No Nausea	8.97%	21.06% [0.7%;
97.5% CI of Delta No Nausea	[-11.2%; 28.2%]	39.7%]

Table 4: Proportion of Patients without Emetic Episodes and without Nausea in the Overall Phase during the First Cycle in PALO-10-20 Study - Patients not treated with rescue medication

Overall Phase 0-120 hrs - First Cycle Unconditional Exact Method Patients not treated with rescue medication		
	Delta Ratio Palo 10mcg/kg-Ond	Delta Ratio Palo 20mcg/kg-Ond
No Emetic episode N Delta No Emetic episode 97.5% CI of Delta Emetic episode	 114 -7.22% [-27.9%; 13.9%]	 123 6.04% [-14.3%; 26.0%]
No Nausea N Delta No Nausea 97.5% CI of Delta No Nausea	 64 -10.15% [-37.2%; 17.6%]	 64 -1.58% [-29.1%; 25.9%]

Time to Treatment Failure during the First Cycle

Similarly to the CR, the composite endpoint time to treatment failure is defined as time to first emetic episode or time to first administration of antiemetic rescue medication, whichever occurred first. Time to treatment failure in the Acute phase of Cycle 1 was summarized by treatment groups, overall, by emetogenicity and by age-emetogenicity stratum for the FAS. In the Acute phase of the first cycle, treatment failure was observed for 76 (45.8%) patients in the palonosetron 10 mcg/kg group, 67 (40.6%) patients in the palonosetron 20 mcg/kg group and 67 (41.4%) patients in the ondansetron group. Due to the low rate of events, the median time to treatment failure and third quartile could not be evaluated.

Figure 3 shows the time to treatment failure for all patients, regardless of emetogenicity. The curves of the probability of treatment failure for palonosetron 10 mcg/kg and ondansetron are extremely similar, while the one for palonosetron 20 mcg/kg is very slightly separated after approximately 5 hours.

Figure 3 Time to Treatment Failure in the Acute Phase - FAS

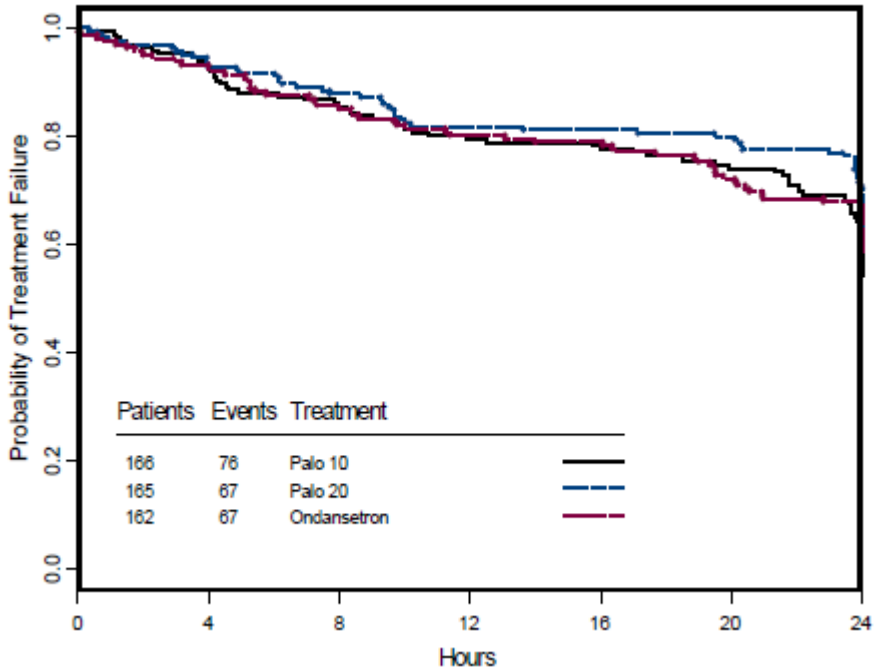
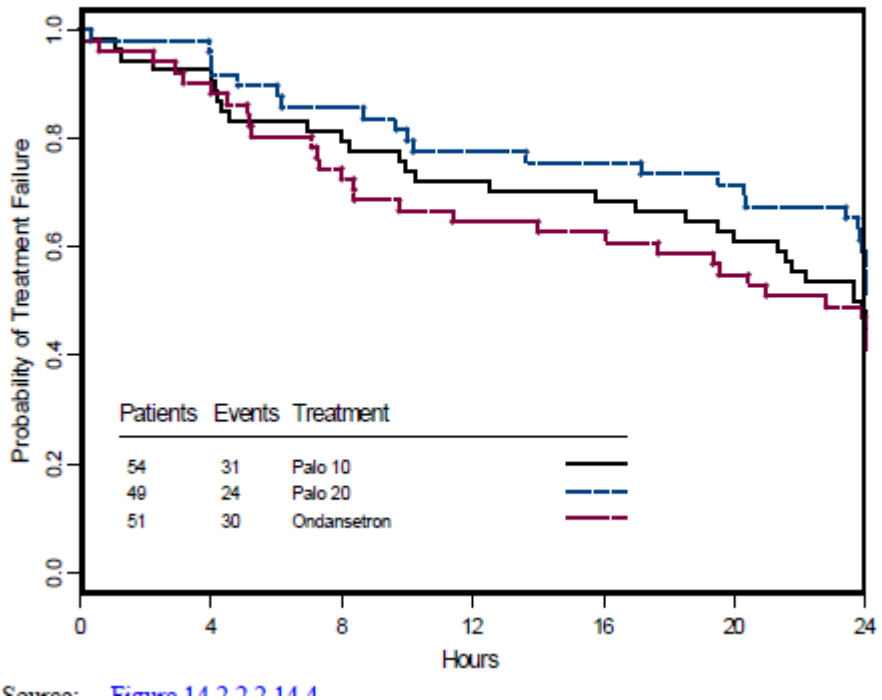


Figure 4 shows the treatment failure curve in the Acute phase of Cycle 1 for HEC patients. There is a modest separation between treatment groups during the Acute phase with a small incremental benefit of

palonosetron 10 mcg/kg and a somewhat larger benefit of palonosetron 20 mcg/kg in patients receiving HEC, with only few points in common at the beginning of the curve and then a complete disjunction.

Figure 4 Time to Treatment Failure in the Acute Phase - HEC patients - FAS



Source: Figure 14.2.2.2.14.4

There is quite no separation among treatments in the graph of CR in patients receiving MEC. In conclusion, for the Acute phase, Figure 5 (MEC) showed quite no separation between the treatments, while Figure 4 (HEC) was partially in favour of a difference between treatments, indicating that the overall separation of treatments observed in Figure 3 (HEC and MEC) was due mostly to the incremental benefit by palonosetron 20 mcg/kg in the HEC subgroup.

Sensitivity Complete Response

As described above, in order to explore the impact of multi-day chemotherapies, the Sensitivity CR was defined as a new endpoint. This parameter was defined as the CR except that any intake of an antiemetic medication within 60 minutes before intake of a HEC/MEC chemotherapy (i.e., antiemetic likely given as a prophylaxis) was not accounted as a use of rescue medication. This endpoint was defined only at Cycle 1 and only for the Delayed phase, since use of prophylactic antiemetics for chemotherapies during Day 2-6 was allowed by the protocol.

The value of the crude rates and the CIs as defined by Wilson for Sensitivity CR are presented in Table 56. As expected Sensitivity CR rates were generally higher than those observed for the key secondary endpoint of CR in the Delayed phase. Comparing the Sensitivity CR and the CR, it appears that Sensitivity CR is higher by 6.6%, 9.1%, and 3.1% for palonosetron 10 mcg/kg, palonosetron 20 mcg/kg, and ondansetron treatment groups, respectively. These differences indicate that more patients in the palonosetron 20 and 10 mcg/kg groups than in the ondansetron group received chemotherapy with antiemetic prophylactic medication during the Delayed phase,

Differences in proportions of patients with Sensitivity CR were higher for palonosetron 10 mcg/kg and even more so for palonosetron 20 mcg/kg versus ondansetron then they were for patients with CR. For the latter 95% CI did not overlap.

Table 56 Proportion of Patients with *Sensitivity CR* and CR during Delayed phase of First Cycle - FAS

Delayed Phase	Palonosetron 10 mcg/kg (N=166)	Palonosetron 20 mcg/kg (N=165)	Ondansetron 3x0.15 mg/kg (N=162)
Patients with *Sensitivity CR*	59 (35.5%)	79 (47.9%)	51 (31.5%)
Wilson 95% CI	[28.4% - 43.4%]	[40.1% - 55.8%]	[24.5% - 39.3%]
Patients with CR	48 (28.9%)	64 (38.8%)	46 (28.4%)
Wilson 95% CI	[22.3% - 36.5%]	[31.4% - 46.7%]	[21.7% - 36.1%]

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial PALO-10-20

Title: A Multicenter, Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Two Different Doses of Palonosetron Compared to Ondansetron in the Prevention of CINV in Pediatric Patients Undergoing Single and Repeated Cycles of MEC or HEC.			
Study identifier	PALO-10-20		
Design	Randomized, Double-Blind, Double-dummy, Parallel Group		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Study drug was administered on Day 1 for up to four study cycles The planned duration of the study was a maximum of 32 days for the first study cycle. The maximum duration of each of the subsequent cycles was 21 days Not applicable Not applicable
Hypothesis	Non-inferiority		
Treatments groups	Palonosetron 10 mcg/kg		10 mcg/kg Palonosetron (max 0.75 mg) single dose IV over 15min , n=169
	Palonosetron 20 mcg/kg		20 mcg/kg Palonosetron (max 1.5 mg) single dose IV over 15min, n=169
	Ondansetron 3x0.15 mg/kg		Ondansetron 0.15 mg/kg x 3 doses (max 32 mg), each IV over 15min, with 2nd and 3rd doses given 4 and 8 hours after 1st dose, n=164
Endpoints and definitions	Primary endpoint	Proportion of patients showing CR in acute phase	No vomiting, no retching, and no use of antiemetic rescue medication from 0 to 24 hours (Acute phase) after T0 (start of administration of the most emetogenic chemotherapy) during first cycle.
	Key Secondary endpoint	Proportion of patients with CR in delayed phase	CR from >24 to 120 hours (Delayed phase) after T0.

	Other Secondary endpoint	CR from 0 to 120 hours (Overall period) after T0. Time to: first vomiting, first emetic episode, first administration of antiemetic rescue medication, treatment failure was either the time to first emetic episode or the time to first administration of antiemetic rescue medication, whichever occurred first, during first cycle Proportion of patients: without vomiting, without emetic episodes, without antiemetic rescue medication, without nausea (patients aged ≥6 years) during all cycles (1-4). CR in acute, delayed and overall phases in cycles 2-4
Database lock	NA	

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full analysis set Acute Phase (0-24h) in First Cycle-			
Descriptive statistics and estimate variability	Treatment group	Palo 10 mcg/kg	Palo 20 mcg/kg	Onda 3x0.15 mg/kg
	Number of subject	166	165	162
	CR 0-24h	90 (54.2%)	98 (59.4%)	95 (58.6%)
	Wilson 95% CI of CR	[46.3%; 61.9%]	[51.5%; 66.9%]	[50.6%; 66.2%]
Effect estimate per comparison	Primary endpoint	Palonosetron 10 mcg/kg minus Ondansetron 3x0.15 mg/kg	Palonosetron 20 mcg/kg minus Ondansetron 3x0.15 mg/kg	
	Weighted Sum of Delta CR	-4.41%	0.36%	
	97.5% CI of the Weighted Sum of Delta CR	[-16.4%:7.6%]	[-11.7; 12.4]	
	p-value	0.0242	0.0022	
Notes	The stratum adjusted Mantel-Haenszel method was used to compute the CI of the difference in proportion. If the lower bound of the 97.5% CI of either the difference was strictly superior to the non-inferiority margin (δ=-0.15) then the null hypothesis (H0) was rejected. H0 is rejected is p value is <0.0125			
Analysis description	**Key Secondary analysis**			
Analysis population and time point description	Full analysis set Delayed phase (24-120 h) in First Cycle-			
Descriptive statistics and estimate variability	Treatment group	Palo 10 mcg/kg	Palo 20 mcg/kg	Onda 3x0.15 mg/kg
	Number of subject	166	165	162
	CR 24-120 h	48(28.9%)	64 (38.8%)	46 (28.4%)

	Wilson 95% CI of CR	[22.3%- 36.5%]	[31.4% - 46.7%]	[21.7% - 36.1%]
Effect estimate per comparison	Primary endpoint	Palonosetron 10 mcg/kg minus Ondansetron 3x0.15 mg/kg	Palonosetron 20 mcg/kg minus Ondansetron 3x0.15 mg/kg	
	Weighted Sum of Delta CR	0.42%	10.17%	
	97.5% CI of the Weighted Sum of Delta CR	[-9.4%; 10.3%]	[-0.1%; 20.4%]	
Analysis description	**Secondary analysis**			
Analysis population and time point description	Full analysis set Overall phase (0-120 h) in First Cycle-			
Descriptive statistics and estimate variability	Treatment group	Palo 10 mcg/kg	Palo 20 mcg/kg	Onda 3x0.15 mg/kg
	Number of subject	166	165	162
	CR 0-120 h	39 (23.5%)	54 (32.7%)	39 (24.1%)
	Wilson 95% CI of CR	[17.4% - 30.8%]	[25.8% - 40.5%]	[17.9% - 31.5%]
Effect estimate per comparison	Primary endpoint	Palonosetron 10 mcg/kg minus Ondansetron 3x0.15 mg/kg	Palonosetron 20 mcg/kg minus Ondansetron 3x0.15 mg/kg	
	Weighted Sum of Delta CR	-0.60%	8.25%	
	97.5% CI of the Weighted Sum of Delta CR	[-10.0%; 8.8%]	[-1.6%; 18.1%]	
Notes	The stratum-adjusted MH analysis provided a confidence interval of the difference in rates (Delta defined as palonosetron rate minus ondansetron rate). The statistical analysis was not powered and was not adjusted to take into account the multiplicity of the non-primary efficacy analyses. The ranges of the CIs were produced for information only			

Analysis performed across trials (pooled analyses and meta-analysis)

The efficacy results from the two phase 3 studies were not integrated by the MAH because of the difference in population sizes in the pilot study (PALO-99-07; n=72) versus the pivotal study (PALO-10-20; n=493), the use of different IV palonosetron doses in the pilot versus the pivotal study, and the use of an active comparator in the pivotal study but not in the pilot study. This in principle is considered adequate.

In any case, results from both studies are presented by the MAH in comparative summaries. The proportion of patients achieving CR 0-24 h was comparable across studies for the palonosetron 10 mcg/kg dose (54.1% and 54.2% for PALO-99-07 and PALO-10-20, respectively); and also similar between the studies in each group for patients who received palonosetron 10 mcg/kg.

Among patients who received palonosetron 10 mcg/kg and MEC, the CR rates were comparable in study PALO-99-07 (61.5%) and study PALO-10-20 (62.5%). In the HEC setting, the CR rates were slightly higher in study PALO-99-07 (50.0%) compared with study PALO-10 20 (42.6%).

Supportive studies

PALO 10-14

Study PALO-10-14 was performed to assess the safety and efficacy of intravenous palonosetron in the prevention of PONV over 24 hour postoperative period in children from 0 up to less than 17 years. Patients were randomized to palonosetron 1 mcg/kg or ondansetron 0.1 mg/kg administered immediately before induction of general intravenous anaesthesia.

The main efficacy endpoint was the proportion of patients showing Complete Response (defined as no vomiting, no retching, and no use of rescue medication) during the first 24 hours postoperatively, starting at T0 (when the patient woke up and was able to show any active reaction. The choice of this primary variable is acceptable and is the normally used for this type of products.

As secondary parameters were evaluated the proportion of patients with no vomiting, without emetic episode, without antiemetic rescue medication, without nausea (patients aged ≥6 years), the time to first vomiting, to first emetic episode, to first administration of rescue medication, to treatment failure.

A total of 670 paediatric patients were randomised and 661 subjects received treatment (60.5% males and 39.5% females): 331 patients in the palonosetron treatment group and 330 patients in the ondansetron treatment group. A greater number of patients of 2 to <6 years and 6 to< 12 years were included: 247 (37.3%) and 234 (35.4%), respectively. The 12 to <17 years age group included 134 (20.3%) patients. Only a 7% of patients (n=46) included belong to <2 years group.

The proportion of patients with CR was 78.2% in the palonosetron group and 82.7% in the ondansetron group. The difference between treatments was -4.4% [-10.5%; 1.7%]. As the lower bound of the 95% CI of the difference between both treatments was not above the non-inferiority margin (-10%), non-inferiority of palonosetron compared to ondansetron was not demonstrated. Results of secondary variables were consistent with primary efficacy analysis. No main concerns of safety were raised from this study (PONV). The type of AEs were common in a PONV setting.

ADDEMDUM PALO-99-07

Study PALO-99-07 was a phase 3, multicenter, randomised, balanced, double-blind, parallel group, stratified study to assess the safety and tolerability, PK, and efficacy of single IV doses of palonosetron, 3.0 mcg/kg or 10.0 mcg/kg, in paediatric patients receiving MEC or HEC. In addition, 12 patients, aged at least 28 days up to 23 months, were treated in an open-label fashion with the same doses of palonosetron. Data from study PALO-99-07 which served as proof of concept are considered only supportive.

This study was already submitted as a Follow-up Measure to the EMA in September 2006 (Ref. EMEA/467342/2006) and in September 2010 as support of a Type II variation to update Aloxi SmPC sections 4.2, 5.1 and 5.2 (Ref. EMEA/H/C/000563/II/0025). An Addendum of this study is submitted now.

The objective of this Addendum was to re-analyze original PALO-99-07 efficacy, safety and PK data according to WR-defined pediatric age groups and other population subsets and criteria which differ from those designated and evaluated in the original PALO-99-07 study protocol. Safety and PK data were also presented by WR-defined age group, gender, and race/ethnicity. The main efficacy endpoint evaluated in the original Study was re-assessed in this Addendum

Main Results:

CR by age: Overall, CR was higher in the palonosetron 10 mcg/kg than in the palonosetron 3 mcg/kg treatment arm, with 54.1% and 37.1% of patients showing CR, respectively. CR was higher in the palonosetron 10 mcg/kg than in the palonosetron 3 mcg/kg arm also in most of the age subgroups. A tendency to higher CR rates in the younger age groups was observed in both treatment arms. The following table summarises the Proportion of patients with CR 0-24 hours by age group - ITT

Table 3.17: Proportion of patients with CR 0-24 hours by age group - ITT

ITT Population	Complete Response 0-24 Hours	
	Palonosetron 3 mcg/kg (N=35)	Palonosetron 10 mcg/kg (N=37)
Age group		
< 2 years		
Patients with CR/n (%)	3/6 (50.0%)	6/6 (100.0%)
Wilson[1] 95% CI of CR	[13.9% - 86.1%]	[51.7% - 100.0%]
2 to < 6 years		
Patients with CR/n (%)	3/4 (75.0%)	3/5 (60.0%)
Wilson[1] 95% CI of CR	[21.9% - 98.7%]	[17.0% - 92.7%]
6 to < 12 years		
Patients with CR/n (%)	3/10 (30.0%)	4/12 (33.3%)
Wilson[1] 95% CI of CR	[8.1% - 64.6%]	[11.3% - 64.6%]
12 to < 18 years		
Patients with CR/n (%)	4/15 (26.7%)	7/14 (50.0%)
Wilson[1] 95% CI of CR	[8.9% - 55.2%]	[24.0% - 76.0%]
Overall		
Patients with CR/n (%)	13/35 (37.1%)	20/37 (54.1%)
Wilson[1] 95% CI of CR	[22.0% - 55.1%]	[37.1% - 70.2%]

CR by gender. The percentage of both female and male patients with CR seemed higher in the palonosetron 10 mcg/kg group than in the palonosetron 3 mcg/kg arm for most of the age groups. Response rates in both genders were similar in the palonosetron 3 mcg/kg treatment arm, but in the palonosetron 10 mcg/kg arm, a higher response rate was found in male patients showing a CR of 63.6% as compared to female patients with a CR of 40.0%.

CR by race and ethnicity. White patients had CR results that showed no particular trend in the dose-age comparison. Hispanic patients had similar results to those observed in White patients.

CR by emetogenicity. Regardless of the emetogenicity of the chemotherapeutic agent, the percentage of patients with CR was higher in the palonosetron 10 mcg/kg arm than in the palonosetron 3 mcg/kg arm.

Overall, higher CR rates were consistently observed in patients administered with palonosetron 10 mcg/kg, also when results were presented by gender, by race/ethnicity and by emetogenicity. Given the low number of patients in most of the subgroups, however, significance of the results may be questionable.

ADDEMDUM PALO-07-29

Study PALO07-29 was a multicenter, double-blind, randomized, stratified, parallel group, phase 3 study 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 year undergoing surgical elective procedures requiring general endotracheal inhalation

anesthesia. 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.

It was already submitted as a FUM in January 2010 (Ref: EMA/333705/2010) and in September 2010 as Type II variation to update Aloxi SmPC sections 4.2, 5.1 and 5.2 (Ref. EMEA/H/C/000563/II/0025). It has been re-analysed according to the different age groups proposed by FDA WR, and it is provided in this application as a report addendum.

The objective of this Addendum to the PALO-07-29 study was to describe and discuss results of Complete Response from 0 to 24 hours and safety data reanalyzed according to Written Request (WR) required age groups, gender and race/ethnicity

Main Results

*CR by age*s

Overall, the proportion of patients [Wilson 95% CI] showing CR 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. Results were comparable between treatment arms and no clinically significant differences were observed. CR 0-24 hour efficacy results for the <2 year, 2 to <6 year, 6 to <12 year and 12 to <17 year WR age groups were 100%, 83.3%, 79.3% and 100%, and 100%, 87.5%, 78.8% and 86.4% for the 1 mcg/kg and 3 mcg/kg dose groups, respectively The following table summarises the Proportion of patients with CR 0-24 hours by age group - FAS

All patients included in the <2 years age group were complete responders in both treatment arms. However only 7 patients were enrolled in this age group hence the low number of patients precluded any meaningful interpretation of data.

Table 3.22: Proportion of patients with CR during the 24 hours after T0 by age group – FAS

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%]

[1]: Percentage of patients in age group with CR versus total number of patients in age group

* Wilson CI includes a correction of continuity

CR by gender. CR rates were numerically higher for male patients than for female patients in the palonosetron 1 mcg/kg treatment arm, whereas they were comparable in the palonosetron 3 mcg/kg treatment arm. These differences were considered not clinically significant

Table 3.23: Proportion of patients with CR during the 24 hours after T0 by gender - FAS

Complete Response 0-24 hours		
Full Analysis Set	Palonosetron 1 mcg/kg (N= 75)	Palonosetron 3 mcg/kg (N= 75)
Population		
Female		
Patients with CR/n (%)[1]	23/29 (79.3%)	24/29 (82.8%)
Wilson* 95% CI of CR	[59.7%-91.3%]	[63.5%-93.5%]
Male		
Patients with CR/n (%)[1]	43/46 (93.5%)	39/46 (84.8%)
Wilson* 95% CI of CR	[81.1%-98.3%]	[70.5%-93.2%]
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%]

[1]: Percentage of patients in age group with CR versus total number of patients in age group

* Wilson CI includes a correction of continuity

CR by race and ethnicity. All patients in the study PALO-07-29 were white, so assessment of efficacy by race was not feasible

Sample sizes for each WR age group and for each gender within each age group for both dose groups were small to allow for definitive conclusions regarding differences in efficacy. However, in general, no clinically significant difference was observed within treatment group, age group or gender

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH has submitted this type II variation to request a new indication for Aloxi IV: Prevention of nausea and vomiting associated with moderate and highly emetogenic cancer chemotherapy in paediatric patients (1 month of age and older).

The main data relevant to this variation are based on one pivotal Phase 3 study performed in paediatric patients (study PALO-10-20) to investigate the prevention of chemotherapy induced nausea and vomiting (CINV). The study was a multicentre, active-controlled, double-blind, randomised, parallel group, stratified (by age and by HEC/MEC), non-inferiority phase 3 trial involving patients receiving palonosetron in two different doses or ondansetron for the prevention of CINV.

Data from the study in PONV (PALO-10-14) are considered as supportive only, as no indication in postoperative nausea and vomiting is being sought. This study formally failed to show non-inferiority over standard comparator in PONV. Additionally, two addenda to the CSRs from the proof-of-concept studies PALO-99-07 (CINV) and PALO-07-29 (PONV) are included in the dossier. The addenda are considered as supportive data as well.

No formal dose-response clinical studies have been carried out in the paediatric population. Regarding CINV development, the selected doses to be tested in the proof-of-concept study PALO-99-07 were based on the

knowledge gained from the adult development (PK data and dose-ranging studies). The results of the mentioned study supported the 10 mcg/kg dose as the lowest effective dose without safety concerns. This dose and a higher dose (20 mcg/kg), were chosen and tested in the pivotal study PALO-10-20 in order to detect a dose/exposure response relationship. The rational for dose selection seems reasonable as well as the proposal to test two doses, although it is noted that these doses were not supported by PK/PD modelling results; in any case, the suitability of one or another regimen was assessed in the pivotal study.

Most of the key design features of pivotal study follow the current recommendations displayed in the CPMP/EWP/4937/03 guideline on non-clinical and clinical development of medicinal products for the prevention of nausea and vomiting associated with cancer chemotherapy. Although the scope of this guideline is adult populations, it might well be also applicable to children.

The **primary efficacy endpoint** was the proportion of patients showing complete response (CR; defined as no vomiting, no retching, and no use of antiemetic rescue medication) from 0 to 24 hours (Acute phase) after T0 (start of most emetogenic chemotherapy) during first cycle in the FAS population. This endpoint is appropriate to assess an effect on nausea and vomiting. Ondansetron, the currently most common used 5-HT3 receptor antagonist for the prevention of CINV in paediatric patients is considered an appropriate comparator.

Secondary endpoints included as key secondary endpoint, the proportion of patients with CR from >24 to 120 hours (Delayed phase) after T0. Additionally, CR from 0 to 120 hours (Overall period) after T0 was evaluated. Other secondary efficacy endpoints to be determined for each period (Acute, Delayed, and Overall) were: Proportion of patients without vomiting; proportion of patients without emetic episodes; proportion of patients without antiemetic rescue medication; proportion of patients without nausea (patients aged ≥6 years); time to first vomiting; time to first emetic episode; time to first administration of antiemetic rescue medication and time to treatment failure was either the time to first emetic episode or the time to first administration of antiemetic rescue medication, whichever occurred first. These endpoints, which a priori facilitate a full characterisation of antiemetic efficacy during the whole period at risk after receiving chemotherapy, (usually lasts 4-7 days) are considered usual and are acceptable.

The posology of ondansetron as the standard therapy for acute emesis was selected in line with the recommended dosing regimen and clinical practice in the paediatric population (3 doses of 0.1 mg/kg). The use of rescue medication (including Ondansetron as decided by the investigator) was permitted to control nausea and vomiting during the delayed period. Considering that the main objective of study PALO-10-20 was to investigate CR in the acute phase this is considered acceptable to show non inferiority for the acute phase.

The efficacy of palonosetron was evaluated during subsequent cycles as secondary end-points. Even though patients were not re-randomized in order to provide non-confounded data on sustained activity, such as it is pointed out in the CPMP/EWP/4937/03 guideline, it is acceptable hence palonosetron is not a new medicine. In addition, safety data from multiple cycles in children result of special interest in order to support the use in this population.

For the secondary endpoints, the tests of Mantel-Haenszel (MH) and Miettinen and Nurminen (MN) were performed. The stratum-adjusted MH analysis provided a confidence interval of the difference in rates (Delta defined as palonosetron rate minus ondansetron rate), while the stratum-adjusted MN analysis provided a p-value for the comparison between the difference in rates and a predefined value (-15% in PALO-10-20 study). However, -15% cannot be considered as a valid non-inferiority margin for the secondary endpoint analyses since it was established in the protocol only for a specific period, the Acute phase, and a specific parameter, the CR. For the other analyses, -15% should be seen as a subjective benchmark.

Additionally, the secondary endpoints are presented with a type I error of 5% for each arm, and without adjustment for multiplicity, so the statistical significance of the test cannot be seen as proof of non-inferiority or difference between the treatment groups.

The PALO-10-20 study was planned to control multiplicity only for the primary efficacy endpoints and not for the secondary endpoints. As the study permitted enrolment of patients treated with multiple days of chemotherapy, it is clear that there will be an impact on the evaluation of the delayed phase, and that evaluation of the drug effect will be confounded by other effects.

There is no option to change the study analysis after study completion without disregarding the validity of the methodology but these considerations limit the statistical validity for CR over 24 to 120 hours.

Efficacy data and additional analyses

A total of 502 patients were randomized. Of the 494 patients that received the study drug, 167 were included in the palonosetron 10 mcg/kg group, 165 in the palonosetron 20 mcg/kg group and 162 in the ondansetron group.

The treatment groups were for the most part similar. Overall, at randomisation the age ranged from 64 days to 16.9 years. The FAS included 53.1% of males and 46.9% of females. Most patients were White/not Hispanic (86.2%). Other patients were White/ Hispanic (8.9%), Mixed: White and native Indian/ Hispanic (3.9%), Asian/ not Hispanic (0.4%), Black or African American/ not Hispanic (0.4%) and Latino /Hispanic (0.2%). The most frequent diagnoses were Acute lymphocytic leukaemia (12.6%), Nephroblastoma (7.9%), Rhabdomyosarcoma (7.7%), Neuroblastoma (6.9%), Medulloblastoma (6.7%), B precursor type acute leukaemia (6.3%) and Ewing's sarcoma (5.1%). While the individual diagnoses were not evenly distributed across the three treatment groups, the combined diagnoses accounted for 50.3% to 56.9% of patients in each treatment group. Overall, 78.5% of patients were non-naïve to chemotherapy (76.0% in the palonosetron 10 mcg/kg group, 78.5% in palonosetron 20 mcg/kg group and 81.1% in ondansetron group). In each of the three groups, 51.5% to 55.1% of patients experienced nausea in previous chemotherapy, and 50.3% to 54.5% of patients experienced vomiting/retching in previous chemotherapy.

The majority of patients in all 3 treatment groups received MEC (69.2%). Within each study, the distribution of patients by emetogenicity of the chemotherapy they received was well balanced across treatment groups. The use of rescue antiemetic and concomitant medication had a similar distribution among 3 treatments groups. The distribution according to age and emetogenicity of the chemotherapy was well balanced for both criteria.

CR was reported for 54.2% of patients treated with palonosetron 10 mcg/kg, 59.4% of patients treated with palonosetron 20 mcg/kg and 58.6% of patients treated with ondansetron. Similar results were obtained in the As-treated and PP populations, with the latter showing a numerically higher, but still comparable, effect of palonosetron 20 mcg/kg compared to that of the other treatment groups.

The primary statistical analysis of MH (stratum adjusted Mantel-Haenszel test) on the FAS indicated that the 97.5% CI of the difference in CR between palonosetron and ondansetron was of [-16.4; 7.6] and [-11.7; 12.4] for patients treated with palonosetron 10 mcg/kg and palonosetron 20 mcg/kg, respectively. The null hypothesis (H0) was composite, therefore two separate tests were conducted comparing these intervals with the non-inferiority margin of δ =-15%. As the H0 10 mcg/kg was not rejected, while H0 20 mcg/kg was rejected, the null hypothesis was rejected but the non-inferiority was achieved only for the dose of palonosetron 20 mcg/kg. As non-inferiority with the lower dose has not been shown use of the higher dose is claimed and supported by the CHMP.

The three co-primary statistical analyses (MH on the As-treated population, stratum adjusted Miettinen and Nurminen test on FAS and As-treated populations), and the four planned supportive sensitivity analyses were performed on the same endpoint with different populations and/or statistical methods, and they all supported conclusions similar to those of the primary efficacy analysis. Additionally, since the emetogenicity was revised by the sponsor at the time of blind data review meeting to ensure consistency of classification, a sensitivity analysis of the primary efficacy endpoint was also conducted using the emetogenicity as entered by Investigator at randomization. The results of this analysis were in line with the ones of the primary efficacy analysis.

The primary efficacy endpoint, CR in the acute phase, was further analysed by age group, emetogenicity, gender, race/ethnicity, and geographic region and the 95% CI of the CR rates were overlapping among the treatment groups. In particular, highly variable CR rates were reported by age group by emetogenicity, with MEC patients generally reporting higher rates than HEC patients.

A higher proportion of patients treated with palonosetron 20 mcg/kg showed a complete response on delayed phase (key secondary end-point) than those in ondansetron arm (38.8% vs 28.8%); CR results in the overall phase (0-120h) were similar to those in delayed stage (32.7% palonosetron 20 mcg/kg vs. 24.1%).

Additionally the MAH performed an analysis of emetic episodes and nausea in the delayed phase for the group of patients with or without rescue medication. Comparing these results to those for the full analysis set (FAS) population, in the sub-population of patients treated with rescue medication the outcome was in favour of palonosetron, while in the subpopulation not treated with antiemetics, comparison was more frequently in favour of ondansetron. It can be concluded that use of antiemetics in the delayed phase did have an effect leading to an uncertainty related to the assessment of the effect in the delayed phase.

During Cycle 1, the proportion of patients reporting no vomiting, or no emetic episode was constantly higher in the palonosetron 20 mcg/kg group compared to the two other groups (analysis of 95% CI for the MH not adjusted for multiplicity).

Use of antiemetic rescue medication during Cycle 1 showed numerical differences in rates but the CIs were overlapping and similarly MH did not show statistical differences.

Assessment of nausea was only performed on patients aged 6 years or more. During Cycle 1, the frequency of absence of nausea in palonosetron 20 mcg/kg group was consistently numerically higher than ondansetron across all phases. This was supported for the Delayed and Overall phases by 95% CI for the MH (not powered, not adjusted for multiplicity), despite a reduced population due to selection of a subset of FAS based on age.

The Kaplan-Meyer curves of time to treatment failure and time to first administration of antiemetic rescue medication showed similar shapes. In particular, for the Overall period these curves were S-shaped. It is suggested that use of antiemetic medication at about 24 hours showing a major impact on the time to treatment failure so that the curve for time to first emetic episode in the Overall period did not show such an S-shaped curve.

Differences in proportions of patients with Sensitivity CR were higher for palonosetron 10 mcg/kg and even more so for palonosetron 20 mcg/kg versus ondansetron then they were for patients with CR. For the latter 95% CI did not overlap.

For the Acute phase, the results of the CR for the PP population and for the subset of patients treated by HEC/MEC only on Day 1, confirm the conclusion of the primary efficacy endpoint.

For the Delayed phase, the results of the CR for the subset of patients treated by HEC/MEC only on Day 1 confirm the outcome of the key secondary endpoint. The additional data obtained with the Sensitivity CR are also in line with those results.

In line with results observed at Cycle 1, throughout study Cycles 2 to 4, palonosetron 20 mcg/kg treatment group most often reported the highest CR rate, the highest proportions of patients with no vomiting, patients with no emetic episodes and patients with no use of antiemetic rescue medications. Overall, rates were not constant within the cycles, which is not surprising also in consideration of the relevant patient drop-out rate between consecutive cycles, approximately halving sample size at each consecutive cycle. Possibly because of the progressively lower number of patients, different response rates were reported across the cycles, and statistical significance could not be ascertained for these comparisons as indicated by overlapping 95% CIs.

All results for the delayed or overall phase suggest efficacy of palonosetron but considering the use of anti-emetics in themselves or specifically in association with further chemotherapy after day1, and considering that from a statistical point of view, the secondary endpoints were not powered to confirm statistical effects, non-inferiority to ondansetron cannot be concluded beyond the first 24 hours after chemotherapy.

The applicant provided different subgroups analyses by age, emetogenicity, gender, race, concomitant use of corticosteroids. Overall, although large variability is detected among treatment groups in the different sub analyses, response rates are generally consistent with overall population in the main efficacy analysis.

The analysis of the primary end-point by age group and emetogenicity is worth highlighting.

Similarly to the overall population, in the HEC strata CR rate for palonosetron 20 mcg/kg were higher than ondansetron in each age group. In contrast, in the MEC setting, the CR rate was higher in the ondansetron group than in either palonosetron groups in the 0 to <2, 6 to <12 and 12 to <17 years age strata (only in the 2 to <6 years age stratum CR response was higher in the palonosetron 20 mcg/kg than in ondansetron). These inhomogeneous results might be attributed to the limited sample size.

The number of patients under 2 years included in the study was very limited (9.1% overall, 15 patients per treatment arm, with even smaller number when broken down by MEC/HEC). To give further assurance on the youngest patients the applicant provided results in the subset of patients <4 years from study PALO-10-20 indicating that palonosetron 20 mcg/kg and 10 mcg/kg were at least as effective as ondansetron for preventing CINV in this subset in the acute phase during the first cycle. Furthermore the safety data reported in the subset of patients <4 years of age were consistent with the profile of palonosetron in the four age groups evaluated in PALO-10-20 study. Nevertheless it is outlined in 4.2 of the SmPC that there is limited data on the use of Aloxi in the prevention of nausea and vomiting in children under 2 years of age.

Poorly controlled nausea and vomiting in previous chemotherapy cycles increases the likelihood of CINV. Most patients were non-naïve to chemotherapy (78.5%) with a similar distribution among the three treatment groups. For the chemotherapy naïve subgroup of patients, the rates of response during the acute phase were substantially higher for the ondansetron group compared to both palonosetron treatment groups. Whereas results need to be taken cautiously given the limited number of patients in this subgroup, information about the percentage of non-naïve patients in the pivotal trial is considered relevant for the prescriber and was included in Section 5.1 of the SmPC.

With regards to the submitted addendum to study PALO-10-14 the applicant doesn't request an indication in PONV. The efficacy results of this study, although negative for palonosetron, along with safety data from this study constitute relevant information for healthcare professionals and were included in 5.1 of the the SPC.

With regards to the submitted Addendum to study PALO-99-07 containing a post-hoc analysis where the CR in the acute phase for subgroups of patients based on WR-specified age groups and as well as by gender, race/ethnicity, and emetogenicity was re-analysed the age groups for this Post-hoc analysis are the same defined in the pivotal study. Only data on acute response has been submitted. The response data by age group support those obtained in the pivotal study (in the sub-group analyses by age) with a higher rates of response in youngest patients. Analyses by subgroups (age and gender) in the Addendum PALO-07-29 display that there aren't differences among treatment groups by age or gender, and data are consistent with results from the original study previously evaluated.

2.4.4. Conclusions on the clinical efficacy

The data provided support the efficacy of palonosetron 20mg in the treatment of acute CINV. The primary efficacy endpoint, representing the proportion of patients showing complete response (CR; defined as no vomiting, no retching, and no use of antiemetic rescue medication) from 0 to 24 hours (Acute phase) after T0 (start of most emetogenic chemotherapy) during first cycle showed significant benefit which was considered non inferior to ondansetron. Although not statistically significant, possibly due to the progressively lower number of patients and despite the absence of re-randomisation, the benefit of palonosetron was maintained in repeat cycles of chemotherapy.

However, it is not possible to conclude on the effectiveness of palonosetron in the prevention of delayed CINV, due to the potential confounding effect of concomitant antiemetics during the study period and the dosing regimen used for the comparator drug. As nausea and vomiting associated with highly emetogenic chemotherapy is showing multiphasic emetic time courses the indication statement will specify the use of Aloxi for the prevention of nausea and vomiting in HEC in the acute setting.

2.5. Clinical safety

Introduction

Safety assessments were based on reports of adverse events (AEs), findings of routine physical examination (PE), vital signs, electrocardiograms (ECG), laboratory tests, pregnancy tests, patient diary on emetic episodes and concomitant and antiemetic rescue medication consumption, as well as unexpected outcomes. Monitoring for AEs was performed at each visit and during follow-up telephone contact at each cycle.

Safety analyses were performed on the safety population (SAF), which allocated patients to treatment groups based on the treatment they actually received. The SAF included one patient who received study drug (palonosetron 10 mcg/kg) but received neither the highly emetogenic (HEC) nor the moderately emetogenic (MEC) chemotherapeutic agents and was therefore excluded from the full analysis set (FAS) and the As-treated populations at Cycle 1.

Patient exposure

The two Integrated Safety Populations for PONV and CINV studies in the overall palonosetron programme is comprised of 1377 paediatric patients including 566 paediatric cancer patients and 811 surgical patients. Among these patients, **883 received a single palonosetron dose** and 494 were treated with ondansetron. Of the 883 patients who received palonosetron in the phase 3 studies, 481 (54.5 %) patients were treated in PONV studies and **402 (45.5%) were treated in CINV studies** while for ondansetron,

330 (66.8%) patients were treated in PONV studies and 164 (33.2%) were treated in CINV studies. The proportion of patients completing the studies was high, with 872 of 883 (98.8%) patients receiving palonosetron and 490 of 494 (99.2%) patients receiving ondansetron. The distribution of patients by age group (< 2 years, 2 to < 6 years, 6 to < 12 years and 12 to < 18 years) was generally well balanced across treatments in the Integrated Safety Populations for PONV and CINV indications. Overall, more male (58.0%) than female (42.0%) patients were treated in the PONV and CINV studies. The distribution of patients by gender was generally balanced across treatments with 56.7% of male patients treated with palonosetron and 60.3% with ondansetron, compared with 43.3% of female patients treated with palonosetron and 39.7% with ondansetron

CINV

A total of 577 paediatric cancer patients receiving MEC or HEC were included in the two phase 3 studies of IV palonosetron for the prevention of CINV. Of these patients, 566 received IV study medication with MEC or HEC chemotherapy. Overall, 402 patients received palonosetron (35 received 3 mcg/kg, 204 received 10 mcg/kg, and 163 received 20 mcg/kg), and 164 patients received ondansetron in Cycle 1. Nearly all (98.4%) of the patients who received palonosetron or ondansetron in the phase 3 studies completed the study. Of the 402 patients treated with a single dose of palonosetron, 6 (1.5%) patients discontinued from the study: 3 patients (0.7%) for other reasons, 2 patients (0.5%) for AE and 1 patient (0.2%) died. Of the 164 patients who received ondansetron, 3 (1.8%) patients discontinued from the study because of withdrawal of consent, AE, and death (1 patient each, 0.6%)

PALO-10-20

Patients were scheduled to receive study treatment on Study Day 1 of each cycle for up to 4 cycles if they were to receive at least one MEC or HEC agent.

Data are included for 494 patients who received at least 1 dose of study medication: 167 patients received palonosetron 10 mcg/kg, 163 received palonosetron 20 mcg/kg, and 164 received ondansetron. It is to be noted that in the palonosetron 20 mcg/kg group, the number of patients remaining on study through the 4 cycles was numerically higher than in the other treatment groups.

Table 81 Number of Patients in the SAF Overall and in Each Cycle

SAF	Palonosetron 10 mcg/kg N	Palonosetron 20 mcg/kg N	Ondansetron 3x0.15 mg/kg N
Overall	167	163	164
Cycle 1	167	163	164
Cycle 2	84	90	86
Cycle 3	43	59	44
Cycle 4	20	31	18

N = Number of patients

Adverse events

PALO-10-20

Adverse events that occurred after signature of the informed consent and those that started before follow-up visit of the last cycle were recorded on the Adverse Events pages of the eCRF. For all Treatment Emergent

Adverse Events (TEAEs), either non-serious AEs, SAEs or Adverse Drug Reactions (ADRs), their severity (mild, moderate, or severe), intensity (CTC grade) and the Investigator's opinion on the relationship to the study treatment were recorded. AEs included illnesses with onset during the study and exacerbation of previous illnesses. Additionally, the Investigator recorded as AEs any clinically significant changes in physical examination (PE) findings and abnormal objective test findings (e.g. electrocardiogram [ECG], laboratory, etc.). For all AEs, the Investigator pursued and obtained information adequate to determine both the outcome of the AEs and whether they met the criteria for classification as SAEs. If the AE or its sequelae persisted, follow-up was performed until resolution or until the patient was lost to follow-up.

Summary of TEAEs by patient overall (through all cycles), showed that the percentage of patients with at least one TEAE was slightly higher in the ondansetron group (88.4%) than in the palonosetron 10 mcg/kg (85.6%) and palonosetron 20 mcg/kg (79.8%) groups (Table 83 on the next page). The percent of patients with at least one TEAE was comparable between palonosetron 10 mcg/kg group and ondansetron group, and lower in the palonosetron 20 mcg/kg. Only for 27 of these patients, TEAEs were judged as drug-related: for 9 patients (5.4%) in the palonosetron 20 mcg/kg group, for 8 patients (4.9%) in the palonosetron 10 mcg/kg group and for 10 patients (6.1%) in the ondansetron group.

Distribution of patients with SAEs was also similar between treatment groups with 68 patients (40.7%) in the palonosetron 10 mcg/kg group, 62 patients (38.0%) in the palonosetron 20 mcg/kg group and 70 patients (42.7%) in the ondansetron group. Only for one of these patients two SAEs were judged as possibly drug-related.

The majority of AEs reported were mild or moderate in intensity. Overall TEAEs of severe intensity were reported for 52 (31.1%) patients in the palonosetron 10 mcg/kg group, 46 (28.2%) patients in the palonosetron 20 mcg/kg group, and 53 (32.3%) of patients in the ondansetron group.

TEAEs with TEAEs with CTC grade ≥3 were reported for 111 (66.5%), 108 (66.3%), and 124 (75.6%) patients in the palonosetron 10 mcg/kg, palonosetron 20 mcg/kg, and ondansetron groups, respectively. However, only 5 TEAEs (1 palonosetron 10 mcg/kg, 3 palonosetron 20 mcg/kg, 1 ondansetron]) in this category were considered to be drug related. No patient died in the palonosetron 10 mcg/kg group, while AEs with fatal outcome occurred in 3 (1.8%) patients in the palonosetron 20 mcg/kg group and in 3 (1.8%) patients in the ondansetron group. One additional patient in the ondansetron group died after the reporting period. All deaths were considered to be unrelated to study drug.

Three patients (2 in the palonosetron 20 mcg/kg group and 1 in the ondansetron group) experienced TEAEs that led to withdrawal from the study. All of these TEAEs were considered to be serious but unrelated to study drug.

Table 83 Overview of Patients with TEAEs Overall - SAF

Category	Palonosetron 10 mcg/kg (N = 167) n (%)	Palonosetron 20 mcg/kg (N = 163) n (%)	Ondansetron 3x0.15 mg/kg (N = 164) n (%)
At least one TEAE	143 (85.6%)	130 (79.8%)	145 (88.4%)
At least one drug related TEAE[1]	9 (5.4%)	8 (4.9%)	10 (6.1%)
At least one serious TEAE	68 (40.7%)	62 (38.0%)	70 (42.7%)
At least one serious drug related TEAE	–	1 (0.6%)	–
At least one severe TEAE	52 (31.1%)	46 (28.2%)	53 (32.3%)
At least one severe drug related TEAE	–	1 (0.6%)	–
At least one TEAE with CTC grade ≥3	111 (66.5%)	108 (66.3%)	124 (75.6%)
At least one drug-related TEAE with CTC grade ≥3	1 (0.6%)	3 (1.8%)	1 (0.6%)
Fatal TEAE	–	3 (1.8%)	3 (1.8%)
Withdrawn due to TEAE	–	2 (1.2%)	1 (0.6%)
Withdrawn due to drug-related TEAE	–	–	–

n = Total number of patients with at least one TEAE.
% = Percentage of patients with at least one TEAE.

TEAEs in the SOC Blood and lymphatic system disorders were represented by 105 (62.9%), 101 (62.0%), and 111 (67.7%) patients treated with palonosetron 10 mcg/kg, palonosetron 20 mcg/kg and ondansetron, respectively. The most frequently reported PTs were Anaemia, Thrombocytopenia, Leukopenia and Neutropenia, all representing expected events after chemotherapy. All of these PTs were reported for ≥20% of patients in at least one treatment group and all represent PTs typically observed in cancer patients, being expected cytotoxic effects of chemotherapy. Moreover, those events were all assessed by the Investigator as unrelated to the study drug. In general, the AEs noted for Blood and lymphatic disorders were balanced across treatment groups, with few exceptions for Leukopenia, Pancytopenia and Lymphopenia occurring at a lower frequency in the palonosetron 20 mcg/kg, while the percent of patients with Neutropenia and Febrile neutropenia was lower in the ondansetron group.

Regarding the SOC Gastrointestinal disorders, the most frequently reported PTs were Vomiting, Abdominal pain, Stomatitis and Diarrhoea, all reported for <15% in each treatment group. In the SOC General disorders and administration site conditions, the most frequently reported PT was Pyrexia, reported by 34 (20.4%), 22 (13.5%), and 25 (15.2%) of patients treated with palonosetron 10 mcg/kg, palonosetron 20 mcg/kg and ondansetron, respectively.

No clinically significant differences were observed between the three treatment groups.

Table 85 Summary of TEAEs by SOC and PTs for all SOCs and for PTs reported for ≥2% of Patients in any Treatment Group - SAF

MedDRA SOC MedDRA PT	Palonosetron 10 mcg/kg (N=167) n (%) E	Palonosetron 20 mcg/kg (N=163) n (%) E	Ondansetron 3x0.15 mg/kg (N=164) n (%) E
Any SOC	143 (85.6%) 940	130 (79.8%) 828	145 (88.4%) 1043
Blood and lymphatic system disorders	105 (62.9%) 438	101 (62.0%) 362	111 (67.7%) 458
Anaemia	77 (46.1%) 128	70 (42.9%) 106	73 (44.5%) 122
Thrombocytopenia	43 (25.7%) 86	38 (23.3%) 72	43 (26.2%) 101
Leukopenia	43 (25.7%) 86	29 (17.8%) 66	50 (30.5%) 120
Neutropenia	44 (26.3%) 74	36 (22.1%) 64	31 (18.9%) 54
Febrile neutropenia	36 (21.6%) 44	34 (20.9%) 42	27 (16.5%) 42
Pancytopenia	6 (3.6%) 9	3 (1.8%) 4	6 (3.7%) 6
Lymphopenia	6 (3.6%) 6	3 (1.8%) 3	4 (2.4%) 4
Gastrointestinal disorders	57 (34.1%) 120	59 (36.2%) 127	68 (41.5%) 155
Vomiting	14 (8.4%) 22	18 (11.0%) 40	22 (13.4%) 31
Abdominal pain	17 (10.2%) 24	13 (8.0%) 16	18 (11.0%) 25
Stomatitis	11 (6.6%) 15	13 (8.0%) 15	13 (7.9%) 17
Diarrhoea	13 (7.8%) 14	8 (4.9%) 9	14 (8.5%) 17
Constipation	9 (5.4%) 10	10 (6.1%) 12	8 (4.9%) 9
Nausea	8 (4.8%) 10	6 (3.7%) 8	13 (7.9%) 19
Abdominal pain upper	2 (1.2%) 2	4 (2.5%) 4	6 (3.7%) 6
General disorders and administration site conditions	47 (28.1%) 75	38 (23.3%) 63	40 (24.4%) 68
Pyrexia	34 (20.4%) 47	22 (13.5%) 38	25 (15.2%) 45
Mucosal inflammation	8 (4.8%) 10	6 (3.7%) 13	6 (3.7%) 9

Investigations	39 (23.4%) 84	37 (22.7%) 82	36 (22.0%) 84
White blood cell count decreased	16 (9.6%) 23	18 (11.0%) 26	19 (11.6%) 28
Platelet count decreased	12 (7.2%) 16	12 (7.4%) 15	10 (6.1%) 20
Lymphocyte count decreased	4 (2.4%) 4	7 (4.3%) 9	6 (3.7%) 6
Neutrophil count decreased	3 (1.8%) 4	8 (4.9%) 10	6 (3.7%) 6
Alanine aminotransferase increased	4 (2.4%) 8	4 (2.5%) 4	7 (4.3%) 7
C-reactive protein increased	3 (1.8%) 4	4 (2.5%) 5	-
Haemoglobin decreased	4 (2.4%) 9	-	1 (0.6%) 1
Infections and infestations	31 (18.6%) 36	34 (20.9%) 46	43 (26.2%) 60
Infection	6 (3.6%) 6	3 (1.8%) 3	5 (3.0%) 8
Device related infection	3 (1.8%) 4	4 (2.5%) 4	3 (1.8%) 3
Respiratory tract infection	-	4 (2.5%) 7	4 (2.4%) 4
Upper respiratory tract infection	1 (0.6%) 1	4 (2.5%) 4	3 (1.8%) 3
Pneumonia	2 (1.2%) 2	1 (0.6%) 1	4 (2.4%) 4
Nervous system disorders	23 (13.8%) 37	20 (12.3%) 24	24 (14.6%) 42
Headache	17 (10.2%) 24	9 (5.5%) 10	17 (10.4%) 29
Metabolism and nutrition disorders	21 (12.6%) 36	19 (11.7%) 34	21 (12.8%) 48
Hypokalaemia	8 (4.8%) 9	4 (2.5%) 6	6 (3.7%) 9
Hypoalbuminaemia	3 (1.8%) 5	5 (3.1%) 5	7 (4.3%) 12
Decreased appetite	3 (1.8%) 3	4 (2.5%) 4	3 (1.8%) 3
Hyponatraemia	2 (1.2%) 3	2 (1.2%) 2	5 (3.0%) 5
Hypocalcaemia	1 (0.6%) 4	2 (1.2%) 3	5 (3.0%) 7
Dehydration	1 (0.6%) 1	4 (2.5%) 4	2 (1.2%) 2
Respiratory, thoracic and mediastinal disorders	21 (12.6%) 24	16 (9.8%) 18	23 (14.0%) 29
Cough	8 (4.8%) 8	4 (2.5%) 4	9 (5.5%) 10
Epistaxis	5 (3.0%) 7	1 (0.6%) 1	6 (3.7%) 7

Looking at TEAEs in each cycle, the most frequently reported PTs were Anaemia, Thrombocytopenia, Leukopenia, Neutropenia, Febrile neutropenia, and Pyrexia. All of these PTs were reported for ≥20% of patients in at least one treatment group. In general, the percentage of patients experiencing these TEAEs was comparable across treatment groups overall and within each cycle.

Progression into subsequent cycles did not appear to induce worsening of TEAEs in any SOC, and rather a slight trend toward reduction in the incidence of TEAEs during progression through cycles was noted.

To assess adverse events per age group, patients were stratified in four groups of <2 years, 2 to <6 years, 6 to <12 years, and 12 to <17 years. Except in the youngest age group where only 15 patients were treated in each treatment group, in the other strata the patients were distributed almost equally, with a minimum of 45 to a maximum of 55 patients in each stratum, the percentages of patients with at least one TEAE were similar across treatments within age strata and across age strata within treatment. Only a slightly higher frequency (not statistically significant) of TEAEs was observed in the ondansetron treatment arm, compared to that of each palonosetron treatment for all age groups, except in the 2 to <6 years age stratum, where the frequency was comparable across treatment groups.

The percentage of patients with TEAEs of severe intensity or CTC grade ≥3 did not appear to be influenced by age either.

In general, it was observed that Blood and lymphatic system disorders, Gastrointestinal disorders, and General disorders and administration site conditions were the MedDRA SOC with the most frequent TEAEs in all age groups.

The very low incidence and absolute numbers of related TEAEs did not permit the identification of any differential trends between HEC- and MEC-treated patients.

The overall number of TEAEs by gender was comparable between male and female patients, although there were some particularities, differences highlighted are considered of unlikely clinical relevance, particularly for the palonosetron 10 mcg/kg group, since opposite or no differences could be observed in the same categories for the higher palonosetron 20 mcg/kg dose group.

Due to the small number of patients in race categories other than white, a clear assessment of the effect of race on the AE profile was not possible. In each ethnicity category, the percentages were comparable across treatment, with palonosetron 20 mcg/kg showing slightly lower percentages. Enrolment of non-White or Hispanic patients was low and there was therefore a limited assessment of any potential impact of these demographic characteristics.

Musculoskeletal and connective tissue disorders	16 (9.6%) 22	11 (6.7%) 13	21 (12.8%) 26
Pain in extremity	6 (3.6%) 8	3 (1.8%) 3	9 (5.5%) 9
Back pain	2 (1.2%) 2	4 (2.5%) 4	4 (2.4%) 4
Skin and subcutaneous tissue disorders	9 (5.4%) 13	13 (8.0%) 14	19 (11.6%) 22
Rash	3 (1.8%) 3	6 (3.7%) 6	1 (0.6%) 1
Vascular disorders	11 (6.6%) 13	4 (2.5%) 6	9 (5.5%) 10
Hypertension	3 (1.8%) 3	2 (1.2%) 3	6 (3.7%) 7
Cardiac disorders	7 (4.2%) 8	5 (3.1%) 6	8 (4.9%) 11
Sinus tachycardia	1 (0.6%) 1	1 (0.6%) 1	5 (3.0%) 7
Hepatobiliary disorders	5 (3.0%) 6	3 (1.8%) 3	8 (4.9%) 10
Hepatotoxicity	2 (1.2%) 2	-	4 (2.4%) 4
Liver disorder	1 (0.6%) 2	-	4 (2.4%) 4
Injury, poisoning and procedural complications	4 (2.4%) 4	8 (4.9%) 10	4 (2.4%) 6
Eye disorders	6 (3.6%) 6	4 (2.5%) 5	3 (1.8%) 3
Psychiatric disorders	5 (3.0%) 8	4 (2.5%) 4	2 (1.2%) 2
Ear and labyrinth disorders	3 (1.8%) 5	1 (0.6%) 1	1 (0.6%) 1
Immune system disorders	1 (0.6%) 1	3 (1.8%) 4	1 (0.6%) 1
Renal and urinary disorders	2 (1.2%) 2	2 (1.2%) 2	1 (0.6%) 1
Congenital, familial and genetic disorders	-	-	3 (1.8%) 5
Endocrine disorders	1 (0.6%) 1	1 (0.6%) 1	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-	2 (1.2%) 2	-
Reproductive system and breast disorders	-	1 (0.6%) 1	1 (0.6%) 1
Surgical and medical procedures	1 (0.6%) 1	-	-

The vast majority of patients had only TEAEs evaluated as not related. TEAEs considered to be drug related were reported for 9 (5.4%) patients in the palonosetron 10 mcg/kg group, 8 (4.9%) patients in the palonosetron 20 mcg/kg group, and 10 (6.1%) patients in the ondansetron group. In the whole study, there was only one patient in the ondansetron arm who reported a TEAE with definite relationship to the study drug. The incidence of related TEAEs was very low across the three treatment groups, and no clear difference could be identified in any of the SOC/PTs, either between palonosetron and ondansetron arms, or between the two palonosetron dose levels. Overall, the number of patients with related TEAEs in each treatment group was similar.

Injection site reactions related to the study drug were reported in 2 patients, for a total of 3 related TEAEs (all non-serious). Infusion site reaction and Infusion site erythema were reported for 1 (0.6%) 5 year-old

female patient [] in the palonosetron 10 mcg/kg group who received MEC. The onset of Infusion site reaction was on the day of treatment of the first cycle, while the onset of Infusion site erythema was on the day of treatment of the second cycle. Both TEAEs resolved within one day. Both TEAEs were considered by the Investigator to be of mild intensity and possibly related to study drug. Neither TEAE was an SAE.

Infusion site pain was reported for 1 (0.6%) 3 year-old male patient [] in the palonosetron 20 mcg/kg group.

Overall TEAEs of severe intensity were reported for 52 (31.1%) patients in the palonosetron 10 mcg/kg group, 46 (28.2%) patients in the palonosetron 20 mcg/kg group, and 53 (32.3%) of patients in the ondansetron group The vast majority of patients with TEAEs of severe intensity was reported during Cycle 1, with 41 (24.6%) patients in the palonosetron 10 mcg/kg group, 34 (20.9%) patients in the palonosetron 20 mcg/kg group, and 41 (25.0%) of patients in the ondansetron group. There was a gradual reduction in the number of patients with severe events from Cycle 1 to Cycle 4, largely corresponding to the overall decrease of patients enrolled in subsequent cycles. Indeed, a small decrease in percentage values could be observed across cycles. A trend of reduced number of severe events for the palonosetron 20 mcg/kg group in comparison to the other two arms can be observed for Cycle 1 and Cycle 2 that also enrolled a higher number of patients.

CINV

In the integrated CINV safety population for palonosetron all doses (N=402) a lower proportion of patients receiving palonosetron (77.4%) than ondansetron (81.7%) had at least 1 TEAE. In the palonosetron dose groups, there was no apparent dose-effect on the frequency of TEAEs, with the lowest proportion of patients with at least 1 TEAE reported in the palonosetron 20 mcg/kg group (69.3%) compared with the palonosetron 10 mcg/kg (83.3%) and 3 mcg/kg groups (80.0%).

The incidences of TEAEs (including severe, leading to withdrawal, serious, and fatal) were comparable or lower in patients receiving palonosetron compared with those receiving ondansetron. There was no apparent effect of palonosetron dose, with the lowest proportions of patients with serious TEAEs and severe TEAEs reported in the palonosetron 20 mcg/kg group compared with the palonosetron 10 mcg/kg and 3 mcg/kg groups.

None of the serious or severe TEAEs were assessed by the Investigators as related to study drug during Cycle 1. Similarly, among the 3 patients withdrawn from the studies because of TEAEs, no events were assessed as drug related. Overall, 1 (0.6%) patient in the palonosetron 20 mcg/kg group and 2 (1.2%) patients in the ondansetron group died during Cycle 1 of the study PALO-10-20 and one patient died after the follow-up period. No death was reported in study PALO-99-07. The Investigators considered all AEs that led to fatal outcomes to be unrelated or unlikely related to study drug.

The proportion of patients reported with at least 1 TEAE was similar across all age groups for both study medications. With the exception of patients aged 2 to < 6 years, the incidence of TEAEs was lower in patients receiving palonosetron compared with those receiving ondansetron. In children aged 2 to < 6 years, 391 events were reported in 98 (83.8%) patients who received palonosetron compared with 154 events in 41 (74.5%) patients who received ondansetron. There was no apparent effect of palonosetron dose in any age group in patients who were reported with at least 1 TEAE.

The incidence of TEAEs reported as drug-related was very low in the palonosetron group with 23 events in 17 (4.2%) patients and 9 events in 7 (4.3%) patients in the ondansetron group and precluded any meaningful comparison of drug-related events across age groups. Headache was the most commonly reported drug-related TEAE overall, with 5 events reported in 4 patients (1.0%) in the palonosetron group and 2 events reported in 2 patients (1.2%) in the ondansetron group. There does not appear to be any dose-relationship; however, the low number of patients with drug-related TEAEs in each palonosetron dose group precludes any meaningful interpretation of the data by palonosetron dose. Moreover the incidence of

drug-related TEAEs was not notably different in the three palonosetron dose groups. Although small differences were observed across age groups and between treatments, no consistent trends were identified. There were no drug-related events reported in patients aged < 2 years. The incidences of drug-related TEAEs were higher in patients aged 2 to < 6 years and 6 to < 12 years in the palonosetron group (6.0% and 7.1%, respectively) compared with the ondansetron group (1.8% and 4.4%, respectively). The incidence of drug-related TEAEs in patients aged 12 to < 18 years was higher in the ondansetron group (8.2%) compared with the palonosetron group (1.5%). The small differences observed between age groups are not likely to be of clinical significance. More female (4.7%) than male (3.8%) patients had drug-related TEAEs for palonosetron compared to 9.1% and 1% in the ondansetron control group. Similar results were observed within each palonosetron dose group. Headache was reported in more female patients receiving ondansetron (3.0%) than palonosetron (1.6%). Drug-related TEAEs were reported more frequently in Hispanic patients receiving ondansetron (15.4%) than those receiving palonosetron (7.1%). Overall, the incidences of all categories of TEAEs were comparable in patients receiving MEC and HEC, although differences were observed between treatment groups, no clear trend was identified for either treatment group.

The incidence of serious TEAEs was slightly lower in patients who received palonosetron (30.3%) compared with patients who received ondansetron (33.5%). At the SOC level, serious TEAEs in the Blood and lymphatic system disorder SOC were the most common overall (22.3%) and in both treatment groups (21.4% for palonosetron and 24.4% for ondansetron). The serious TEAE febrile neutropenia was the most commonly reported PT overall (11.1%), with 10.9% in the palonosetron and 11.6% in the ondansetron treatment groups. None of the serious TEAEs reported in the studies during Cycle 1 was assessed by the Investigator as drug-related. There was no apparent effect of palonosetron dose on the types or incidences of serious TEAEs.

Only 3 paediatric patients withdrew from the studies because of a TEAE; 2 (0.5%) patients in the palonosetron group and 1 (0.6%) patient in the ondansetron group. In the palonosetron group one patient was discontinued due to febrile neutropenia and one due to a haemorrhagic stroke while in the ondansetron treatment group one patient was withdrawn due to febrile neutropenia.

Common AEs CINV

The most common TEAEs across the two paediatric trials were as expected in the context of cancer patients receiving chemotherapy. There were no apparent effects of palonosetron dose, and no meaningful differences in the palonosetron and ondansetron treatment groups. TEAEs in the Blood and lymphatic system disorders SOC were the most common in both palonosetron and ondansetron groups, followed by TEAEs in the Gastrointestinal disorders, General disorders and administration site conditions, Investigations, Infections and infestations, Nervous system disorders and Metabolism and nutrition disorders SOCs. TEAEs belonging to other SOCs occurred in the overall database at a frequency <10% [Module 2.7.4 CINV, Table 2-5].

TEAEs in the Blood and lymphatic system disorders SOC were the most common in both treatment groups (51.2% for palonosetron and 59.1% for ondansetron). Anaemia was the most commonly reported TEAE in the palonosetron (33.1%) and ondansetron (33.5%) treatment groups followed by thrombocytopenia (18.2% palonosetron, 20.1% ondansetron), neutropenia (7.4% palonosetron, 14.0% ondansetron) and leukopenia (14.4% palonosetron, 20.7% ondansetron).

TEAEs in the Gastro-intestinal disorders SOC were reported in 30.1% of patients receiving palonosetron compared to 34.1% of patients receiving ondansetron. With the exception of constipation (6.2% of palonosetron patients compared with 4.3% of patients in the ondansetron group), TEAEs in the Gastrointestinal disorders SOC were generally reported with similar or lower frequencies in the palonosetron treatment groups compared with the ondansetron group. None of the 25 constipations reported in 25 patients receiving palonosetron were assessed by the Investigators as related to study drug.

TEAEs in the General disorders SOC occurred in 25.9% of patients in the palonosetron and 19.5% in ondansetron treatment groups. Events in this SOC included pyrexia, mucosal inflammation and fatigue. The frequency for all of these events was higher in the palonosetron group compared to ondansetron. There was no apparent effect of palonosetron dose on the frequency of these events.

TEAEs in the Investigations SOC were 17.2% of patients in the palonosetron and 16.5% in the ondansetron treatment groups. The most common events within this SOC were decreases in white blood cells, platelets, neutrophils and lymphocytes. There were no differences between treatment groups and no effect of palonosetron dose on the frequency of events.

TEAEs in the Infections and infestations SOC occurred in 16.2% of patients in the palonosetron and 18.3% in the ondansetron groups. There was no individual PT that occurred in greater than 2% of patients.

TEAEs in the Nervous system disorders SOC were 11.7% in the palonosetron group and 13.4% in the ondansetron group. Headache was reported with a higher incidence in patients receiving ondansetron (10.4%) compared with patients receiving palonosetron (6.5%). Headache assessed by the Investigators as drug-related was reported for 3 (1.5%) patients receiving 10 mcg/kg palonosetron, 1 (0.6%) patient receiving 20 mcg/kg palonosetron, and 2 (1.2%) patients receiving ondansetron. All other TEAEs in this SOC were reported in less than 2% of patients.

TEAEs in the Metabolism and nutrition disorders SOC occurred in 12.4% of patients in the palonosetron and 10.4% in the ondansetron groups. The only events that occurred in greater than 2% of patients overall were hypoalbuminaemia, hypokalaemia and hyponatraemia. There were no meaningful differences in event frequencies between treatment groups or between palonosetron doses.

By age group the most common TEAEs across age groups were those reflected in the overall population. There were no notable differences between age groups in the frequency of the most common TEAEs including anaemia, neutropenia, thrombocytopenia or leukopenia. The frequency of pyrexia was also similar across the age groups although it was slightly lower in the ondansetron 2 to <6 year age group. For Gastrointestinal disorders, frequencies were similar between palonosetron and ondansetron-treated patients except in the oldest age group where 31.5% of palonosetron patients reported GI disorders compared to 42.9 % of ondansetron-treated patients. Constipation was not reported for any patient <2 years old; the relevant frequencies in the palonosetron-treated age groups ranged from 6.0% to 7.7% while in the ondansetron age groups they ranged from 3.6% to 8.9%. For Nervous system disorders TEAEs, there were some differences in the incidence by age group between palonosetron and ondansetron, however there was no pattern. This finding is considered to be due to the small numbers of patients reporting nervous system events in each age group.

Serious adverse event / deaths / other significant events

Deaths PALO-10-20

All deaths occurred during the study, including the post treatment follow-up period, and deaths that resulted from a process that began during the study, were considered in this section. The deaths of the patients deceased during the study or after the observational period, were all considered by the Investigators to be unrelated to study drug and are briefly described here below.

Patient (palonosetron 20 mcg/kg) was an 11-year-old male patient who received MEC. TEAEs with fatal outcome included Cardiac arrest, Respiratory arrest, and Loss of consciousness.

Patient (ondansetron) was a 2-year-old female patient who received MEC. She died in the post-observational period (89 days after study drug administration) due to Respiratory failure.

Patient (ondansetron) was a 15-year-old male patient who received MEC. The TEAE with fatal outcome was Respiratory failure.

Patient (ondansetron) was a 15-year-old female patient who received HEC. TEAEs with fatal outcome included Multi-organ failure, Pulmonary haemorrhage and Staphylococcal sepsis.

Patient (palonosetron 20 mcg/kg) was a 2-year-old male who received HEC. The TEAE with fatal outcome was Neoplasm progression.

Patient (palonosetron 20 mcg/kg) was a 9-year-old male patient who received MEC. TEAEs with fatal outcome included Brain oedema, Haemorrhagic stroke and Multi-organ failure; this last event started after the observational period (40 days after study drug administration).

Patient (ondansetron) was a 13-year-old female patient who received MEC. TEAEs with fatal outcome included Febrile neutropenia, Candidiasis, and Multi-organ failure.

SAEs PALO-10-20

Overall, SAEs were reported for 68 (40.7%) patients in the palonosetron 10 mcg/kg group, 62 (38.0%) patients in the palonosetron 20 mcg/kg group and 70 (42.7%) in the ondansetron group (Table 102).

Table 102 Summary of SAEs Reported for ≥2% of Patients by SOC and PT - Overall - SAF

MedDRA SOC MedDRA PT	Palonosetron 10 mcg/kg (N=167) n (%) E	Palonosetron 20 mcg/kg (N=163) n (%) E	Ondansetron 3x0.15 mg/kg (N=164) n (%) E
Any SOC	68 (40.7%) 171	62 (38.0%) 147	70 (42.7%) 182
Blood and lymphatic system disorders	52 (31.1%) 105	49 (30.1%) 89	53 (32.3%) 104
Febrile neutropenia	27 (16.2%) 31	30 (18.4%) 38	23 (14.0%) 35
Anaemia	17 (10.2%) 21	14 (8.6%) 17	15 (9.1%) 17
Neutropenia	12 (7.2%) 14	10 (6.1%) 13	11 (6.7%) 14
Thrombocytopenia	14 (8.4%) 17	8 (4.9%) 11	9 (5.5%) 11
Leukopenia	10 (6.0%) 12	4 (2.5%) 7	9 (5.5%) 16
Pancytopenia	6 (3.6%) 9	2 (1.2%) 2	6 (3.7%) 6
Infections and infestations	15 (9.0%) 16	10 (6.1%) 10	17 (10.4%) 23
Infection	4 (2.4%) 4	1 (0.6%) 1	3 (1.8%) 5
Gastrointestinal disorders	8 (4.8%) 9	7 (4.3%) 8	12 (7.3%) 14
Abdominal pain	4 (2.4%) 4	–	1 (0.6%) 1
General disorders and administration site conditions	10 (6.0%) 13	6 (3.7%) 6	11 (6.7%) 12
Pyrexia	6 (3.6%) 7	3 (1.8%) 3	7 (4.3%) 7
Investigations	9 (5.4%) 14	7 (4.3%) 12	4 (2.4%) 5
White blood cell count decreased	6 (3.6%) 9	6 (3.7%) 8	4 (2.4%) 4
Nervous system disorders	2 (1.2%) 2	5 (3.1%) 7	6 (3.7%) 7
Metabolism and nutrition disorders	1 (0.6%) 2	5 (3.1%) 5	6 (3.7%) 6
Respiratory, thoracic and mediastinal disorders	4 (2.4%) 4	3 (1.8%) 3	3 (1.8%) 4

The overall percentage of patients experiencing SAEs was comparable across treatment groups within subgroup categories and generally was similar for subgroup categories within treatment. Most of the SAEs observed in this study are in the SOCs of Blood and lymphatic system disorders, followed by Infections and infestations as expected in the context of cancer patients receiving chemotherapy. Drug-related SAEs were reported for only 1 patient, with positive outcome.

Patient was a 9-month-old, white, non-Hispanic male with rhabdomyosarcoma. Relevant medical history included radical tumour resection, cystectomy with prostatectomy, and bilateral uretero-cutaneous fistulae. He was administered palonosetron 20 mcg/kg on 4 April 2012 (Cycle 2) and developed Diarrhoea (CTC Grade 4/severe) on 12 April 2012 (29 days after the first administration of study drug) and Dehydration (CTC Grade 3/severe) on 17 April 2012 (34 days after the first administration of study drug). These SAEs prolonged his hospitalisation and then resolved after treatment. Both SAEs were considered by the Investigator to be possibly related to study drug.

CINV

The incidence of serious TEAEs was slightly lower in patients who received palonosetron (30.3%) compared with patients who received ondansetron (33.5%). At the SOC level, serious TEAEs in the Blood and lymphatic system disorder SOC were the most common overall (22.3%) and in both treatment groups (21.4% for palonosetron and 24.4% for ondansetron). The serious TEAE febrile neutropenia was the most commonly reported PT overall (11.1%), with 10.9% in the palonosetron and 11.6% in the ondansetron treatment groups. None of the serious TEAEs reported in the studies during Cycle 1 was assessed by the Investigator as drug-related. There was no apparent effect of palonosetron dose on the types or incidences of serious TEAEs

Laboratory findings

PALO-10-20

Clinical laboratory evaluations were performed at baseline and at Visit 7 of each cycle for haematology, serum chemistry and urinalysis. An additional sample for serum chemistry was taken immediately after the end of the first study drug infusion. Hepatic and renal functions were monitored through measurements of AST, ALT, bilirubin and creatinine levels, whereas impact of EDTA was evaluated by measuring levels of ionised calcium.

The percentages of patients with abnormal haematology parameters reported as TEAEs was comparable across treatment groups. The only abnormal haematology parameter considered by the Investigator to be drug related was reported for Patient (palonosetron 10 mcg/kg, HEC), a 4-year-old female who developed Thrombocytopenia 7 days after administration of study drug during Cycle 2. This TEAE was non serious and resolved 3 days later. SAEs relevant to haematology abnormalities were all judged as not related to study drug, being effects of chemotherapy administration.

Values of AST, ALT, bilirubin and creatinine showed no concerns regarding hepatic or renal functions in patients of all treatment groups. SAEs relevant to blood chemistry abnormalities were all judged as not related to study drug and their incidence was very low (<2% of patients).

No drug-related TEAEs were reported for urinalysis parameters.
SAEs relevant to urinalysis abnormalities were all judged as not related to study drug and their incidence was very low (<2% of patients).

Integrated CINV

The incidences of laboratory shifts were generally comparable across doses and between treatment groups, and were consistent with shifts that would be expected in cancer patients undergoing chemotherapy.

Vital Signs: PALO-10-20

Changes from baseline in SBP, DBP, and PR were generally similar across treatment group, overall and within age strata. The small number of patients in the <2 years old age group and progressively decreasing numbers of patients in study Cycles 2, 3 and 4 precluded robust assessment of these results. The only drug related TEAE regarding vital signs was Hypertension reported for 1 (0.6%) patient in the ondansetron group

PALO-10-20: ECG

ECG abnormalities that the Investigators considered to be drug-related TEAEs were Electrocardiogram QT prolonged (0.6% in palonosetron 20 mcg/kg and 1.2% in ondansetron arms), Sinus tachycardia (0.6% in palonosetron 10 mcg/kg and 1.2% in ondansetron arms), and Conduction disorder (0.6% in palonosetron 10 mcg/kg and 1.2% in ondansetron arms)

ECG outliers reported as AEs were Electrocardiogram QT prolonged for 1 patient treated with palonosetron 20mcg/kg and for 2 patients treated with ondansetron.

Integrated CINV: ECG

The most common ECG abnormalities, occurring in ≥ 10% of patients in the Integrated Safety Population for palonosetron and/or ondansetron treatment groups were increases from baseline in heart rate ≥ 25% and heart rate values > 100 beats/min (9.5% and 12.2% for palonosetron and ondansetron, respectively), changes in QTcB values from ≤ 450 msec at baseline to > 450 msec post-baseline (14.9% and 22.6% for palonosetron and ondansetron, respectively), and changes from baseline in QTcB values of > 30 msec to ≤ 60 msec (9.7% and 12.8% for palonosetron and ondansetron, respectively).

The most frequently reported ECG abnormalities occurred with lower frequencies in the palonosetron group compared with ondansetron control group. In general, ECG findings were reported with similar frequencies in the palonosetron 10 mcg/kg and 20 mcg/kg groups. When evaluated by age group, small differences were observed between treatment groups that are not likely to be of clinical importance. There was no apparent effect of treatment or dose on the 3 most commonly reported ECG abnormalities when evaluated by age groups

Table 4-1 Summary of ECG Abnormality in CINV Studies in Paediatric Patients (Safety Population - Cycle 1)

Abnormality in ECG	Palonosetron 3 mcg/kg (N=35) n (%)	Palonosetron 10 mcg/kg (N=204) n (%)	Palonosetron 20 mcg/kg (N=163) n (%)	Palonosetron All Doses (N=402) n (%)	Ondansetron 3x0.15 mg/kg (N=164) n (%)	All Drugs, All Doses (N=566) n (%)
HR decrease ≥ 25% from baseline and HR< 50 beat/min	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	0 (0.0)	1 (0.2)
HR increase ≥ 25% from baseline and HR > 100 beat/min	2 (5.7)	21 (10.3)	15 (9.2)	38 (9.5)	20 (12.2)	58 (10.2)
PR abnormality (increase ≥25% from baseline and PR > 200 msec)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QRS abnormality (increase ≥ 25% from baseline and QRS > 100 msec)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QT post-baseline value > 450 msec and baseline value ≤ 450 msec	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	0 (0.0)	1 (0.2)
QT post-baseline value > 480 msec and baseline value ≤ 480 msec	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	0 (0.0)	1 (0.2)
QT post-baseline value > 500 msec and baseline value ≤ 500 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
QTcB post-baseline value > 450 msec and baseline value ≤ 450 msec	4 (11.4)	29 (14.2)	27 (16.6)	60 (14.9)	37 (22.6)	97 (17.1)
QTcB post-baseline value > 480 msec and baseline value ≤ 480 msec	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	4 (2.4)	5 (0.9)
QTcB post-baseline value > 500 msec and baseline value ≤ 500 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
QTcB change from baseline > 30 to ≤ 60 msec	4 (11.4)	20 (9.8)	15 (9.2)	39 (9.7)	21 (12.8)	60 (10.6)
QTcB change from baseline > 60 msec	1 (2.9)	3 (1.5)	1 (0.6)	5 (1.2)	0 (0.0)	5 (0.9)
QTcF post-baseline value > 450 msec and baseline value ≤ 450 msec	0 (0.0)	0 (0.0)	2 (1.2)	2 (0.5)	3 (1.8)	5 (0.9)
QTcF post-baseline value > 480 msec and baseline value ≤ 480 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QTcF post-baseline value > 500 msec and baseline value ≤ 500 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QTcF change from baseline > 30 to ≤ 60 msec	3 (8.6)	16 (7.8)	11 (6.7)	30 (7.5)	16 (9.8)	46 (8.1)
QTcF change from baseline > 60 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Safety related to drug-drug interactions and other interactions

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

Discontinuation due to adverse events

SAEs PALO-10-20 Leading to Withdrawal

Three patients were withdrawn from the study due to SAEs. Febrile neutropenia led to withdrawal of 1 patient in the palonosetron 20 mcg/kg group and 1 patient in the ondansetron group. Haemorrhagic stroke led to withdrawal of 1 patient in the palonosetron 20 mcg/kg group [patient died]. All of these SAEs were considered to be unrelated to study drug.

2.5.1. Discussion on clinical safety

The general safety profile observed in PALO-10-20 was as expected considering the context of cancer paediatric patients receiving MEC or HEC chemotherapy. Clinically relevant differences between treatments in the safety profile were not observed in the overall study population or in subgroups of patients based on age (although a limited number of patients under 2 years of age were included), gender, race, ethnicity or emetogenicity of chemotherapy.

The type and frequency of TEAEs was similar for palonosetron 10 mcg/kg, palonosetron 20 mcg/kg and ondansetron. In particular, when compared to the 10 mcg/kg palonosetron lower dose level, there was no obvious increase in toxicity following treatment with the higher 20 mcg/kg palonosetron dosage.

The most frequently reported TEAEs were those commonly observed following chemotherapy in cancer patients and belonged to MedDRA SOCs of Blood and lymphatic disorders (most frequently reported PTs: Anaemia, Thrombocytopenia, Leukopenia and Neutropenia), Gastrointestinal disorders (most frequently reported PTs: Vomiting, Abdominal pain, Stomatitis and Diarrhoea) and General disorders and administration site conditions (most frequently reported PT: Pyrexia).

There was no SOC or PT in which any treatment was less well tolerated than the others; progression into subsequent cycles did not appear to induce worsening of TEAEs in any SOC. With repeated cycles, the safety profile was not worse.

Most TEAEs in each treatment group was evaluated by the Investigators as not related. Drug-related TEAEs were reported only during the first and second cycles of treatment for the three groups. Only 5.4% patients in the palonosetron 10 mcg/kg group, 4.9% in the palonosetron 20 mcg/kg group and 6.1% in the ondansetron group reported TEAEs considered to be drug related. All related TEAEs were assessed as ‘possibly related’ with the exception of one TEAE in the palonosetron 20 mcg/kg group and one TEAE in the ondansetron group considered ‘probable related’ and only one TEAE from the ondansetron group with a definite relationship to the study drug.

The most frequently drug-related TEAEs belong to MedDRA SOC Nervous system disorders (most frequently reported PTs: Headache, Dizziness and Dyskinesia), which were reported in Cycle 1 in 1.8% patients in both the palonosetron groups and 1.2% patients in the ondansetron group, and in Cycle 2 in 1.2% patient in palonosetron 10 mcg/kg group and ondansetron group (none in palonosetron 20 mcg/kg group). In Cycle 1 only, there were 0.6% patients in the palonosetron 20 mcg/kg group and 1.2% patients in the ondansetron group presenting Cardiac disorders (reported PTs: Sinus tachycardia and Conduction disorder). Events of the SOC Investigations (reported PT: Electrocardiogram QT prolonged) occurred in 0.6% and 1.1% of patients in the palonosetron 20 mcg/kg group, and in 1.2% and 1.2% of patients in the ondansetron group during Cycle 1 and Cycle 2, respectively.

Most ECG abnormalities were not considered as drug-related TEAEs by the Investigators. None of these abnormalities was considered as serious with one exception: a Sinus tachycardia in the ondansetron group. Treatment-emergent abnormalities were observed most frequently for rhythm and conduction but these abnormalities should be considered in a setting of cancer paediatric patients with confounding factors and chemotherapy administration. The DMC, after evaluating all cardiac abnormalities and performing a thorough review of the ECG outliers, concluded that no increased risks in children receiving palonosetron were found.

In the whole study, no patients had drug-related TEAEs with fatal outcome or discontinued the study because of drug-related TEAEs. Study treatment was not unblinded for any patient due to SUSAR.

The overall percentage of patients experiencing SAEs was comparable across treatment groups within subgroup categories and generally was similar for subgroup categories within each treatment arm.

SAEs in the SOCs of Blood and lymphatic system disorders and Infections and infestations are commonly observed following chemotherapy. Only one patient in the palonosetron 20 mcg/kg group had SAEs (Diarrhoea, Dehydration) considered by the Investigator to be possibly drug-related and whose outcome was recovered.

The percentages of patients with abnormal haematology parameters reported as TEAEs were comparable across treatment groups. There were no safety concerns for haematology and blood chemistry parameters in this study. Changes from baseline in clinical laboratory tests observed during the study are typical side effects of chemotherapy. The only abnormal haematology parameter considered by the Investigator to be drug-related was reported as Thrombocytopenia. This TEAE was non serious and resolved 3 days later. Values of AST, ALT, bilirubin and creatinine showed no concerns regarding hepatic or renal functions in patients of all treatment groups, confirming the safety profile similar to the one seen in adults.

The applicant considered significant AEs, regardless of seriousness: Cardiac disorders, Renal and urinary disorders, Hepatobiliary disorders, and Vascular disorders. Additionally, any reported event indicating seizures/convulsion, constipation or infusion site reaction (including thrombophlebitis) or events leading to withdrawal were also considered as significant. A total of 173 significant AEs were reported by 110 patients; only a small number of TEAEs were considered related to palonosetron (2 patients in each treatment arm) or ondansetron (4 cases). The three treatment groups can be considered comparable and no safety signal was detected.

2.5.2. Conclusions on clinical safety

Adverse reactions were for the most part those expected in the context of the illnesses and chemotherapy. There were no new safety issues in the paediatric population in this study, and no clinically relevant differences between treatments in the safety profile in the overall study population or in subgroups of patients based on age, gender, race, ethnicity or the emetogenicity of chemotherapy. Regarding age, a limited number of patients under 2 years of age were included (9%). This information has been included in section 4.2 for the consideration of the prescriber. Taking into account that safety data reported in patients <4 years of age were consistent with the profile of palonosetron in the four age groups evaluated in the PALO-10-20 study this is considered acceptable (see also discussion on efficacy).

2.5.3. PSUR cycle

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

Safety concerns

Summary of safety concerns

Important identified risks	Severe constipation Severe hypersensitivity reactions
Important potential risks	QT/QTc prolongation Convulsive events Serotonin syndrome
Missing information	Effect in pregnancy Effect in lactating women Effects on fertility Effect in children aged less than 1 month (potential off-label use for CINV prevention) Effects in patients with end stage renal disease undergoing haemodialysis

The table above has been updated from Version 5 to Version 6 of the RMP.

The following changes have occurred:

1. Under Important Identified Risks, the terms “constipation related complications” and “Anaphylaxis, anaphylactoid reactions and shock” were renamed to “severe constipation” and “severe hypersensitivity reactions”.

2. Under Important Potential Risks, the additional risk of Serotonin Syndrome was added.

3. Under Missing Information, the risk of “Effect in children (potential off label use)” was renamed as “Effect in children aged less than 1 month (potential off label use for CINV prevention)”.

No clinically relevant differences between treatments in the safety profile were observed in the overall study population or in subgroups of patients based on age, gender, race, ethnicity or the emetogenicity of chemotherapy. Regarding age, a limited number of patients under 2 years of age were included (9%), so no firm conclusions can be drawn for this subset of patients. On the basis of the available data (and in the absence of a formal comparison), the safety profile of palonosetron in children seems in line with the established safety profile in adults and to other anti-emetics belonging to same pharmacological class. Having considered the updated data in the safety specification, the PRAC agrees that the safety concerns listed by the MAH are appropriate.

Pharmacovigilance plan

Ongoing and planned studies in the PhV development plan

Not applicable

The PRAC, having considered the updated data submitted, was of the opinion that routine pharmacovigilance remains sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Severe constipation	Warnings and precaution for use in association with this safety concern are included in section 4.4. Listed in section 4.8. Prescription only medicine	Not applicable
Severe hypersensitivity reactions	Appropriate contraindication is included in section 4.3. Listed in section 4.8 (IV formulation). Statement relating to hypersensitivity reactions in section 4.8 (oral formulation). Prescription only medicine	Not applicable
QT/QTc prolongation	Warnings and precaution for use in association with this safety concern are included in section 4.4. Listed in section 4.8 (IV formulation): Electrocardiogram QT prolonged as uncommon ADR. Section 5.1 summarises the results of the thorough QT/QTc study. Prescription only medicine	Not applicable
Convulsive events	None proposed Prescription only medicine	Not applicable
Effect in pregnancy	Relevant information is included in section 4.6. Preclinical data are summarised in section 5.3. Prescription only medicine	Not applicable
Effect in lactating women	Relevant information is included in section 4.6. Prescription only medicine	Not applicable
Effects on fertility	Relevant information is included in section 4.6. Prescription only medicine	Not applicable
Effect in children aged less than 1 month (potential off-label use for CINV prevention)	Statement about this missing information is included in section 4.2 Prescription only medicine	Not applicable
Effects in patients with end stage renal disease undergoing haemodialysis	Statement about this missing information is included in sections 4.2 and 5.2. Prescription only medicine	Not applicable
Serotonin syndrome	Warnings and precaution for use in association with this safety concern are included in section 4.4. Information about the potential interaction is included in section 4.5 Prescription only medicine	Not applicable

The above table has been updated to include the following changes:

- The terms “constipation related complications” and “Anaphylaxis, anaphylactoid reactions and shock” were renamed to “severe constipation” and “severe hypersensitivity reactions”.
- The risk of “Effect in children (potential off label use)” was renamed as “Effect in children aged less than 1 month (potential off label use for CINV prevention)”.
- The additional safety concern of Serotonin Syndrome was added and the related routine RMMs outlined.

The PRAC, having considered the updated data submitted, was of the opinion that the proposed risk minimisation measures remain sufficient to minimise the risks of the product in the proposed indications.

The PRAC considered that the risk management plan version 6 is acceptable.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this application, sections 4.1, 4.2, 4.8, 4.9, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed by QRD and accepted by the CHMP.

2.7.1. User consultation

The changes proposed to the package leaflet within this variation do not involve the addition of a large amount of text to the previously approved leaflet and do not require user consultation.

As the package leaflet has undergone many changes since the original user testing was performed the Applicant is recommended to perform and submit user consultation on the Aloxi package leaflet with the next variation that involves amendments to the package leaflet.

2.8. Significance of paediatric studies

Article 8 of the Paediatric Regulation does not apply to this application, since the authorised medicinal product is not protected by a supplementary protection certificate under Regulation (EC) No 469/2009 or by a patent which qualifies for the granting of the supplementary protection.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The main proof of efficacy of palonosetron in paediatric patients in the indication of prevention of CINV comes from study PALO-10-20 which was a large (502 cancer patients) comparative, randomised double-blind trial for assessment of palonosetron non-inferiority with ondansetron, the currently most common used 5-HT3 receptor antagonist for the prevention of CINV in paediatric patients.

For the primary efficacy endpoint complete response during first cycle CR was reported for 54.2% of patients treated with palonosetron 10mcg/kg, 59.4% of patients treated with palonosetron 20 mcg/kg and 58.6% of patients treated with ondansetron showing non-inferiority to ondansetron for the higher dose.

In the key secondary endpoint a higher proportion of patients treated with palonosetron 20 mcg/kg showed a complete response on delayed phase (key secondary end-point) than those in ondansetron arm (38.8% vs 28.8%); CR results in the overall phase (0-120h) were similar to those in delayed stage (32.7% palonosetron 20 mcg/kg vs. 24.1%).

During Cycle 1, the proportion of patients reporting no vomiting, or no emetic episode was numerically higher in the palonosetron 20 mcg/kg group compared to the two other groups (analysis of 95% CI for the MH not adjusted for multiplicity). The frequency of absence of nausea in patients aged 6 years or more in palonosetron 20 mcg/kg group was consistently numerically higher than ondansetron across all phases.

In line with results observed at Cycle 1, throughout study Cycles 2 to 4, palonosetron 20 mcg/kg treatment group most often reported the highest CR rate, the highest proportions of patients with no vomiting, patients with no emetic episodes and patients with no use of antiemetic rescue medications. Although not statistically significant, possibly due to the progressively lower number of patients and despite the absence of re-randomisation, the benefit of palonosetron can be considered maintained in repeat cycles of chemotherapy.

Uncertainty in the knowledge about the beneficial effects

Although the CR rates in the delayed phase were numerically higher for palonosetron 20 mcg/kg than for ondansetron, the efficacy of palonosetron for the prevention of delayed CINV after receiving chemotherapy (until 120 hours) could not be confirmed.

Around 85% of patients in the 3 treatment arms used concomitant antiemetic as allowed if they received additional MEC or HEC during day 2 to day 6 of the cycle. Therefore, the activity of these concomitant antiemetic agents on delayed nausea and vomiting and its contribution to the observed effect of palonosetron during the overall period cannot be ruled out.

Furthermore the dosing of the comparator Ondansetron in order to prevent delayed nausea and vomiting did not follow SPC recommendation as the 3 initial IV doses should be usually followed by oral doses during the first 5 days after chemotherapy. Consequently, efficacy of palonosetron in delayed phase was compared with a weak regimen of comparator.

Risks

Unfavourable effects

Adverse reactions were for the most part those expected in the context of the illnesses and chemotherapy. There were no new safety issues in the paediatric population in this study, and no clinically relevant differences between treatments in the safety profile in the overall study population or in subgroups of patients based on age, gender, race, ethnicity or the emetogenicity of chemotherapy.

Uncertainty in the knowledge about the unfavourable effects

As labelled in the SmPC data on Efficacy and safety in children less than 2 years are relatively limited. Whereas for the youngest children covered by the indication (<4 years of age and older than one month) the safety data were consistent with the profile of palonosetron in the four age groups evaluated in the pivotal

study no children aged less than one month were enrolled. The RMP includes potential off label use for CINV prevention in these latter patients as missing information.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Nausea and vomiting are distressing side effects of chemotherapy in adult and paediatric patients and may lead to dehydration, electrolyte imbalance, poor nutrition anorexia imbalances, renal failure, oesophageal tears, mental deterioration, the discontinuation of potentially beneficial therapies and prolonged hospitalisation if inadequately controlled. Palonosetron has demonstrated patient benefit from treatment because it prevents and/or control incapacitating nausea and vomiting.

Adverse reactions were for the most part those expected in the context of the illnesses and chemotherapy. The favourable and unfavourable effects in these studies did not differ significantly from those seen in the adult population.

Benefit-risk balance

Palonosetron 20 mcg/kg could be shown to be as effective as ondansetron in the acute phase for preventing CINV in children aged 1 month and older. In repeat cycles of chemotherapy, although not statistically significant possibly due to the progressively lower number of patients and despite the absence of re-randomisation, the benefit of palonosetron was maintained.

Discussion on the benefit-risk balance

CINV are amongst the most frequently and distressing adverse events associated with the treatment of cancer. 5-HT3 receptor antagonist are the first-line treatment for moderately and highly emetogenic chemotherapy and radiotherapy regimens in adults and children.

Palonosetron is a selective serotonin receptor subtype 3 (5-HT3) antagonists that was approved for the prevention of CINV in HEC and MEC in adults.

According to the provided information the effect of palonosetron for the prevention of acute CINV can be regarded as non-inferior to ondansetron in the overall paediatric population. However, the efficacy of palonosetron in the prevention of delayed CINV in paediatric patients could not be confirmed in the pivotal trial due to the potential confounding effect of concomitant antiemetics (associated with use of further chemotherapy) during the study period and the dosing regimen used for the comparator drug.

The SmPC already mentions in 4.4 that Aloxi should not be used to prevent or treat nausea and vomiting in the days following chemotherapy if not associated with another chemotherapy administration.

It is also noted that palonosetron has a prolonged half-life in comparison to ondansetron making it reasonable to understand that palonosetron could have activity beyond the acute phase of CINV. On the other hand in highly emetogenic CINV the emesis has a multiphasic time course whereas, in moderately emetogenic settings, emesis is described as a continuous phenomenon lasting for days after chemotherapy and fading off in days 4 to 5.

Therefore, in accordance with the adult indication statement, the indication states that palonosetron is to be used for the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy.

The Benefit-Risk balance of Aloxi in the indication: Paediatric patients 1 month of age and older for:

The prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy

is considered positive.