Clinical Pharmacology Review

NDA	**NDA 21-372/S-019/SDN: 640**
Submission Date:	11/27/2013
PDUFA Date:	5/27/2014
Brand Name:	Aloxi ®
Generic Name:	Palonosetron
Formulation:	0.05 mg/ml solution for intravenous injection
Submission Type:	Pediatric Efficacy Supplements
Proposed dosing regimen:	20 μg/kg single-dose I.V. infusion over 15 minutes beginning approx. 30 min before the start of chemotherapy
Indication:	Chemotherapy-Induced Nausea and Vomiting (CINV)
Sponsor:	Helsinn Healthcare SA (Switzerland)
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1 EXECUTIVE SUMMARY

Palonosetron hydrochloride is a serotonin (5-hydroxytryptamine or 5-HT3) receptor antagonist. Aloxi® (Palonosetron hydrochloride) injection for intravenous use was approved in 2003 for prevention of acute chemotherapy-induced nausea and vomiting (CINV) associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) or highly emetogenic cancer chemotherapy (HEC) with a single 0.25 mg dose. In addition, in 2008 Aloxi® was approved for post-operative nausea and vomiting (PONV) in adults.

The current NDA submission is in support of use of ALOXI I.V. in pediatric patients ≥ 1 month for prevention of acute nausea and vomiting associated with chemotherapy. In response to the Pediatric Written Request (PWR), two clinical trials for CINV were conducted, a dose-ranging trial (PALO 99-07) and a phase 3 non-inferiority trial in comparison to an active comparator (PALO 10-20). The proposed dosage regimen for pediatric patients is a single dose administration of 20 μg/kg (maximum 1.5 mg) palonosetron as a 15 min infusion starting 30 minutes prior to highly or moderately emetogenic chemotherapy.

Based on FDA's analyses of the data submitted in this pediatric efficacy supplement, we conclude the following:

- The proposed pediatric dose of 20 μg/kg based on non-inferiority test is acceptable for the prevention of CINV in pediatrics. The dose regimen is supported by exposure-response for efficacy and population pharmacokinetics in pediatrics.
- The analyses indicate that higher systemic exposure to palonosetron as compared to adults is needed for prevention of CINV in pediatric patients. These results indicate that matching pediatric exposure to adult exposure is not appropriate to select pediatric doses for palonosetron and possibly for other 5-HT3 antagonists for the prevention of CINV in pediatric patients.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the submission, and has the following recommendations:

- The proposed pediatric dose of 20 μg/kg based on non-inferiority test is acceptable for the prevention of CINV in pediatrics. The dose regimen is supported by exposure-response for efficacy and population pharmacokinetics in pediatrics.

Phase IV Requirement or Commitment

None.

Labeling Recommendations

Please see Section 3 - Detailed Labeling Recommendations.

1.2. CLINICAL PHARMACOLOGY FINDINGS

In the pediatric clinical development program, two clinical trials (PALO-99-07 and PALO-10-20) for CINV were conducted in which single-dose intravenous palonosetron at the dose of 0.3-20 μg/kg was administered to 402 pediatric patients aged 64 days to <18 years 30 minutes prior to highly or moderately emetogenic chemotherapy. Both trials included an assessment of palonosetron PK in pediatric patients. In trial PALO 99-07, palonosetron was intravenously administered at the doses of 3 μg/kg and10μg/kg over 30 seconds. In trial PALO 10-20, palonosetron was given over 15 min infusions at 10 and 20 μg/kg. Summarized below are the main findings of the review pertaining to dose selection and lack of applicability exposure matching to select doses for CINV in pediatrics for palonosetron and possibly other 5-HT3 antagonists.

Population Pharmacokinetics: At the proposed dose of 20 μg/kg, the mean systemic exposure ($AUC_{0-\infty}$) in pediatric patients was 3.1-fold of the mean systemic exposure in adults at 3 μg/kg (or 0.21 mg/70 kg[1]) dose. Population PK analysis indicates that the variability in palonosetron CL was mainly affected by body weight. Age did not explain the variability in clearance after inclusion of body weight in the model. At 20 μg/kg dose, there are no significant differences of $AUC_{0-\infty}$ among age groups < 17 years old. Therefore, body weight- based dosing in pediatric patients is acceptable.

Dose-Response for efficacy: The efficacy of 20 μg/kg palonosetron for the prevention of CINV in pediatric cancer subjects aged ≥1 month is mainly supported by Study PALO-10-20. In this trial, the proportion of patients with complete response (no emetic episode and no use of rescue medication) in acute phase (CRA; 0-24 hr post-dosing) was 54.2% and 59.4% after single dose administration palonosetron 10 μg/kg and 20 μg/kg, respectively while the CRA rate was 58.6% for ondansetron, the active comparator. The trial demonstrated that proportion of patients with CRA for palonosetron at the dose of 20 μg/kg was non-inferior to that for the active comparator using a pre-specified non-inferiority margin of 15%. Palonosetron failed to demonstrate the non-inferiority to the active control at the dose of 10 μg/kg.

Exposure-Response for efficacy: The exposure-response (E-R) analyses provide supportive evidence for the selection of 20 μg/kg dose in pediatric CINV patients. There is an evident exposure-response relationship between palonosetron $AUC_{0-\infty}$ and CRA response in pediatric patients over the dose range from 3 μg/kg to 20 μg/kg which provides supportive evidence of effectiveness. The CRA response at the proposed 20 μg/kg dose is at the plateau phase of the exposure-response curve indicating that more patients will have probability of responding at 20 μg/kg compared to 10 μg/kg.

A logistic E_{max} model was used to describe the relationship between exposure metrics (C_{max}, $AUC_{0-\infty}$) and clinical response (CRA[2]). An E-R relationship was established between AUC estimated by the final population PK model and CRA response in patients from Study 10-20 and 99- 07. An increased response with increased average $AUC_{0-\infty}$ was observed in the range 7.63-342 μg*h/L and the response reaches the plateau at an AUC of ~100 μg*h/L. Further

[1] Approved dosage for adult patients: a single 0.25 mg intravenous dose administered over 30 seconds
[2] Complete response in acute phase (0-24 hr post-dose)

examination of the distribution of body weight and age indicate that both are evenly distributed across the four AUC quartiles, indicating that age and weight are not confounding factors in the observed palonosetron exposure.

On the other hand, the observed data from 400 pediatric patients showed that patients less than 6 years of age appear to have higher CRA response than pediatric patient older than 6 years after palonosetron treatment. As mentioned above, this difference cannot be explained by exposure since the exposures were similar across body weight and age. Additionally, the reviewer's E-R analyses indicate that age is a significant covariate for CRA response. It is unclear which age related factors contributed to the apparent higher CRA response in younger pediatric patients than in older pediatric patients while the systemic exposure was generally similar across age groups among pediatric patients.

More importantly, the study results and FDA's analyses indicate that higher systemic exposure to palonosetron is needed for prevention of CINV in pediatric patients. These results further suggest that matching pediatric exposure to adult exposure is not appropriate to select pediatric doses of palonosetron in pediatrics.

Safety: There was no clear safety signals and was no clear or consistent dose-response trend, trend in specific subgroups (e.g., age groups), or trend with repeat cycles of study drug administration in the pediatric CINV studies. In this pediatric cancer study population, treatment-emergent AEs (TEAEs) in the blood and lymphatic system disorders system organ class (SOC) were the most common overall (54%) and in both treatment groups (51% for palonosetron and 59% for ondansetron). Anemia was the most commonly reported TEAE overall (33%) and in the palonosetron (33%) and ondansetron (34%) treatment groups, followed by thrombocytopenia and neutropenia.

QTc prolongation potential: Although the weight-based dose is higher in pediatric patients compared to adults, there is no concern in QT prolongation for the proposed pediatric dose as explained below.

In a previously conducted thorough QTc study in healthy volunteers, palonosetron did not have a significant effect on QTc interval at doses up to 2.25 mg given over 30 seconds (i.e., 9-fold of the approved adult dose; ~ 32 μg/kg). The concentrations found in this TQT study covers the observed Cmax (range: 9-16.2 ng/mL) at the proposed dose in pediatric patients. Therefore, the proposed pediatric dose given over 15 minutes is not expected to cause QTc prolongation.

2 QUESTION BASED REVIEW

General clinical pharmacology of palonsetron has been has been reviewed previously under NDA 21-372 (submission 09/27/02). For brevity, only QBR questions pertinent to the current pediatric NDA submission will be addressed below. Please see Clinical Pharmacology Review for NDA 21-372 by Drs. Sue-Chih Lee and Suliman Al-Fayoumi in DARRTS (dated 06/24/2003) for more details.

KEY REVIEW QUESTIONS

2.1.1 Is there evidence of exposure-response for efficacy?

Yes, there is evidence of an exposure-response (E-R) relationship for efficacy that provides supportive evidence of effectiveness for palonosetron in the treatment of CINV in pediatrics. A logistic E_{max} model was used to link exposure (C_{max}, $AUC_{0-\infty}$) to response (CR in the acute phase: 0-24 hours post-dose, or in the delayed phase: 24-120 hours post-dose; hereinafter abbreviated as CRA and CRD, respectively). An evident E-R relationship was demonstrated between AUC predicted by population PK model and CRA in patients from Trial PALO 10-20 and 99-07. In trial PALO 99-07, palonosetron was intravenously administered at the dose of 3 μg/kg and 10μg/kg over 30 seconds. In trial PALO 10-20, palonosetron was given over 15 min infusions at 10 and 20 μg/kg.

An increased response with increased AUC was observed and the response appeared to reach the plateau when AUC ≥ 100 μg*h/L(**Figure 1**). Further examination of the distribution of body weight and age indicate that both are evenly distributed among the four exposure quartiles, indicating that age and weight are not correlated with palonosetron exposure.

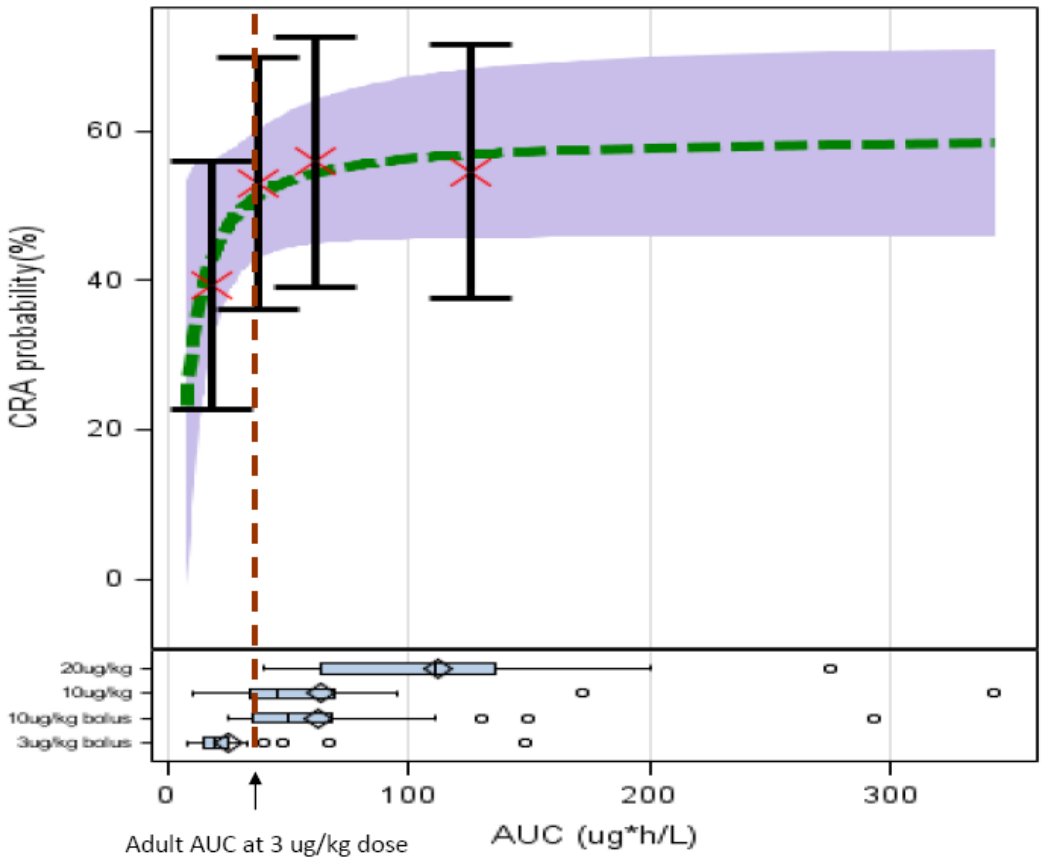


Figure 1. Exposure-response relationship of palonosetron between $AUC_{0-\infty}$ and CRA in pediatric patients. Logistic regression model includes the probability of CRA responder during the first cycle as a function of palonosetron $AUC_{0-\infty}$. The mean and 95% CI of the observed response rate versus the mean palonosetron $AUC_{0-\infty}$ is represented by black bars while dashed green line and purple band represent the model predicted mean and 95% interval of CRA response rate. The box plots at the bottom represent the distribution of palonosetron $AUC_{0-\infty}$ in each dose group.

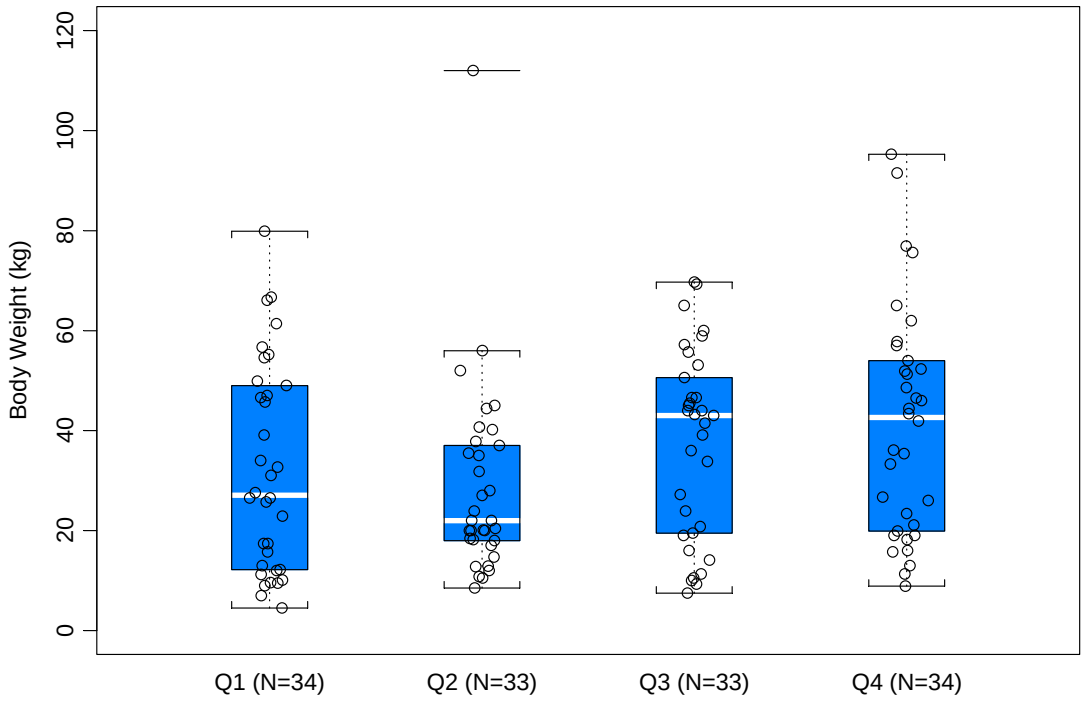


Figure 2. Distribution of body weight in palonosetron $AUC_{0-\infty}$ quartiles.

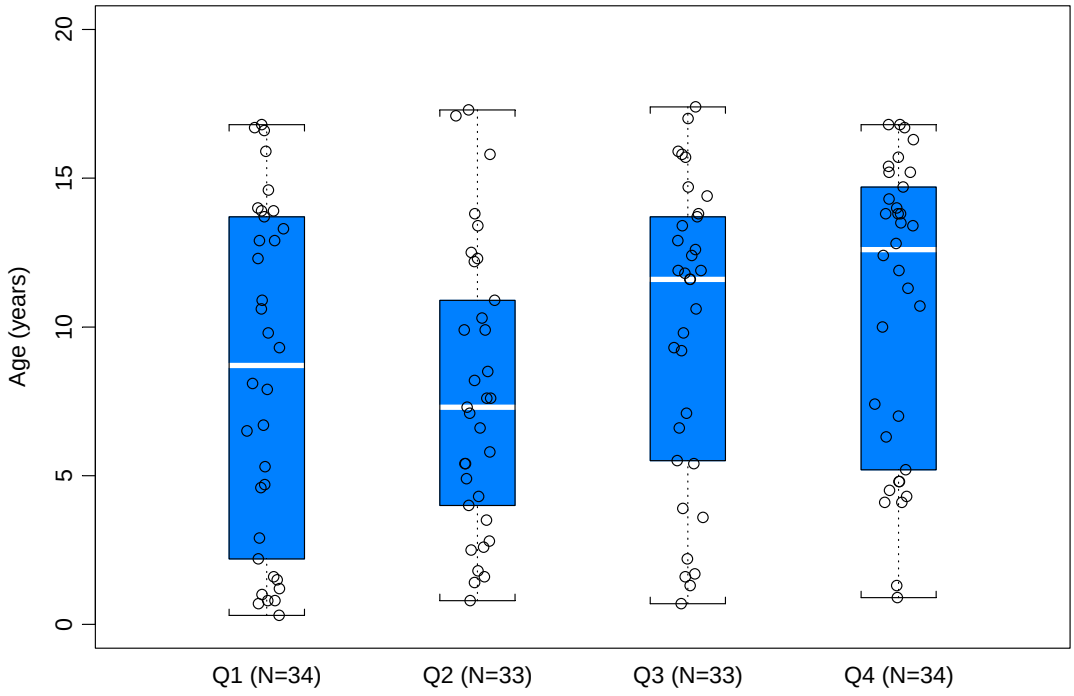


Figure 3. Distribution of age in palonosetron $AUC_{0-\infty}$ quartiles.

2.1.2 Is there evidence of exposure-response for safety?

Safety data were consistent with the established profile of palonosetron in adults and did not reveal additional safety risk in pediatric patients receiving up to 4 chemotherapy cycles. Therefore, the E-R relationship for safety is not assessed. The clinical review noted that no clear safety signals and was no clear or consistent dose-response trend, trend in specific subgroups (e.g., age groups), or trend with repeat cycles of study drug administration in the pediatric CINV studies. As expected in this pediatric cancer study population, treatment-emergent AEs (TEAEs) in the blood and lymphatic system disorders system organ class (SOC) were the most common overall (54%) and in both treatment groups (51% for palonosetron and 59% for ondansetron). Anemia was the most commonly reported TEAE overall (33%) and in the palonosetron (33%) and ondansetron (34%) treatment groups, followed by thrombocytopenia and neutropenia. Please see the clinical review for detailed safety assessment.

2.1.3 Does exposure-response and population PK support the proposed dose in CINV patients?

Yes, the exposure-response and population PK support the proposed palonosetron dose of 20 μg/kg in pediatric CINV patients based on the following evidences:

1) An exposure-response (E-R) analysis using E_{max} logistic regression showed that CRA response was close to or reached a plateau of the E-R curve for the patients receiving 20 µg/kg dose (**Figure 1**). The CRA response at the proposed 20 µg/kg dose is at the plateau phase of the exposure-response curve indicating that more patients will have probability of responding at 20 µg/kg compared to 10 µg/kg. Considering there is no safety concern at 20 µg/kg dose, it is better to recommend this dose so that exposures with this dose lie on the flat part of the exposure-response.

2) Based on the final population PK model, variability in palonosetron CL was mainly explained by body weight (**Figure 4**). Inter-subject variability of the estimated PK parameters decreased by 16 % for CL. The expected range of CL explained by weight at the typical value was 1.26 L/hr to 14.1 L/hr, based on the body weight distributions in pediatric patients. Given the magnitude of this effect, these results support the proposed body-weight based dosing regimen in pediatric patients.

3) The results of the PK analyses indicated that although minor trends were reported among age groups for AUC, the ranges remained within the observed variability of these parameters and were mostly overlapping between age groups (**Figure 4**). Therefore, no adjustment of dosing is required for pediatric patients, beyond dosing palonosetron on based on individual weight.

4) The 20 µg/kg single dose given by IV infusion in study PALO-10-20 demonstrated non-inferiority compared to ondansetron as standard therapy. A dose-response trend is observed (**Figure 6**).

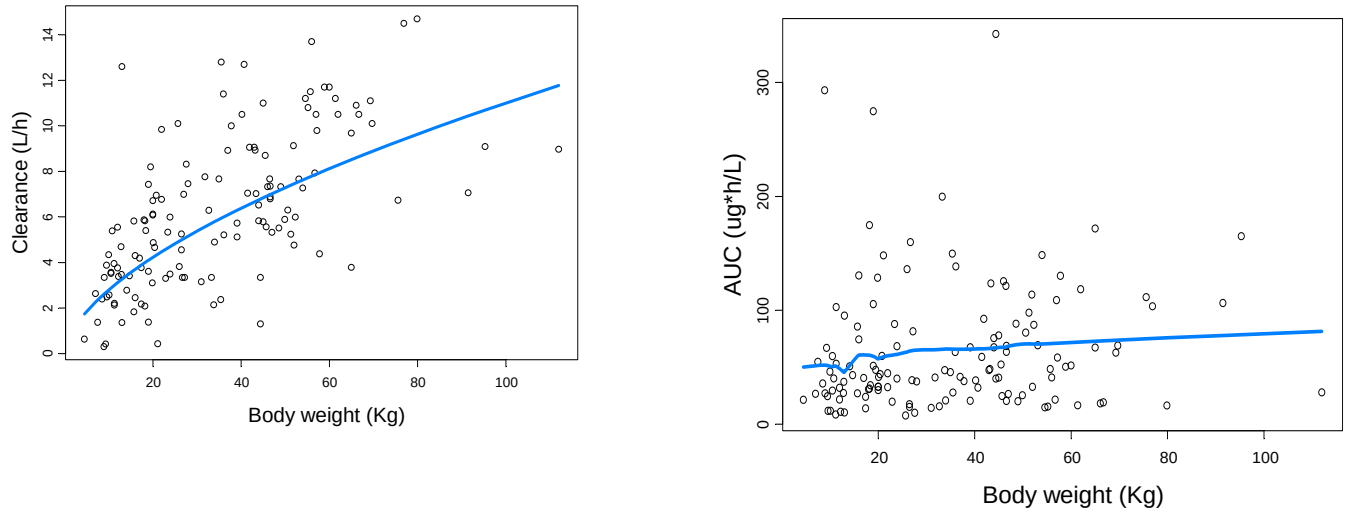


Figure 4. Plots of CL vs body weight (left) and predicted $AUC_{0-\infty}$ at 20 ug/kg dose vs. body weight (right) under the final population PK model. Left: Solid blue line corresponds to the body weight-CL relationship from the population estimates. The open solid circles are individual clearance estimate of pediatric patients. Right: Solid blue line corresponds to the *LOESS* curve. The open

solid circles are individual $AUC_{0-\infty}$ of pediatric patients following the body-weight based dosing.

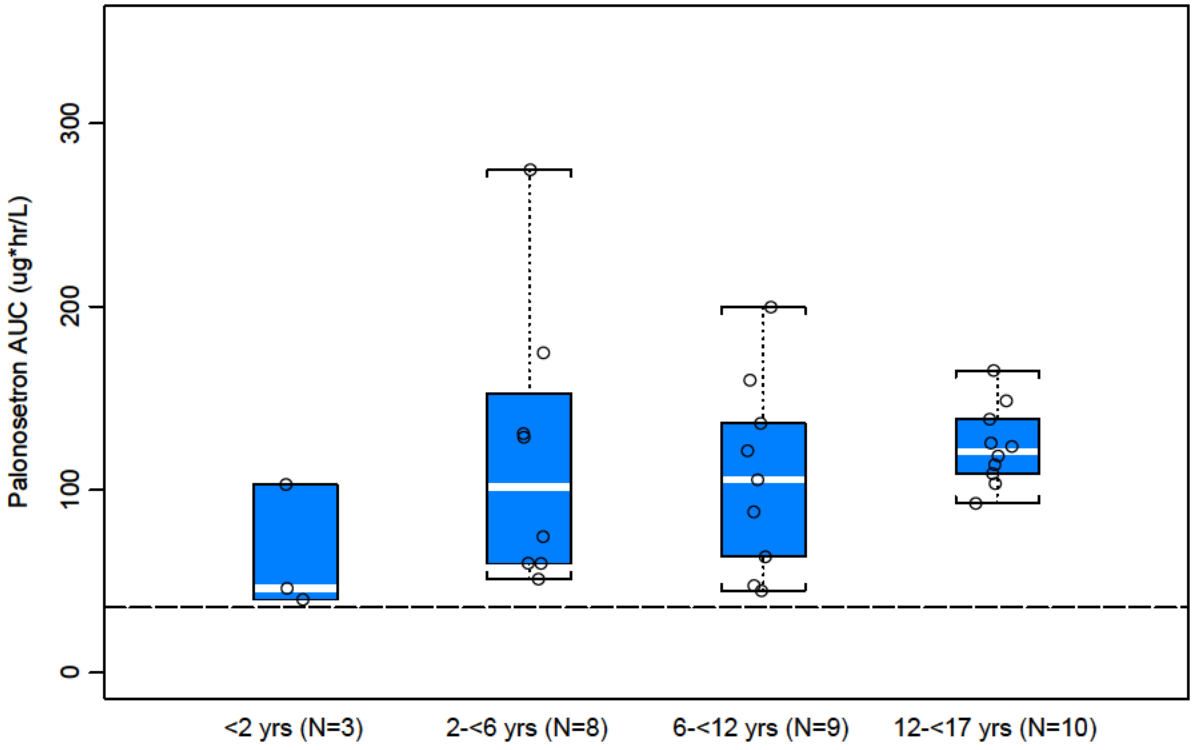


Figure 5. Palonosetron Exposure predicted by the final Population PK model by Age Groups at 20 µg/kg dose (Study 1020).

Reviewer's comment: it should be noted that the population PK analysis was conducted 134 patients, whose age ranged from 0.3 years to 17.4 years of age. There are only 3 patients less than 2 years of age. It should be cautious when interpreting the effects of age on patients less than 2 years of age.

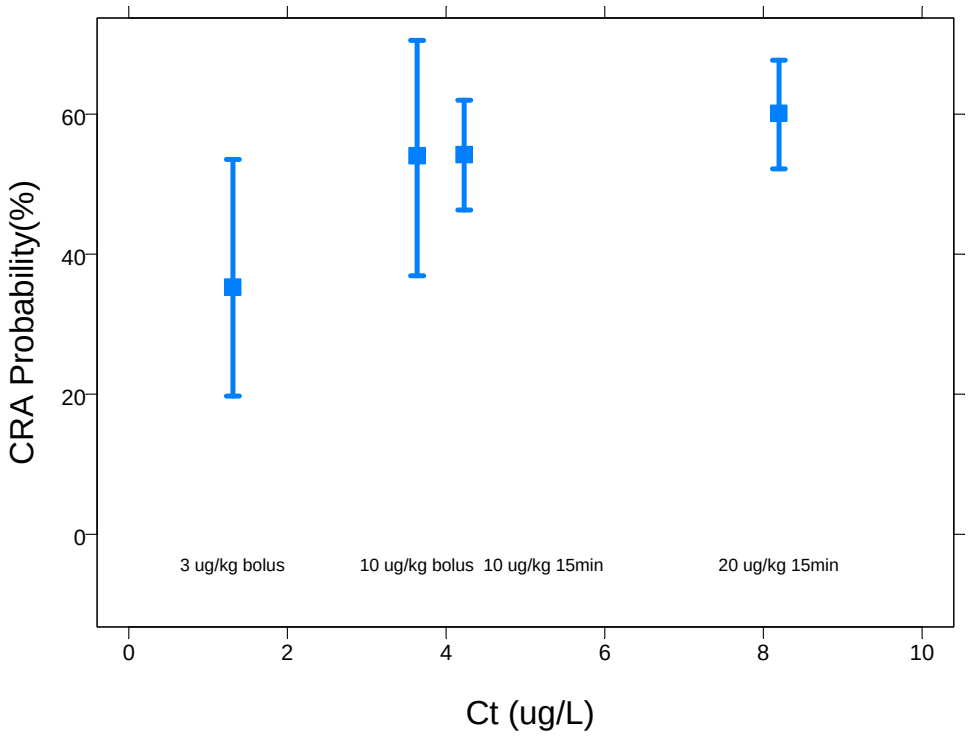


Figure 6. Palonosetron CRA response by different dosing regimen and the relevant plasma concentration at the end of the infusion (Ct). Each bar represents the CRA probability based on four different dosing regimens.

2.1.4 Is exposure-matching to the adults appropriate for palonosetron dose selection in pediatric CINV patients?

No, the reviewer's analyses do not support the exposure matching method for dosing palonosetron in pediatric CINV patients based on the following:

- At the proposed dose of 20 µg/kg, the mean systemic exposure (AUC) in pediatric patients is about 3.1 fold higher than the mean systemic exposure in adults at the approved dose of 0.25 mg (~3 µg/kg) (**Figure 1**). Furthermore, the average exposures following 10 µg/kg in pediatrics are higher compared to adult dose level, the median exposure in pediatrics matched well with the adult reference. However, the efficacy data failed the non-inferiority test.
- In the E-R analysis for efficacy, age has been identified as a significant covariate for CRA response. It should be noted that there might be other confounding factors that are correlated with age. The age-dependent factors included *Weight, Total dose of palonosetron administered, Body Mass Index, Primary Cancer High Level Group Term,*

Baseline Serum aspartate aminotransferase and Bilirubin, Use of Corticosteroids, Use of CYP2D6 Inhibitors and Use of Doxorubicin. Concomitant use of these drugs may be explained by different therapeutic approaches used among the patients, and may in part be attributable to different cancer types across the age ranges of these children. Adding these covariates into the model did not significantly improve the model. It should be noted that the applied models are not expected to completely eliminate the confounded effects of these factors in our E-R analysis, due to the unknown structure of the relationship between these risk factors and the hazard of the event and the complex interaction among these risk factors. Nevertheless, our finding of age as a covariate for response indicates that there may be a potential difference of E-R relationship between pediatrics and adults. In addition, the observed data from 400 pediatric patients showed that patients with less than 6 years of age had markedly higher CRA response than pediatric patient older than 6 years (**Figure 7**).

Taken together, the analyses suggest that matching pediatric exposure to adult exposure may not be an optimal approach for dose selection in pediatric CINV.

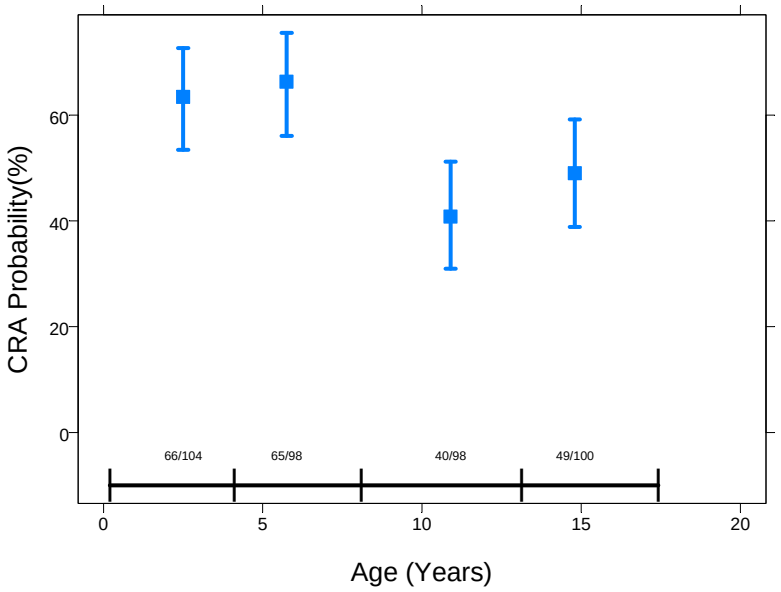


Figure 7: Plot of age and CRA response in all pediatric CINV trials (N=400).

Table 1. Comparison of Palonosetron and Ondansetron Doses in Pediatric and Adult Patients

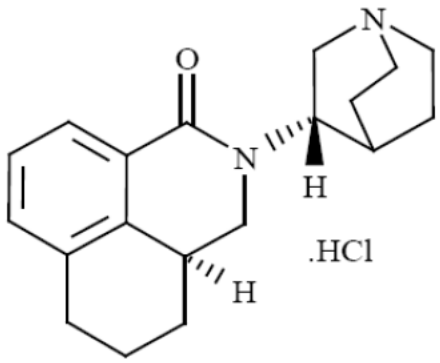
	CINV		PONV	
Drugs	**Palonosetron**	**Ondansetron**	**Palonosetron**	**Ondansetron[3]**
Pediatrics	20 µg/kg	3x 0.15 mg/kg	1 and 3 µg/kg (studied)	<= 40kg: 0.1 mg/kg >40 kg: 4 mg
Adults	0.25 mg	3x 0.15 mg/kg	0.075 mg	4 mg

GENERAL ATTRIBUTES

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Physico-chemical properties

1. Structural formula:



2. Established name: Palonosetron hydrochloride
3. Molecular Weight: 332.87 g/mol
4. Molecular Formula: C19H24N2O•HCl
5. Chemical Name: (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[de]isoquinoline hydrochloride.

2.2.2 For pediatric patients, the approved formulation of palonosetron for injection (0.05 mg/ml) will be used. What are the proposed mechanisms of action and therapeutic indications?

Palonosetron hydrochloride is a serotonin (5-hydroxytryptamine or 5-HT) receptor antagonist. Chemotherapy-induced nausea and vomiting (CINV), the proposed pediatric use, is triggered by release of 5-HT in a cascade of neuronal events involving both the central nervous system and the gastrointestinal tract.

[3] Approved dose

2.2.3 What are the proposed dosage and route of administration?

The applicant proposed the following dose recommendation: a single intravenous infusion of 20 µg/kg dose of palonosetron in pediatric patients for the prevention of chemotherapy induced nausea and vomiting (CINV).

GENERAL CLINICAL PHARMACOLOGY

2.3.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Table 2 provides an overview of these clinical studies conducted in support of prevention of CINV in pediatric aptients.

Table 2. Overview of Studies with CINV Clinical Pharmacology Data in the Current Submission

Study	Description	Dose regimen	Efficacy endpoint
PALO 99-07: "*Double-blind Pediatric Study to Assess the Safety, Pharmacokinetics and Efficacy of Single IV Doses of Palonosetron, 3.0 µg/kg or 10.0 µg/kg, in the Prevention of Chemotherapy-Induced Nausea and Vomiting*"	Design: Randomized, double-blind, parallel, stratified design. Objectives: assess safety and tolerability, PK and efficacy. CINV: pediatric patients receiving moderately (MEC) or highly emetogenic (HEC) chemotherapy. (n=72)	3 µg/kg Palonosetron (max 0.25 mg) single dose given by 30 sec IV bolus, or 10 µg/kg Palonosetron (max 0.75 mg) single dose given by 30 sec IV bolus.	Complete Response 0-24h (no emetic episodes, no rescue medication) after starting chemotherapy.
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*"	Design: Randomized, double-blind, double-dummy, parallel, noninferiority active-control, stratified, repeat cycle design. Objectives: assess efficacy, safety, tolerability and PK. CINV: pediatric patients scheduled to undergo highly (HEC) or moderately emetogenic chemotherapy (MEC) on Day 1. (n=492)	10 µg/kg Palonosetron (max 0.75 mg) single dose IV over 15min 20 µg/kg Palonosetron (max 1.5 mg) single dose IV over 15min 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.	Complete Response 0-24h (no vomiting, no retching, no use of antiemetic rescue medication) after starting chemotherapy during the first chemotherapy cycle.

Exposure-response analyses are conducted based on the data from PALO 99-07 and PALO 10-20. Table 3 summarizes the patients numbers, exposure and efficacy endpoints used for the E-R analyses.

Table 3. Data used for exposure-response analysis in CINV Patients

Study	9907	1020
Design	Proof-of-concept, Randomized	Pivotal, Randomized
N for E-R	71	63
Doses	3 µg/kg,10 µg/kg IV over 30 seconds	10 µg/kg, 20 µg/kg IV over 15 min
Patients	Pediatric pts receiving HEC/MEC	Pediatric pts receiving HEC/MEC
Exposure endpoints	AUC_{inf}, Cmax	AUC_{inf}, Cmax
Efficacy endpoints	CRA	CRA, CRD

2.3.2 How are the response endpoints measured in clinical pharmacology and clinical studies?

In study PALO-10-20, 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.

In study PALO-99-07, the efficacy parameter of major interest was the proportion of patients with Complete Response (defined as no emetic episode and no rescue medication) during the first 24 hours after the start of chemotherapy.

2.3.3 Are the palonosetron appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. See Section 2.6 for more details.

2.3.4 Exposure-response

2.3.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Please refer to 2.1.1 and 4.2.1 for details.

In Study PALO-10-20, palonosetron was compared to the active comparator at two dose levels i.e. 10 µg/kg and 20 µg/kg. In Study PALO-99-07 which was conducted prior to PALO-10-20, a trend of increasing CR rate by AUC was observed between 3 µg/kg and 10 µg/kg to support the selection of 10 µg/kg for a subsequent trial. Based on the increasing trend of CR rate, a higher dose was proposed to be included in Study PALO-10-20 and 20 µg/kg dose was selected as opposed to the initially proposed 15 µg/kg by the sponsor to maximize the chance to detect the difference between doses if present.

The dose of 20 mcg/kg resulted in numerically higher proportion of patients with CR for acute CINV and the dose of 20 µg/kg met the pre-specified non-inferiority margin (15%) in comparison to ondansetron while the dose of 10 µg/kg failed to meet the criteria.

Table 4. Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) During First Cycle

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

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

Table 5. Primary Efficacy Analysis: Difference Between Treatments – Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) During First Cycle

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

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

Table 6. Proportion of Subjects with Complete Response in the Acute Phase (0-24 Hours) During First Cycle by Age Group

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

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

Table from the clinical review by Dr. Sohrabi.

2.3.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Safety data were consistent with the established profile of palonosetron in adults and did not indicate additional safety issue in pediatric patients receiving up to 4 chemotherapy cycles.

The overall incidence of TEAEs was similar between 10 µg/kg and 20 µg/kg treatments. Detailed review of safety is deferred to the clinical review.

Table 7. Patients with TEAEs

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.
[1] Drug Related AEs are AEs assessed by the Investigator as having definite, probable, possible, unassessable or missing relationship to study drug.
Source: Table 14.3.1.1.1.1.

2.3.5 Pharmacokinetic characteristics of palonosetron in pediatric patients

PK blood samples were collected in both PALO -99-07 and PALO-10-20. In PALO-10-20, a sample for the end-of-infusion concentration was collected from most patients while dense PK sampling was performed for a subset of patients. Palonosetron was administered as an infusion over 30 second in PALO-99-07 and as an infusion over 15 minutes in PALO-10-20. Population PK analysis and PK/PD analysis were conducted using combined datasets from PALO 10-20 and PALO 99-07.

In Study PALO 10-20, palonosetron was distributed rapidly after intravenous dosing followed by a slower elimination phase. Exposure as measured by AUC was generally dose-proportional between 10 to 20 µg/kg dose levels, across all three age groups.

When clearance is expressed as L/hr/kg and Vss is expressed as L/kg, there are no apparent differences in the distribution of individual patient values across the age groups and doses evaluated. Mean terminal elimination half-life values ranged from 21-37 hours across the three age groups (individual values ranging from approximately 11 to 81 h).

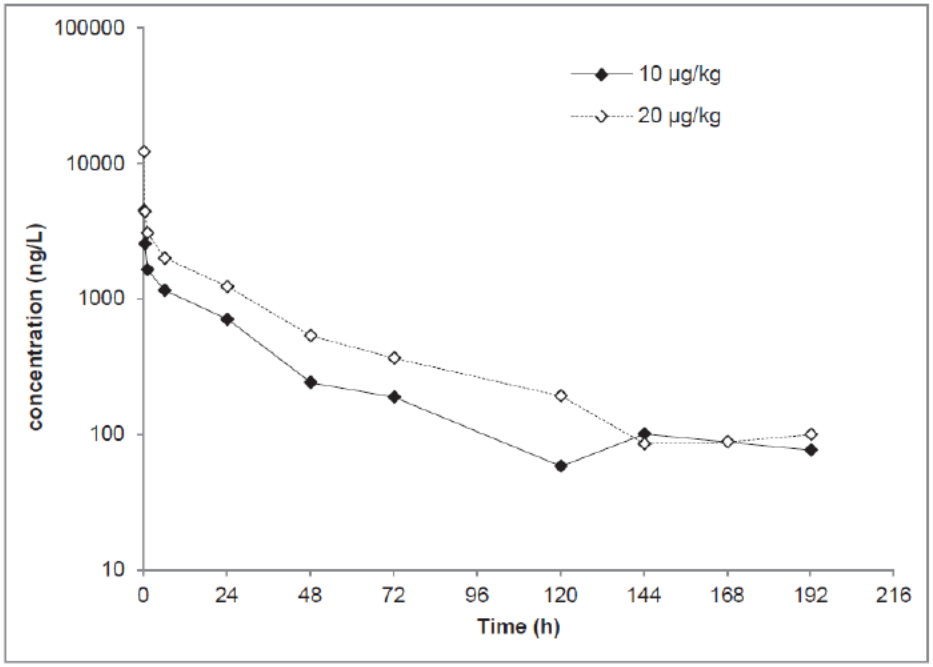
Table 8: Mean (SD) PK parameters for palnosetron after intravenous infusion over 15 min (PALO-10-20)

	10 µg/kg	20 µg/kg
Cmax (ng/L)	14604 (31128)	59362 (115356)
	GM: 6343	GM:19322
Tmax (h)	0.27	0.28
	(0.25-1.25)	(0.25-1.25)
AUCt	50 (26.0)	101.6 (45.7)
(ng*h/L)	GM: 43.7	GM:86.5
AUCinf	53.8 (26.5)	113.9 (39.6)
(ng*h/L)	GM:47.8	GM: 106.6
CL (L/h/kg)	0.24 (0.12)	0.20 (0.09)
	GM: 0.21	GM:0.19
Vss (L/kg)	6.3 (2.5)	6.8 (2.8)
	GM:5.8	GM: 6.1

Table 9. Geometric Mean (%CV) PK parameters by age and dose after intravenous infusion of palonosetron over 15 min

Parameters	Dose	Age group (years) < 2	2-6	6-12	12-17
Cmax (ng/L)	10 µg/kg	8300 (102.6) (n=4)	8490.0 (205) (n=10)	5204 (174) (n=6)	5022 (102) (n=12)
	20 µg/kg	9820 (153) (n=4)	34779.0 (143) (n=8)	26084.9 (95) (n=8)	11635 (85) (n=10)
AUC_t (mcg*h/L)	10 µg/kg	28.3 (44.9) (n=4)	35.1 (70.0) (n=8)	50.4 (44) (n=6)	55.5 (39.6) (n=12)
	20 µg/kg	57.7 (47.5) (n=4)	66.3 (63) (n=8)	88.2 (51) (n=8)	118.7 (19) (n=10)
AUC_{inf} (mcg*h/L)	10 µg/kg	31.4 (41) (n=3)	39.4 (65) (n=9)	54.6 (40) (n=6)	63.7 (34.5) (n=9)
	20 µg/kg	69 (45) (n=2)	103.5 (40) (n=5)	98.6 (47.7) (n=7)	124.5 (19) (n=10)
CL (L/h/kg)	10 µg/kg	0.32 (34) (n=4)	0.25 (51) (n=9)	0.18(39.4) (n=6)	0.157 (34) (n=9)
	20 µg/kg	0.29 (50) (n=2)	0.19 (45) (n=5)	0.2 (53) (n=7)	0.156 (21) (n=10)
Vss (L/kg)	10 µg/kg	5.2 (42) (n=4)	5.9 (50) (n=9)	6.2 (41) (n=6)	5.9 (28) (n=9)
	20 µg/kg	8.3 (16) (n=2)	4.3 (79) (n=5)	7.5 (34) (n=7)	6.4 (30) (n=10)

Source: Tables 14.4.2.1.1.2-5 in PALO-10-20



N=32 for the 10 mcg/kg group and N=29 for the 20 mcg/kg
Source: Table 14.4.2.2.1.

Figure 8. Median palonosetron plasma concentration vs. time profiles in PK sub-study population (PALO-10-20)

The end-of-infusion plasma concentration (Ct) was collected from the most of patients in PALO 10-20. The Ct was highly variable and substantially high concentrations were noted in some patients. The contribution of the procedural variability associated with the blood sampling to the high variability in Ct cannot be ruled out.

Table 10. Geometric mean (%CV) end of infusion plasma concentration (ng/L)

		Age group (years)			
Dose	All	< 2	2 to < 6	6 to < 12	12 to < 17
10 µg/kg	5589 (372.7) (n=144)	4599.99 (92.9) (n=14)	5868.8 (340.7) (n=46)	4233.7 (162.7) (n=38)	7104.9 (368.6) (n=46)
20 µg/kg	11716.9 (227.5) (n=136)	9024.8 (196.5) (n=12)	9413.6 (252.3) (n=42)	16275.6 (202.6) (n=38)	11831.2 (176.3) (n=44)

Source: Table 14.4.2.1.2

2.4. ANALYTICAL SECTION

2.4.1 How are palonosetron and its major metabolite M9 identified and measured in the plasma/urine in the clinical pharmacology studies?

Palonosetron was measured in plasma using a validated reversed phase high performance liquid chromatography with MS/MS-detection (LC-MS/MS) in the positive electrospray ionization mode (ESI(+)). Two validation reports for bioanalytical assay method were submitted in support of bioanalytical assay for trials PALO-99-07 and PALO-10-20. The same central laboratory was involved for the determination of palonosetron concentrations in the clinical samples.

The first LC/MS/MS assay was used to quantify plasma palonosetron and M9 concentrations for pediatric study PALO-99-07. The same method was used in adult Phase 2 and 3 trials performed for Aloxi Injection NDA (NDA 21-372) and the validation of bioanalytical assay was previously reviewed and found acceptable[4] (113/00-05.PE: Validation of a sensitive LC/MS/MC method for determination of palonosetron and its metabolite M9 in human plasma).

In brief, palonosetron, M9 and the internal standard were isolated from human plasma by solid-phase extraction (SPE). An aliquot of the extract was injected into the HPLC system and analyzed by LC-MS/MS in the positive electrospray ionization mode (ESI(+)).

The bioanalytical assay method using LC/MS/MS for PALO-10-20 was validated for the sample extraction in the 96w format instead of single-tube extraction palonosetron in 96-well plate

[4] The review of clinical pharmacology and biopharmaceutics for original submission by Dr. Sue-Chih Lee

format and a change in chromatography column (047/11- 052.NP: Validation of palonosetron in 96w format).

Reviewer's comments: *The initial validation bioanalytical assay method for palonosetron was limited by the insufficient concentration range for linearity and the lack of long-term storage stability at high concentrations in plasma (see Section 2.6.3 for more details). Nevertheless additional validation for dilution integrity supported the concentration determined to be higher than the established ULOQ. Therefore the bioanalytical assay methods are reasonably acceptable.*

2.4.2 Which metabolites have been selected for analysis and why?

The concentrations of an N-oxide metabolite, M9, in plasma samples were determined in PALO-99-07. The metabolite, M9 was measured because it was formed more than other metabolites. Nevertheless, the metabolite, M9 has less than 1% of the 5-HT3 receptor antagonist and the exposure to the metabolite M9 was less than 10% of palonosetron exposure in PALO-99-07. Therefore M9 was not measured in the subsequent study PALO-10-20.

2.4.3. What is the range of the standard curve? What are the lower and upper limits of quantification (LLOQ/ULOQ)? What is the accuracy, precision and selectivity at these limits?

Table 11. Validation of a sensitive LC/MS/MC method for determination of palonosetron and its metabolite M9 in human plasma [5]

Parameter	Palonosetron	M9
Detection Limit	~ 5 ng/L	~ 5 ng/L
Linearity	43.34 - 2167.04 ng/L	10.27-513.68 ng/L
Precision (%CV)	≤ 18.75%	≤18.40 %
Accuracy (%bias)	≤11.51%	≤9.75%
Stability (freeze/thaw, 24h at RT, 60h in autosampler)	Mean: 92.25-106.39%	Mean: 94.21- 132.79% Precision (%bias): 35.70%* (24h at RT)
Selectivity	No interference observed in blank plasma samples	No interference found in blank plasma samples

* Although the precision for assay of M9 at times reached as high as 35.7%, this is not considered critical. The reason is that M9 was determined at the end not a crucial compound in the assessment of safety and efficacy of the subject drug product.

Reviewer's comments: The anti-coagulant used in the first assay method was not specified while the second method was validated using lithium heparinate plasma.

[5] From the clinical pharmacology review of original NDA 21-372

Table 12. Validation of palonosetron in 96w format (047/11- 052.NP)

Analyte:	Palonosetron
Short description of the method:	LC-MS/MS 96w format with solid phase extraction (SPE)
Biological matrix:	Lithium heparinate (LH) human plasma
Internal standard:	Palonosetron-D3 hydrochloride
Calibration concentrations :	45.000, 90.000, 225.000, 750.000, 1200.000, and 1500.000 pg/mL
Lower limit of quantification :	45.000 pg/mL
Average recovery:	95.6%
QC concentrations:	125.000, 550.000, and 1100.000 pg/mL
QC Between-batch precision	2.2% to 5.6%
QC Between-batch accuracy:	0.0% to 1.8%
QC Within-batch precision:	1.1% to 7.2%
QC Within-batch accuracy:	0.1% to 3.3%
QC Precision (optimized Chromatography):	2.4% to 3.2%
QC Accuracy (optimized Chromatography):	-0.7% to 3.6%
Matrix effect (mean)	-35%
Freeze/thaw stability:	3 cycles
Autosampler storage stability:	147 hours
Long-term storage stability:	-20°C for at least 13 months (CRS study number 026/10-03.NP)
Dilution integrity:	6500.000 pg/mL diluted 5-fold 2500.000 pg/mL diluted 2-fold
Carry over:	None
Selectivity:	No interfering peaks noted in blank plasma samples.

Table 13. Dilution Integrity

	DQC20	DQC250	DQC500
	Spiked concentration [pg/mL]		
	20000.000	300000.000	600000.000
	Determined concentration [pg/mL]		
	20584.807	316301.682	637260.448
	20820.853	317601.033	690562.003
	21921.709	300201.974	608323.355
	20176.561	308929.802	597022.063
	21345.558	322628.772	594946.350
n	5	5	5
Mean [pg/mL]	20969.897	313132.653	625622.844
SD [pg/mL]	679.514	8732.867	40033.900
Precision [%]	3.24	2.79	6.40
Accuracy [%]	4.85	4.38	4.27

SD: standard deviation

The freeze/thaw stability during 4 cycles and long-term stability in plasma at -20 ºC up to 27 months were established by additional validation conducted during the in-study bioanalytical

assay.

In particular, the dilution integrity was expanded for factors 20, 250, and 500. In PALO 10-20, 406 out of 1062 samples were reanalyzed due to concentrations above the ULOQ and the mean Cmax and Ct after 10 or 20 mcg/kg dosing were substantially higher than the established upper limit of detection in PALO-10-20.

Reviewer's comments: *The results of dilution integrity up to 500 fold dilution were acceptable. However, ideally the concentration range for calibration curve should have been re-established to cover the peak plasma concentrations based on the observed high plasma concentrations. The long-term storage stability in plasma at high concentrations was not studied at concentrations beyond the ULOQ.*

For PALO-99-07, the mean Cmax was still higher than the ULOQ but generally within the established dilution integrity range i.e. 5-fold dilution in the original validation. Compared to PALO 10-20 where the higher dose i.e. 20 mcg/kg was administered and the end-of-infusion plasma concentration was measured, in PALO-99-07, the plasma PK sampling was not done until 15 min or 1 h after dosing given as a 30 second infusion so the peak plasma concentrations were lower compared to those in PALO-10-20.

According to the sponsor, in PALO-99-07, the protocol deviation was documented at one study site where blood samples for PK analysis at 0.25 h were drawn from the same port (central or peripheral line) used for palonosetron administration without flushing the insertion line (samples drawn in 9 patients receiving 3.0 μg/kg and 10 patients receiving 10.0 μg/kg). Palonosetron plasma concentrations at 0.25 h in a large number of these patients were considerably higher than those obtained at the other sites participating in this study. Values up to 279,172 ng/L were reported for the 0.25 hr post-dose samples from this site, whereas maximum concentrations at this 0.25 hr time-point for all but a few patients were below 10,000 ng/L at other sites. The concentrations in samples taken at later time points at this site were in the same range as those at the other sites. Therefore, the 0.25 h concentration values from Site 711 were considered to be unreliable due to experimental error, and none of these values were included in the PK analysis for palonosetron (M9 values at this timepoint were not excluded as the failure to flush the line should not impact the metabolite concentration).

Reviewer's comments: *The sponsor's justification to exclude those values from PK analysis for palonosetron is acceptable.*

3 DETAILED LABELING RECOMMENDATIONS

3.1 SPONSOR'S PROPOSAL

The sponsor's proposed labeling change in Section 12. 3 is as below (submission date: 11/22/2013).

12.3 Pharmacokinetics

Pediatric Patients

Single-dose I.V. ALOXI pharmacokinetic data obtained from a subset of pediatric cancer patients that received 20 mcg/kg (b) (4). Peak concentrations reported at the end of the 15 minute infusion were (b) (4) here are no apparent differences in volume of distribution when expressed as L/kg.

Table 3. I.V. ALOXI Pharmacokinetics in Pediatric Cancer Patients

PK Parameter [1]	Pediatric Age Group			
	<2 y	2 to <6 y	6 to <12 y	12 to <17 y
	N=12	N=42	N=38	N=44
C_T [2], ng/L	9025 (197)	9414 (252)	16275 (203)	11831 (176)

(b) (4)

1- Geometric Mean (CV) except for t1/2 which is median values .
2- C_T is the plasma palonosetron concentration at the end of the 15 minute infusion.
3- Clearance and Vss are weight adjusted

(b) (4)

3.2 AGENCY RECOMMENDATION

[Labeling revisions are ongoing. Detailed recommendations will be updated.]

Main labeling comments are (b) (4)

12.3 Pharmacokinetics

Pediatric Patients

Single-dose I.V. ALOXI pharmacokinetic data was obtained from a subset of pediatric cancer patients that received 10 mcg/kg or 20 mcg/kg. When the dose was increased from 10 mcg/kg to 20 mcg/kg a dose-proportional increase in mean AUC was observed. Following single dose intravenous infusion of Aloxi 20 mcg/kg, peak plasma concentrations (C_T) 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 than in older patients. Median half-life ranged from about 20 to 30 hours across all age groups.

The total body clearance (L/h/kg) in patients 12 to 17 years old was similar to that in healthy adults and a trend of higher clearance was observed in younger patients. There are no apparent differences in volume of distribution when expressed as L/kg.

Table Y. Pharmacokinetics Parameters in Pediatric Cancer Patients following intravenous infusion of ALOXI at 20 mcg/kg over 15 min

PK Parameter [a]	Pediatric Age Group			
	<2 y	**2 to <6 y**	**6 to <12 y**	**12 to <17 y**
	N=12	**N=42**	**N=38**	**N=44**
C_T [b], ng/L	9025 (197)	9414 (252)	16275 (203)	11831 (176)
		N=7	**N=9**	**N=10**
$AUC_{0-\infty}$, h·mcg/L		103.5 (40.4)	98.7 (47.7)	124.5 (19.1)
T½, h		28.0	23.3	30.5

a Geometric Mean (CV) except for t1/2 which is median values .

b C_T is the plasma palonosetron concentration at the end of the 15 minute infusion.

4 APPENDICES

4.1 SPONSOR'S ANALYSIS

4.1.1 Exposure-Response Analysis

Two PK/PD analyses were undertaken to assess the possible relationship between plasma exposure parameters versus response.

The early PK/PD study PALO-07-34 evaluated whether a fixed or allometric scale dosing scheme would be appropriate in pediatric patients. Data indicated that a 10 mcg/kg palonosetron dose administered on either a fixed or allometric scale was predicted to meet or exceed the adult exposure associated with the 3 mcg/kg dose. The large safety margin observed with palonosetron in adult patients provided additional assurance of the safety of 10 and 20 mcg/kg weight-based pediatric palonosetron doses to be used in PALO-10-20.

E-R analyses performed by the Applicant using PALO-99-07 data found no clear evidence of a relationship between palonosetron exposure and complete response. This outcome was confirmed in PK/PD study PALO-11-20 using data from PALO-10-20.

In study PALO-11-20 the logistic regression analysis of CR in the acute and delayed phases, using measures of palonosetron exposure as predictors of response, indicated no clear relationship was evident between drug exposure and response in pediatric 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 or delayed phases.

Reviewer's comments: *This reviewer does not agree with the Applicant's conclusion. Please refer to reviewer's analysis for details.*

4.1.2 Population PK analysis

A total of 779 concentrations from 134 pediatric patients (71 patients from PALO-99-07 and 63 patients from Study PALO-10-20), whose ages ranged from 0.3 years to 17.4 years of age, were included in this population PK analysis. The demographic and baseline characteristics for patient used in population PK analyses are listed below.

Table 14. Demographics and baseline characteristics for patients (N=134) used in the palonosetron PK analysis

Covariate	Summary
Continuous Variables	*Median (range)*
Age (years)	9.2 (0.3-17.4)
Body mass index (kg/m^2)	16.9 (13 – 41.6)
Body weight (kg)	33 (4.5 – 112)
Baseline ALT (IU/L)	27 (6 – 332)
Baseline AST (IU/L)	27.5 (5 – 96)
Baseline alkaline phosphatase ALP (IU/L)	146 (53 -576)
Baseline total bilirubin (μmol/L)	0.3 (0.07 – 1.23)
Baseline creatinine clearance (mL/min)	121 (51 – 150)
Dose (mg)	0.245 (0.0134-1.50)
Dose (mcg/kg)	
Study PALO-99-07	
3 mcg/kg dose group (n=34)	2.99 (1.45-3.11)
10 mcg/kg dose group (n=37)	10 (8.19-10)
Study PALO-10-20	
10 mcg/kg dose group (n=33)	10 (10-10)
10 mcg/kg dose group (n=30)	20 (15.73-20)
Categorical Variables	*Count (%)*
Age (yrs)	
<2 years old	18 (13.4%)
2 to <6 years old	27 (20.2%)
6 to <12 years old	37 (27.6%)
12 to 17years old	52 (38.8%)
Sex (males/females)	
Males	76 (56.0%)
Females	58 (44.0%)
Race/Ethnicity	
American Indian or Alaska Native	0
Asian	2 (1.5%)
Black or African American	2 (1.5%)
Native Hawaiian or Other Pacific Islander	0
White	96 (71.6%)
Multiracial	3 (2.2%)
Missing	31 (23.1%)
Race Categorization	
Hispanic or Latino	34 (25.3%)
Not Hispanic or Latino	61(45.5%)
Missing information	39 (29.1%)
Taking CYP2D6 Inducer	26 (19.4%)
Taking CYP2D6 Inhibitor	60 (44.8%)
Taking CYP3A4 Inducer	2 (1.5%)
Taking CYP3A4 Inhibitor	26 (19.4%)
Taking Cyclophosphamide	37 (27.6%)
Taking Dexamethasone	26 (19.4%)
Taking Cytarabine	18 (13.4%)
Taking Doxorubicin	52 (38.8%)
Taking Fluconazole	15 (11.2%)
Taking Ranitidine	7 (5.2%)

Sources: Applicant's population PK report; Page 42

Figure 9: Final PK model parameter estimates for palonosetron

	FINAL ESTIMATE	%RSE	95% CONFIDENCE INTERVAL LBOUND	UBOUND	DESCRIPTOR/ VARIABILITY
THETA					
1	5.72	7.74%	4.85	6.59	CL;1
2	27.5	25.1%	14.0	41.0	V1;2
3	47.6	17.3%	31.5	63.7	Q ;3
4	130	4.48%	119	141	V2;4
5	1.10	6.45%	0.961	1.24	WT-V2;5
6	0.715	11.7%	0.551	0.879	WT-CL;6
7	1.37	20.8%	0.811	1.93	WT-Q;7
8	0.855	31.6%	0.326	1.38	WT-V1;8
OMEGA					INTERINDIVIDUAL VARIABILITY
1,1	0.306	11.6%	0.236	0.376	CV = 55.3%
2,2	3.14	23.2%	1.71	4.57	CV = 177%
3,3	1.50	18.8%	0.947	2.05	CV = 122%
4,4	0.0721	32.2%	0.0266	0.118	CV = 26.9%
SIGMA					RESIDUAL VARIABILITY
1,1	0.0729	6.54%	0.0636	0.0822	CV = 27.0%
2,2	2.50e+003	...	...	...	SD = 50.0

*Indicates 95% confidence interval that includes zero
%RSE is percent relative standard error (100% x SE/EST)

CL: Clearance
V1: Volume of the central compartment
Q: Intercompartmental clearance
V2: Volume of the peripheral compartment
WT: Body weight

Sources: Applicant's population PK report; Page 43

Reviewer's comments: the Applicant's analysis is acceptable.

4.2 REVIEWER'S ANALYSIS

4.2.1 Exposure-Response Analysis for Efficacy

4.2.1.1 Objectives

The primary objectives for these analyses were to:

- To characterize the exposure-response relationship for efficacy to evaluate the proposed dose of 20 µg/kg in pediatric CINV.
- To assess the effects of covariates on CRA response.

4.2.1.2 Methods

4.2.1.3 Datasets

Name	Link to EDR
pkpd.xpt	\\Cdsesub1\evsprod\NDA21732\0000\m5\datasets

4.2.1.4 Software

NONMEM 7.1, SAS 9.2 and S-PLUS 7.0 were used for analyses.

4.2.1.5 Results

Logistic regression

A multivariate logistic regression based on log-linear model was conducted to identify the covariates that predict response. Several models including linear, log-linear and E_{max} models were tested. Logistic regression using the E_{max} model appeared to describe the data better as compared to linear or log-linear logistic regression models.

In the exposure-response analyses for efficacy, the exposure endpoints are AUC and C_{max} predicted from the final population PK model. The efficacy endpoints are CRA and CRD. The reviewer conducted the analysis for individual trials and with the data combined from both CINV trials.

The evident exposure-response relationship for efficacy supports the proposed dose. The E_{max} logistic model of CRA, using measures of palonosetron exposure as predictors of response, indicated that theE-R relationship was evident between drug exposure and combined CRA response in pediatric patients from trial 1020 and 9907.

CRA:

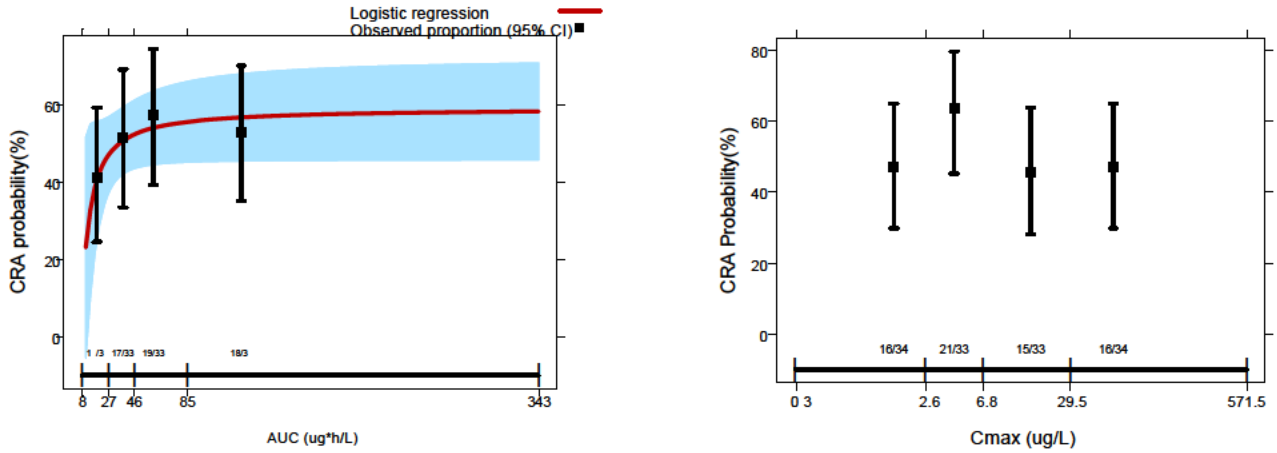


Figure 10. Exposure-response relationship of palonosetron between AUC or Cmax and CRA response in pediatric patients.

The applicant submitted CRA data from the adult trial PALO2230 with 35 patients. There is no apparent E-R relationship based on the data available. However, this may be due to limited data from 35 adult patients available for exposure-response analysis. The AUC was based on NCA analysis provided by the Applicant and there are no time-concentration data available for population PK analysis.

Reviewer's comment: It should be noted that this analysis is suffered from limited patients numbers, and the AUC data provided by the Applicant was not analyzed by the reviewer since the time-concentration data are not available.

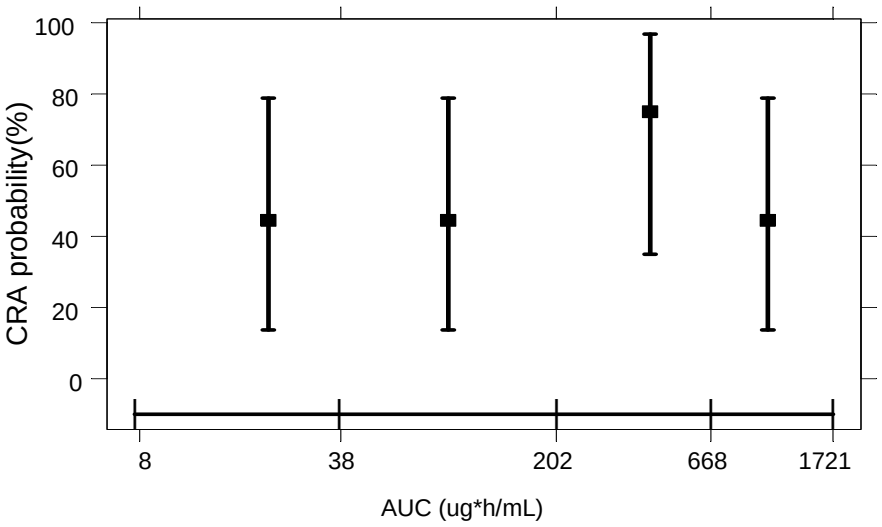


Figure 11: Exposure-response relationship for CRA response in Adult CINV Patients (N=35).

Covariate analysis

The reviewer conducted covariate analysis based on the PK-PD model using the step-wise approach. The following covariates are screened:

- Age, body weight, body mass index
- Race
- Use of CYP2D6 inhibitors
- Use of CYP2D6 inducers
- Use of dexmathesone
- Use of doxorubicin
- Baseline s*erum aspartate aminotransferase*
- Baseline b*ilirubin*
- Baseline *Creatinine cleatance*

Among them, age has been identified as a significant covariate for CRA response. It should be noted that there might be other confounding factors that are correlated with age. The age-dependent factors included *Weight, Total dose of palonosetron administered, Body Mass Index, Primary Cancer High Level Group Term, Baseline Serum aspartate aminotransferase and Bilirubin, Use of Corticosteroids, Use of CYP2D6 Inhibitors, and Use of Doxorubicin*.

Concomitant use of these drugs may be explained by different therapeutic approaches used

among the patients, and may in part be attributable to different cancer types across the age ranges of these children. Adding these covariates into the model did not significantly improve the model. It should be noted that the applied models are not expected to completely eliminate the confounded effects of these factors in our E-R analysis, due to the unknown structure of the relationship between these risk factors and the hazard of the event and the complex interaction among these risk factors. Nevertheless, our finding of age as a covariate for response indicates that there may be a potential difference of E-R relationship between pediatrics and adults. In addition, the observed data from 400 pediatric patients showed that patients with less than 6 years of age had markedly higher CRA response than pediatric patient older than 6 years (**Figure 7**).

There may be several possible mechanisms that explain the age effects on CRA response. Based on our discussion with the medical officer Dr. Sohrabi, one of those possible mechanisms is that younger pediatric patients may have higher sensitivity to the drug response (lower EC_{50}) than the older pediatric patients. This scenario is incorporated into the covariate model by including age as a covariate on EC_{50}. Based on this mechanism and the final population estimate, the figures below show the predictions of E-R curve at different ages with the underlying mechanism as discussed above.

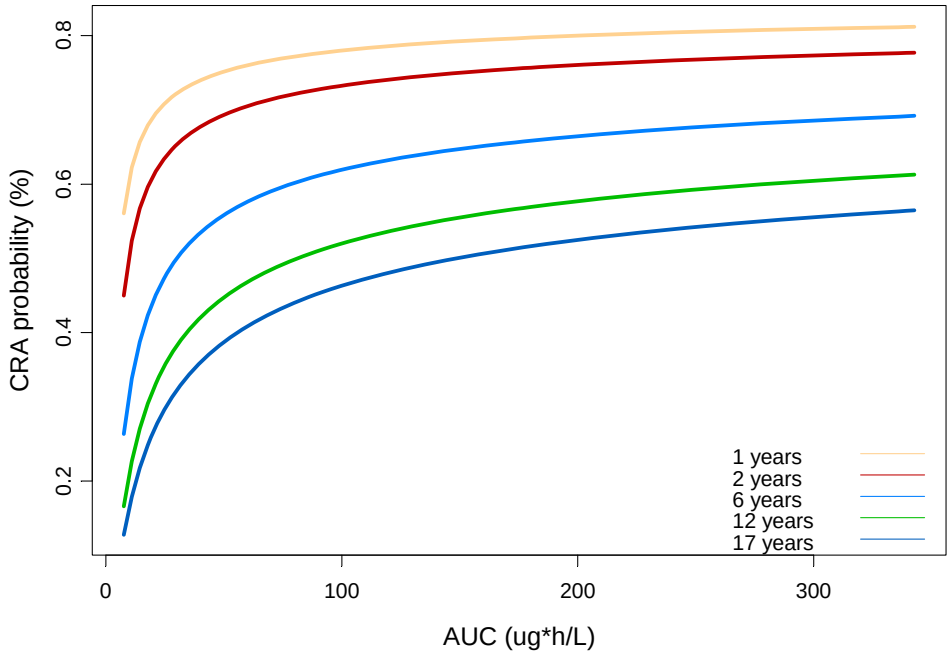


Figure 12. Exposure-CRA Relationship in Pediatric CINV patients.

CRD:

CRD data are available from trial 1020, but not trial 9907. The analyses of E-R relationship using AUC or C_{max} did not identify significant relationship between the palonosetron exposure and

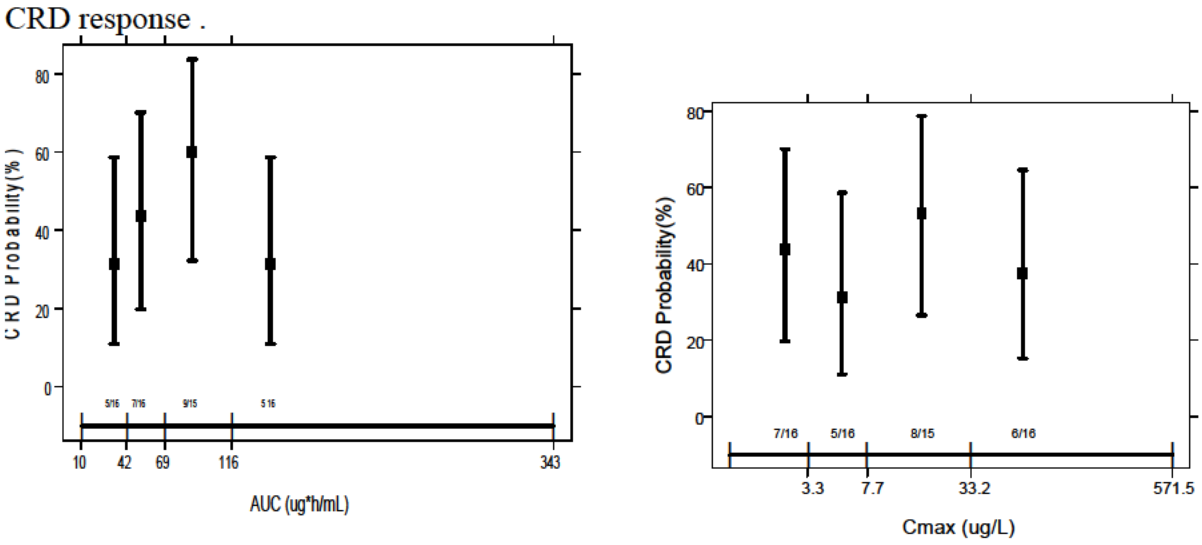


Figure 13. Exposure-CRD Relationship in Pediatric CINV Patients.

CRA+CRD:

E-R relationship was further examined by combined CRA and CRD together as overall response. There is a slight increasing trend of CR response with increasing AUC. The analysis was based on the data from trial 1020 only as there was no CRD data from trial 9907.

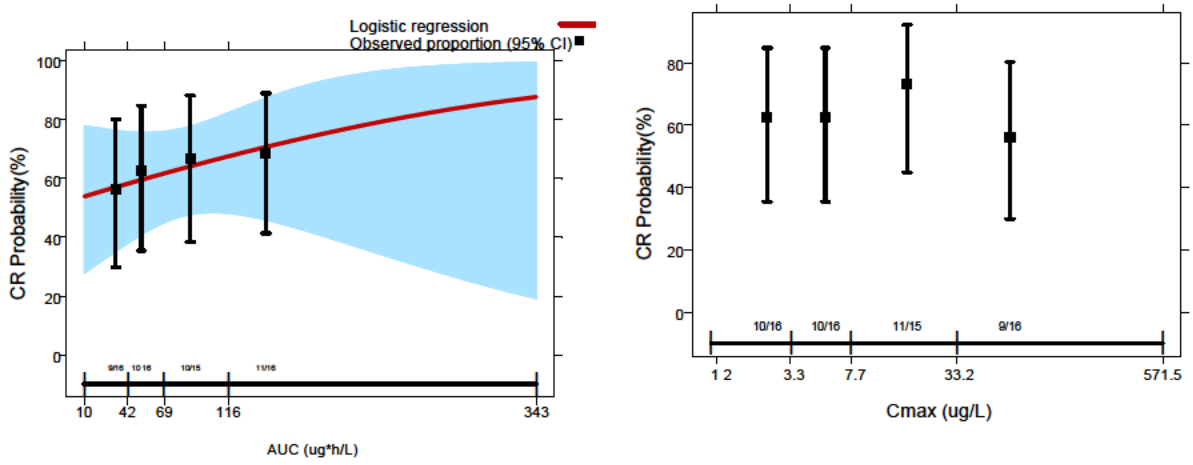


Figure 14. Exposure-CR Relationship Pediatric CINV Patients.

4.2.2 Population PK analysis

4.2.2.1 Objectives

- to assess the PK parameters in the full range of pediatric ages, for the three palonosetron doses administered during the two pediatric trials performed in the CINV
- to provide good estimation of the palonosetron PK parameters of interest (Cmax, AUCs,) for E-R analysis

4.2.2.2 Methods

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.

4.2.2.3 Datasets

Name	Link to EDR
pkall.xpt	\\Cdsesub1\evsprod\NDA21732\0000\m5\datasets

Based on body weight, patients underwent the following maximum number of PK samplings:

Patient weight [kg]	PK samples [Time]								Number of samples
	Pre-dose	T_T	0.25	1	6	24 (A) or 48 (B)	72 (A) or 120 (B)	144/ 216	
	Visit 2 (Day 1)					V3 or V4	V5 or V6	V7	
≥7.5	X	X	X	X	X	X	X	X	8
≥6.7 and <7.5		X	X	X	X	X	X	X	7
≥6.3 and <6.7		X	X	X	X	X	X		6
≥5.9 and <6.3		X		X	X	X	X		5
≥5.5 and <5.9		X		X	X	X			4
≥4.6 and <5.5		X		X		X			3
≥4.2 and <4.6		X		X					2
<4.2		X							1

4.2.2.4 Software

Population PK models were built using a nonlinear mixed effects modeling technique with NONMEM® software (ICON Development Solutions). TIBCO Spotfire S+® 8.1 was used for analysis.

4.2.2.5 Results

The plasma palonosetron concentration versus time data were best described using a two compartment model with IV infusion and first order elimination. The reviewer's analysis indicates that the final model provided by the Applicant is acceptable. Following covariate evaluation the final model was determined to include:

WT on CL
WT on V1
WT on V2
WT on Q

Adding age into the model did not significantly decrease in objective function value (χ^2>0.01). . Although there is a slight decreasing trend of palonosetron CL and V1 with increasing patient age and a slight increasing trend of palonosetron Q and V2, this analysis demonstrates that no further adjustment of dosing, beyond dosing palonosetron on a body weight basis, is required for pediatric patients.

The results of the PK analyses indicated that although minor trends were reported among age groups for AUC, the ranges remained within the observed variability of these parameters and were mostly overlapping between age groups (**Figure 16**). Therefore no adjustment of dosing is required for pediatric patients, beyond dosing palonosetron on an individual patient weight basis.

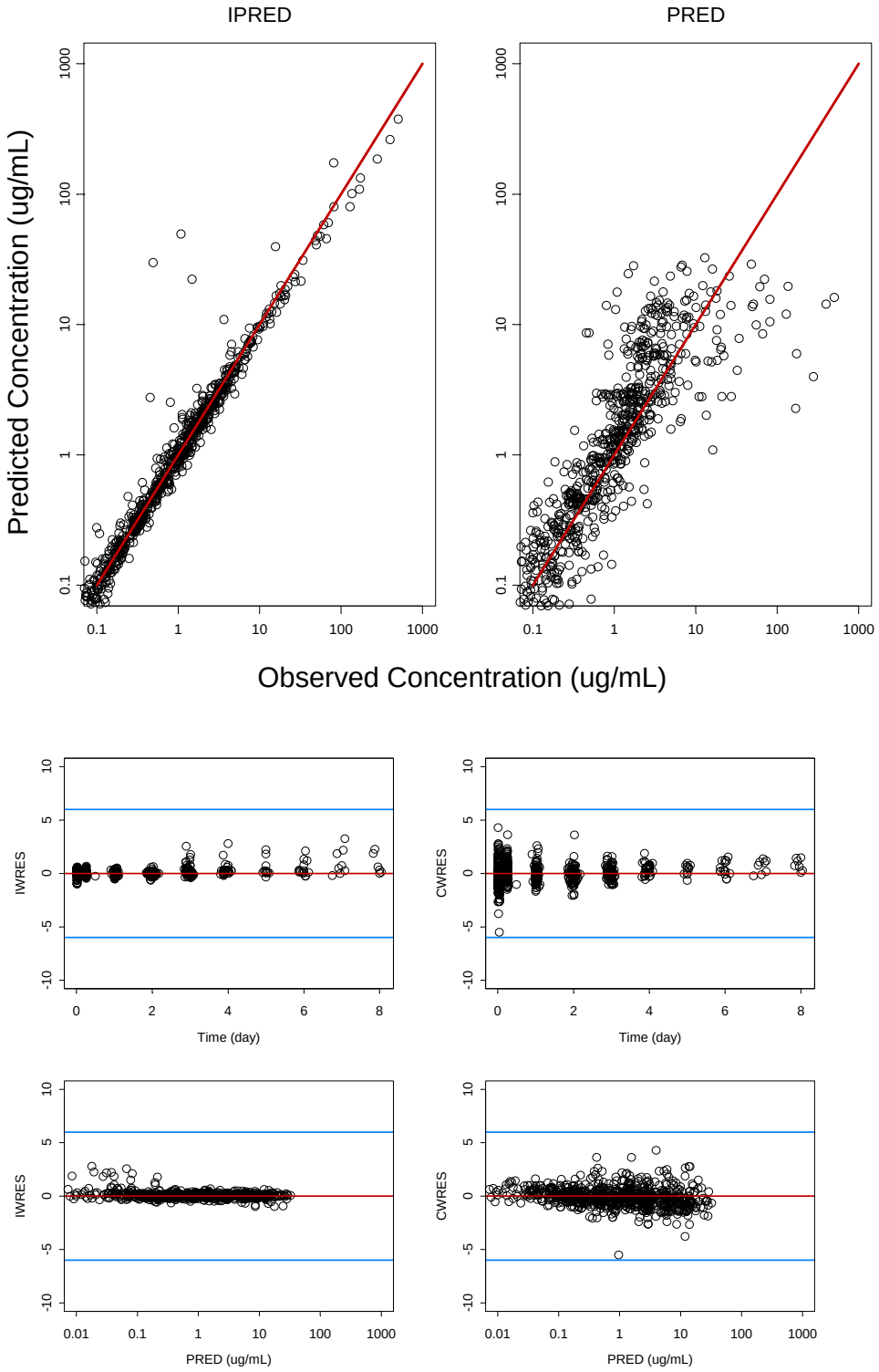


Figure 15. Goodness-of-fit plot for the final population PK model.

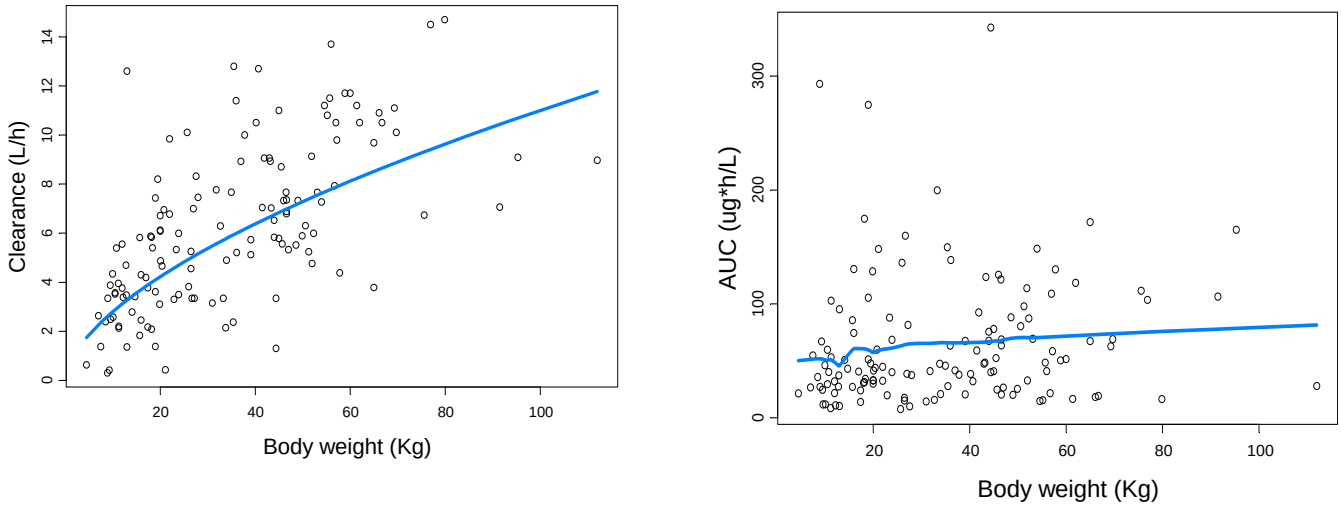


Figure 16. Plots of CL vs body weight (left) and predicted AUC at 20 ug/kg dose vs. body weight (right) under the final population PK model. Left: Solid blue line corresponds to the body weight-CL relationship from the population estimates. The open solid circles are individual clearance estimate of pediatric patients. Right: Solid blue line corresponds to the *LOESS* curve. The open solid circles are individual AUC of pediatric patients following the body-weight based dosing.

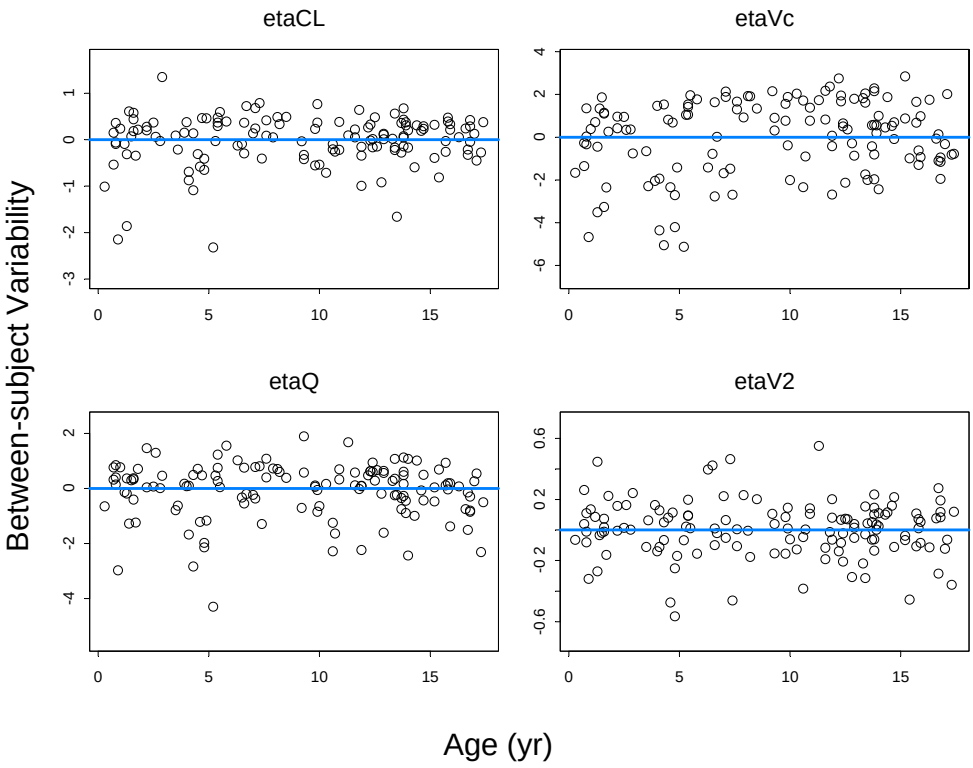


Figure 17. Plots of between subject variability *vs* age under the final population PK model.

Conclusion:

- A two compartment open model (IV infusion as input) and first order elimination was determined to provide the best fit to the palonosetron concentration data. The structural model parameters were assumed to be log normally distributed. The median clearance was estimated to be 5.27 L/h for patients of median body weight (33 kg).
- In the covariate analysis, the body weight was the only covariate that had an influence on PK parameters of clearance (CL), central and peripheral volume of distribution (V1 and V2), and inter-compartmental clearance (Q).
- When CL, V1, Q, and V2 were adjusted for patient body weight, there were no significant differences across the patient ages. The data do, however, suggest a trend for a slightly lower clearance with increasing patient age, although not significant.
- A consistent trend when comparing AUCs across age groups was not evident.

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/s/

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05/12/2014

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05/12/2014

SUE CHIH H LEE
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