CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-372/S008/S010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: TQT Study Review

NDA	21372
Brand Name	Aloxi®
Generic Name	Palonosetron
Sponsor	Helsinn Healthcare SA
Drug Class	Selective serotonin subtype 3 (5-HT_3) receptor antagonist
Approved Indication	Prevention of chemotherapy induced nausea and vomiting (CINV)
Sought Indication	Prevention of postoperative nausea and vomiting (PONV)
Dosage Form	IV Solution
Therapeutic Doses	Chemotherapy Induced Nausea and Vomiting: • 0.25 mg injected intravenously over 30 seconds 30 minutes before starting chemotherapy Postoperative Nausea and Vomiting: • 0.075 mg injected intravenously over 10 seconds immediately before induction of anesthesia
Duration of Therapeutic Use	Acute
Application Submission Date	27 Jun 2007
Review Classification	TQT Study Report
Date Consult Received	28 Jun 2007
Clinical Division	DGP / HFD-180
PDUFA Date	01-September 2007

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant effect of palonosetron administration on the QT interval was detected in this thorough QT study. The maximum increase (and corresponding upper two-sided 90% bound) in the placebo-corrected mean change in QTcI from baseline for the 0.25 mg, 0.75 mg and 2.25 mg dose groups were -0.6 ms (3.3 ms), 0.6 ms (5.1 ms) and 1 ms (4.8 ms). Similar results were observed for QTcF.

The study was a randomized, double-blind, positive- and placebo-controlled parallel study in which 221 healthy subjects were administered single doses of palonosetron 0.25 mg, palonosetron 0.75 mg, palonosetron 2.25 mg, moxifloxacin 400 mg, or placebo. At the supratherapeutic dose (2.25 mg), palonosetron plasma concentrations were 9-fold

higher than concentrations following the therapeutic dose (0.25 mg). The plasma concentrations attained are sufficient to cover the increase in plasma concentrations expected due to known intrinsic factors.

A single dose of 400 mg moxifloxacin increased the QT interval by 11 ms (lower 95% confidence bound 8 ms) 2 hours after dosing indicating that the study was adequately designed and conducted to detect a mean increase in the QTc of about 5 ms.

1.2 ADDITIONAL QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

1.2.1 Postmarketing experience

ICH E14 recommends post-marketing adverse event reports if available can be an additional source of information on a drug's proarrhythmic potential. The QT-IRT suggests that the division consider evaluating the postmarketing experience of ALOXI®.

1.2.2 Labeling

The QT-IRT suggests that the sponsor's proposed label be changed so that the final sentence state "The study demonstrated no ***significant*** effect on any ECG interval including QTc duration (cardiac repolarization) at doses up to 2.25 mg." Aloxi® has an effect on the QT interval but it is small. Additionally, we recommend that the statement in the current label "In non-clinical studies palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarization and to prolong action potential duration" be retained.

2 PROPOSED LABEL

The sponsor proposed the following label:

12. CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

The effect of palonosetron on QTc interval was evaluated in a double blind, randomized, parallel, placebo and positive (moxifloxacin) controlled trial in adult men and women. The objective was to evaluate the ECG effects of IV administered palonosetron at single doses of 0.25, 0.75 or 2.25 mg in 221 healthy subjects. (b) (4)

(b) (4)

The current label states:

"The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in clinical trials. In non-clinical studies palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarization and to prolong action potential duration. In clinical trials, the dose-response relationship to the QTc interval has not been fully evaluated."

"Although palonosetron has been safely administered to 192 patients with pre-existing cardiac impairment in the Phase 3 studies, ALOXI should be administered with caution in patients who have or may develop prolongation of

cardiac conduction intervals, particularly QTc. These include patients with hypokalemia or hypomagnesemia, patients taking diuretics with potential for inducing electrolyte abnormalities, patients with congenital QT syndrome, patients taking anti-arrhythmic drugs or other drugs which lead to QT prolongation, and cumulative high dose anthracycline therapy. In 3 pivotal trials, ECGs were obtained at baseline and 24 hours after subjects received palonosetron or a comparator drug. In a subset of patients ECGs were also obtained 15 minutes following dosing. The percentage of patients (<1%) with changes in QT and QTc intervals (either absolute values of > 500 ms or changes of > 60 ms from baseline) was similar to that seen with the comparator drugs."

3 BACKGROUND

Palonosetron is an antiemetic and antinauseant agent. It is a selective serotonin subtype 3 ($5\text{-}HT_3$) antagonist with a prolonged duration of action.

3.1 MARKET APPROVAL STATUS

ALOXI® (palonosetron) is approved in the USA for prevention of acute CINV associated with highly or moderately emetogenic chemotherapy and for prevention of delayed CINV associated with moderately emetogenic chemotherapy. The recommended dosage of ALOXI® is 0.25 mg administered as a single dose approximately 30 minutes before the start of chemotherapy. The sponsor has submitted a sNDA seeking approval to market ALOXI® for prevention of postoperative nausea and vomiting.

Palonosetron has also been approved for use for the prevention of chemotherapy induced nausea and vomiting (CINV) in 52 countries outside the US. Palonosetron has not been denied market approval in any country due to safety reasons, and palonosetron has not been withdrawn from the market in any country where it has been approved.

3.2 PRECLINICAL INFORMATION

The sponsor states the following in the Dec 2005 IB:

"Palonosetron inhibited hERG and hHNa channels stably expressed in HEK293 cells in a concentration dependent manner. The IC_{50} values were 1.9-2.04 μM and 6.5 μM for hERG and hHNa channels, respectively."

"In dog Purkinje fibers, Palonosetron induced a dose dependent increase in action potential duration (APD_{70} and APD_{90}) at 0.3 μM and 3.0 μM, under normal (60 ppm) and - to a larger extent - under low (12 ppm) stimulation rates, suggesting a reverse use-dependency."

"In conscious dogs administered Palonosetron by the intravenous route and monitored via telemetry for 24 hours (10 and 100 μg/kg) or 72 hours (1000 μg/kg), there were no pharmacologically relevant effects on arterial blood pressures, heart rate, PR interval, QRS complex duration, QT interval, QTc and in the frequency and occurrence of atrioventricular blocks."

3.3 PREVIOUS CLINICAL EXPERIENCE

The sponsor states in the Dec 2005 IB that through September 21, 2005, approximately (b) (4) vials of palonosetron have been sold worldwide and only one case of ventricular tachycardia has been reported (which is termed "unassessable")

Reviewer's comment: The QT-IRT did not review data from other portions of the current sNDA. Nor did the QT-IRT query AERS to assess if palonosetron is associated with an unusual frequency of adverse events that might be associated with QT-prolongation, i.e. sudden death, torsade de pointes, ventricular tachycardia, syncope, seizures, and QT prolongation.

3.4 CLINICAL PHARMACOLOGY

Table 1 summarizes the key features of palonosetron's clinical pharmacology.

Table 1: Highlights of Clinical Pharmacology

Therapeutic Dose	0.25 mg IV
Maximum tolerated dose	Approx 6 mg (90 µg/kg tested in humans, Study 2330) NOAEL (chronic tox studies) 7 mg/kg/d in rat 6 mg/kg/d in dog ALD50: 10-30 mg/kg in mice 30-100 mg/kg in rat >20 mg/kg in dog
Principal adverse events	headache, constipation, diarrhea, dizziness, fatigue, abdominal pain, insomnia
Maximum dose tested	
Single dose	Approx 6 mg (90 µg/kg) (Study 2330)
Multiple dose	0.25 mg qd x 3 (PALO-02-12)
Exposures achieved at maximum tested dose [mean (%CV) for C_{max} and AUC]	
Single Dose; Mean (%CV)	90 µg/kg (Study 2330) C_{max} = 336,000 ng/L (280) $AUC_{0\text{-last}}$ = 870,000 ng*hr/L (43)
Multiple Dose; mean (%CV)	0.25 mg qd x 3 (PALO-02-12) Day 3 C_{max} = 2430 ng/L (47) Day 3 $AUC_{(0\text{-last})}$ = 49,200 ng*hr/L (26)
Range of linear PK	0.03 µg/kg through 90 µg/kg in healthy volunteers and cancer patients (Study 2092, 2330)
Accumulation at Steady state [mean (%CV) or SD]	PALO-02-12; 3 daily doses of 0.25 mg IV Accumulation Ratio Day 3 = 2.10 (21) C_{max} = 2.43 ± 1.14 ng/L on Day 3 PK simulation, dosing to steady state Day 7 (PALO-02-17) C_{max} = approx 3.30 ng/L at steady-state
Metabolites	M4, M9; Activity is 1% of parent
Absorption	N/A [oral formulation, NDA to be submitted in 4Q07 shows F = 97-100% for (b) (4) capsule formulations; 90% CIs were 91.5 – 101.9 and 94.6 – 105.4, for the two formulations respectively. (PALO-04-04)]
Distribution [mean (SD)]	Approx 62% bound to plasma proteins Vd = 8.3 L/kg ±2.5 (SD) (Study 2330)
Elimination [mean; (%CV)]	• 50% cleared metabolically (primarily CYP450 2D6 and to a lesser extent 3A4 and 1A2) • 40% cleared renally • Clearance: 1.66 ml/min/kg (36) (Study 2330) • Terminal elimination half-life: approx 40 hours • Terminal elimination half-life M9: 110 hours (104) for 90 ug/kg dose (Study 2330) • Terminal elimination half-life M4: unable to reliably determine

Intrinsic Factors; mean (CV)	• No effect of age on PK (PALO-99-33) • No effect of race on PK (PALO-99-33); however total body clearance was 25% higher in Japanese subjects (Study 0100). No dosage adjustment necessary. • No effect of gender elucidated in population PK (PALO-99-33); in recent studies in healthy subjects C_{max} and AUC appeared slightly higher in females compared to males (PALO-02-12) Day 1: Female C_{max}= 2610 ng/L (38) Male C_{max} = 2250 ng/L (59) Female $AUC_{0\text{-last}}$ = 54,500 ng*hr/L (20) Male $AUC_{0\text{-last}}$ = 44,000 ng*hr/L (29) • Renal Impairment: no dosage adjustment necessary Healthy Subjects C_{max} = 2549 ng/L (35) $AUC_{0\text{-last}}$ = 73.3 ug*hr/L (38) Mild/Mod Impairment C_{max} = 2574 ng/L (40) $AUC_{0\text{-last}}$ = 78.2 ug*h/L (23) Severe Impairment C_{max} = 2600 ng/L (47) $AUC_{0\text{-last}}$ = 106 ug*h/L (44) • Hepatic Impairment: no dosage adjustment necessary Healthy Subjects C_{max} = 2549 ng/L (35) $AUC_{0\text{-last}}$ = 53.9 ug*hr/L (35) Mild Impairment C_{max} = 1779 ng/L (46) $AUC_{0\text{-last}}$ = 64.3 ug*h/L (47) Moderate Impairment C_{max} = 1799 ng/L (31) $AUC_{0\text{-last}}$ = 64.3 ug*h/L (47) Severe Impairment C_{max} = 994 ng/L (36) $AUC_{0\text{-last}}$ = 58.0 ug*h/L (49) • No difference in PK profile between rapid and slow metabolizers of CYP2D6.
Extrinsic Factors	Drug Interaction Studies; effect on palo PK • No effect on PK with administration of metoclopramide (PALO-99-34) • No effect on PK with administration of dexamethasone (PALO-03-10) • No effect on PK with administration of aprepitant (PALO-03-05)
	• No effect on co-meds per population PK model (PALO-99-33)
Food Effects	N/A for IV formulation. Oral formulation NDA to be submitted in 4Q07 shows no effect of a high fat meal on absorption of palonosetron (PALO-04-02)
Expected High Clinical Exposure	Doses are administered by a healthcare provider, overdosage is considered unikely. Doses administered qd x 3 days in Study PALO-02-12 provided less exposure than a single 0.75 mg dose, which was studied in Phase 3.

3.5 'THOROUGH QT' (TQT) STUDY

3.5.1 Title

Dose-response evaluation of single doses of IV palonosetron 0.25, 0.75, 2.25 mg and oral moxifloxacin 400 mg versus placebo on ECG parameters: a double blind, randomized, parallel study in male and female healthy volunteers

3.5.2 Protocol Number

PALO-03-11 / SPC 343-3

3.5.3 Objectives

- To evaluate the dose response for the effects of palonosetron on ECG parameters in male and female healthy volunteers.
- To evaluate the safety and tolerability of palonosetron and the relative safety in comparison with moxifloxacin with focus in ECG parameters in male and female healthy volunteers.

3.5.4 Design

3.5.4.1 Description

Randomized, single-dose, double blind, double dummy, parallel group, placebo and active comparator controlled study.

3.5.4.2 Sponsor's Justification for Design

A parallel design was used due to the long half life of palonosetron (about 40 hours). A crossover design would have required too long a washout time between treatment periods to be practical.

3.5.4.3 Controls

The Sponsor used both negative (placebo) and positive (moxifloxacin) controls.

3.5.4.4 Blinding

The study was double blind using a double dummy approach. Each subject received three separate 5 ml injections of palonosetron and/or its placebo and an oral tablet of moxifloxacin or its placebo.

3.5.5 Dosing Regimens

3.5.5.1 Treatment Arms

Treatment group	Treatment Administration	No of planned subjects
Treatment A-Placebo	placebo IV (3 x 5 ml) + placebo oral	46
Treatment B-Palonosetron 0.25 mg IV	palonosetron 0.25 mg IV (1 x 0.25 mg palonosetron in 5ml + 2 x 5 ml placebo IV) + placebo oral	46
Treatment C-Palonosetron 0.75 mg IV	palonosetron 0.75 mg IV (1 x 0.75 mg palonosetron in 5 ml + 2 x 5 ml placebo IV) + placebo oral	46
Treatment D-Palonosetron 2.25 mg IV	palonosetron 2.25 mg IV (3 x 0.75 mg palonosetron in 5 ml) + placebo oral	46
Treatment E-Moxifloxacin 400 mg	placebo IV (3 x 5 ml) + moxifloxacin 400 mg oral (b) (4)	46

3.5.5.2 Sponsor's Justification for Doses

"The upper dose foreseen in the study is 2.25 mg which seems sufficiently high to cover the dose range requested by the guidelines. This dose is indeed 9 times higher than the recommended dose (0.25 mg) and approximately 3 times lower than the highest dose ever employed in humans. This dose, corresponding to 90 μg/kg, is equivalent to a fixed dose of approximately 6 mg and it has been administered to healthy subjects and cancer patients in early phase 1 and 2 dose-ranging studies (N=104)."

3.5.5.3 Instructions with regard to meals

The dosing of palonosetron relative to the timing of meals was not described.

3.5.5.4 Study Assessments

Table 2: Highlights of Schedule of Interventions

Study Day	**-1**	**1**
Intervention	No treatment	Single dose
12-Lead ECGs	Record ECGs[#] (Baseline)	Record ECGs[##]
PK Samples for drug	None collected	Collected[###]

15 min, 30 min, 1h, 2h, 4h, 6h, 8h, 10h, 12h, 14h, 16h
##Pre-dose and 15 min, 30 min, 1h, 2h, 4h, 6h, 8h, 10h, 12h, 14h, 16h, 24h, 26h, 30h, 36h, 40h and 48 hours post start of dosing.
###Pre-dose and 15 min, 30 min, 1h, 2h, 4h, 8h, 10h, 12h, 24h, 36h, and 48h post start of dosing.

3.5.5.5 Baseline

Time-matched baselines were used in the study.

3.5.6 ECG Collection

Twelve-lead ECGs were acquired in digital format and transmitted to a central ECG laboratory. Triplicate interval duration measurements were first obtained by trained analysts using the proprietary (b) (4) system applied on a computer

screen. A cardiologist then verified the interval durations and performed the morphology analysis being careful to note any T-U wave complex that suggested an abnormal form compatible with an effect on cardiac repolarization. Manual on-screen measurements of the RR, PR, QRS and QT interval durations were performed.

Readers were blinded to time, treatment and subject identifier. A single reader interpreted all the ECG recordings from a given subject. The degree of inter- and intra-reader variability should be established by having a subset of them reread.

3.5.7 Sponsor's Results

3.5.7.1 Study Subjects

239 healthy male and female subjects with normal baseline ECGs and BMIs were randomized (48 to placebo, 48 to palonosetron 0.25 mg, 48 to palonosetron 0.75 mg, 48 to palonosetron 2.25 mg, and 47 to moxifloxacin). Eighteen of the total 239 subjects enrolled did not receive any study treatment and were excluded from analysis. A total of 220 subjects (92.1 %) of the 239 randomized completed the study (41 were administered placebo, 44 palonosetron 0.25 mg, 46 palonosetron 0.75 mg, 46 palonosetron 2.25 mg, and 43 moxifloxacin). Nineteen subjects (7.9%) discontinued the study; including the 18 subjects who were not administered any study medication and one other who was treated with placebo and discontinued for personal reasons.

3.5.7.2 Statistical Analyses

3.5.7.2.1 Primary Analysis

Table 3 displays the results of the time-matched analysis, presented as upper one-sided 95% ANOVA model based confidence limit in milliseconds at each time point for values of the QTcI adjusted for both placebo and baseline (delta delta analysis) for the three palonosetron dose groups and moxifloxacin.

Table 3: Upper boundary of the one-sided 95% ANOVA model based confidence interval for the placebo and baseline corrected values (delta delta analysis) of QTcI

Time Point (hr)	Palonosetron 0.25 mg	Palonosetron 0.75 mg	Palonosetron 2.25 mg	Moxifloxacin 400 mg
0.25	2.1	4.8	6.6	2.8
0.5	4.1	3.7	6.7	5.0
1	4.9	6.7	8.1	12.4
2	5.6	5.1	7.6	14.5
4	2.7	4.5	5.2	12.8
6	6.4	4.0	4.4	10.7
8	4.4	3.6	5.2	10.7
10	4.2	4.5	4.7	8.0
12	2.2	3.3	6.7	8.0
14	2.3	7.4	6.6	8.4
16	2.6	2.1	5.7	9.0
24	5.4	5.1	4.3	9.8
26	4.0	6.0	5.8	5.7
30	5.7	5.6	6.9	7.8
36	1.8	3.4	3.1	3.5
40	4.0	4.3	6.2	7.2
48	3.3	3.5	3.6	5.2

(Source: Final report study Palo-03-11 / SPC 343-3 Table 11.4-1)

3.5.7.2.2 Categorical Analysis

A categorical analysis was done to identify the percentage of subjects that exhibit a change in QTcI from baseline of 30-60 or > 60 ms and a new absolute QTcI > 500 ms or > 480 ms or > 450 ms in the palonosetron dose groups compared to placebo.

The following Table 4 summarizes the mean change from baseline (average analysis) and the new outliers from baseline for Day 1 for the different Palonosetron dose groups, the Moxifloxacin group and the Placebo group. Only one outlier for QTcI was found in the palonosetron dose groups. This subject, from the 2.25 mg palonosetron dose group, had a 30-60 ms change from baseline.

Table 4: Mean change from baseline and new outliers from baseline to Day 1

	Placebo	Palonosetron 0.25 mg	Palonosetron 0.75 mg	Palonosetron 2.25 mg	Moxifloxacin
Evaluable subjects	42	44	46	46	43
Heart Rate in bpm					
Change in mean value Day -1 to Day 1*	0.9	-0.7	-0.6	-0.8	0.1
Heart Rate tachycardic outliers N	0	0	0	0	0
Heart Rate bradycardic outliers N	0	0	0	0	0
PR in msec					
Change in mean value Day -1 to Day 1*	0.5	-1.5	-2.2	-1.6	-1.5
PR outliers N	0	0	0	0	0
QRS in msec					
Change in mean value Day -1 to Day 1*	0.0	0.1	0.4	0.0	-0.1
QRS outliers N	0	0	0	0	0
QT in msec					
Change in mean value Day -1 to Day 1*	-5.8	-2.6	-2.4	-0.2	1.6
QT new >500 msec N	0	0	0	0	0
QT new>480 msec N	0	0	0	0	0
QT new>450 msec N	0	0	0	2	1

(Source: Final report study Palo-03-11 / SPC 343-3 Table 11.4-2)

Table 5: Mean change from baseline and new outliers from baseline to Day 1

	Placebo	Palonosetron 0.25 mg	Palonosetron 0.75 mg	Palonosetron 2.25 mg	Moxifloxacin
Evaluable subjects	42	44	46	46	43
QTcI in msec					
Change in mean value Day -1 to Day 1*	-4.1	-3.6	-2.9	-1.5	1.8
Change in maximum value Day -1 to Day 1*	6.1	6.4	7.5	9.0	12.9
QTcI new >500 msec N	0	0	0	0	0
QTcI new >480 msec N	0	0	0	0	0
QTcI new >450 msec N	0	0	0	0	0
QTcI 30-60 msec inc N (%)	0	0	0	1	0
QTcI >60 msec inc N	0	0	0	0	0
QTcF in msec					
Change in mean value Day -1 to Day 1*	-4.0	-4.3	-3.6	-2.0	2.0
QTcF new >500 msec N	0	0	0	0	0
QTcF new >480 msec N	0	0	0	0	0
QTcF new >450 msec N	0	0	0	0	0
QTcF 30-60 msec inc N	0	0	0	0	0
QTcF >60 msec inc N	0	0	0	0	0
QTcB in msec					
Change in mean value Day -1 to Day 1*	-3.0	-5.1	-4.2	-2.8	2.1
QTcB new >500 msec N	0	0	0	0	0
QTcB new >480 msec N	0	0	0	0	0
QTcB new >450 msec N	0	0	0	0	3
QTcB 30-60 msec inc N (%)	0	1	0	1	1
QTcB >60 msec inc N	0	0	0	0	0
Morphology					
New abnormal U waves N	0	0	0	0	0
New ST segment elevation changes N	0	0	0	0	0
New ST segment depression changes N	0	0	0	0	0
New T wave inverted N	0	0	0	0	0
New Second & Third Degree Heart Block, Complete RBBB & LBBB, MI N	0	0	0	0	0

Source: Section 14.2, Tables 1 to 16.
N= number of subjects
* negative values mean that predose value is higher than post dose value
bpm =beats per minute; msec=milliseconds; QTcI: Individual Correction; QTcB: Bazett correction; QTcF= Fridericia correction; RBBB=right bundle branch block; LBBB= left bundle branch block, MI= myocardial infarction pattern; "new" means not present at baseline and only seen post baseline.

(Source: Final report study Palo-03-11 / SPC 343-3 Table 11.4-2)

3.5.7.3 Safety Analysis

There were no deaths or SAEs observed. No subject withdrew while experiencing an AE. The frequency and intensity of AEs were about the same in all treatment groups. Only one cardiac AE, palpitations, was observed and it occurred in a subject receiving placebo.

3.5.7.4 Clinical Pharmacology

3.5.7.4.1 Pharmacokinetics

The sponsor did not derive PK parameters from the concentration-time data.

One subject (Subject 382) had extraordinarily high plasma concentrations, approximately 1000-fold higher than other subjects. Subject 382 receiving palonosetron at the dose 2.25 mg had a Cmax > 10^6 ng/mL at 15 minutes with plasma concentrations at 30 minutes (b) (4) 1 hour (b) (4) and 2 hours (b) (4) in this subject higher than the next highest Cmax in any subject (8 x 10^3 ng/mL). The analytical laboratory confirmed the accuracy of these results for these samples. A possible explanation based on feedback from the clinical study investigator is that blood samples for PK analysis were drawn from the same catheter used for palonosetron administration; it appears the catheter may not have been flushed after palonosetron injection. The QT data for subject 382 is presented in Table 6.

Table 6: ECG Data for Subject 382

Subject: 382 Treatment: Palonosetron 2.25 mg

(b) (4)

Reviewer's Comment: The reviewer computed mean concentration-time data for this study in section 4.2.

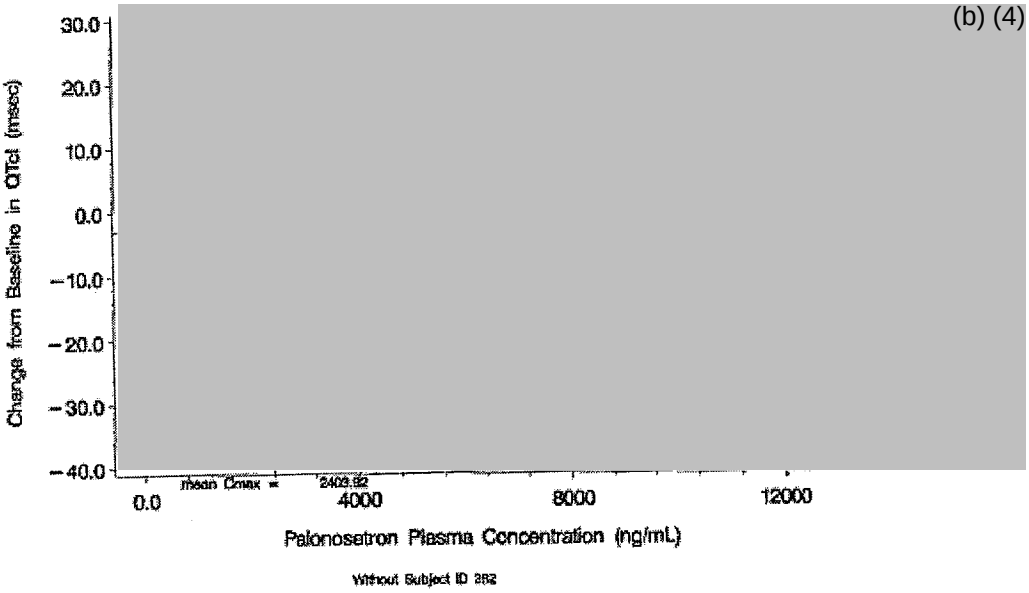
3.5.7.4.2 Exposure-Response Relationship

A linear mixed effects model was calculated as the ΔQT or ΔQTc versus the plasma concentration (as a fixed effect) with subject included in the model as a random effect. The model is: ΔQTc= α + ß*(plasma concentration) + y*(subject effect), where Δ is the change from baseline (calculated as time-match difference), α is the intercept, ß is the slope of the plasma concentration, and y is the subject random effects parameter.

If the p-value of the slope for plasma concentration (ß in the above model) is less than 0.05, then a linear effect of delta QTc would be declared. In addition, two calculations were performed: (1) a predicted Δ QTc (maximum mean effect or a "model predicted QTc effect") at the mean Cmax and (2) the one-sided upper 95% confidence bound of this model predicted QTc effect. The primary analysis used the QTcI parameter, but was repeated for QTcF, QTcB, and QT intervals.

The result of the linear mixed effects model is shown in Figure 1 for QTcI. Similar results were observed for QTcF.

Figure 1: Sponsor's Analysis: QTcI Change from Baseline versus Palonosetron Plasma Concentration



Cross-reference: Figure 1a, page 10 of Addendum 01 to CSR PALO-03-11

The sponsor concluded that no statistical or experimental evidence was found to demonstrate any potential relationship for corrected QT interval or QT intervals with plasma palonosetron concentrations after single dose administration of intravenous palonosetron including supratherapeutic doses up to 2.25 mg, 9-fold greater than the current marketed 0.25 mg intravenous dose.

Reviewer's Comments: The sponsor's exposure-response analysis is acceptable. We prefer, however, that the placebo response is also accounted for in the model. The reviewer did not re-analyze the concentration and QTc data because the primary statistical endpoint was negative and there was no concentration- ΔQTc relationship.

4 REVIEWERS' ASSESSMENT

4.1 STATISTICAL ASSESSMENTS

This was a parallel, double blind, placebo and positive (moxifloxacin) controlled study evaluating single doses in healthy male and female subjects to evaluate the electrocardiographic effects of three doses of Palonosetron (0.25, 0.75 and 2.25 mg IV).

The moxifloxacin group was used as a positive control to determine the assay sensitivity of this study.

The sponsor presented the QTcI change from baseline for the primary analysis using a mixed model that included classification variables for treatment, subject (random effect), gender, time point, treatment by time point interaction. We did similar calculations for QTcI as well as for QTcF and reached the similar results. We also conducted a GLM statistical model which included the baseline QTc as a covariate and reached the similar results. We confirmed that the upper limits of the two sided 90% CI for the QTcI intervals for the difference in least square means between the respective palonosetron (0.25, 0.75 and 2.25 mg IV) and placebo were all less than 10 ms. The differences in treatment least square means were less than 5 ms for all time points and for all Palonosetron groups. Results conducted for QTcF were consistent with those for QTcI.

Table 7: Analysis of Time-Matched and Baseline Adjusted QTcI (ms) by Time Point

Time Point (hr)	Least Square Means				95% Upper Limit		
	Placebo (n = 42)	Palonosetron 0.25 mg (n = 44)	Palonosetron 0.75 mg (n = 46)	Palonosetron 2.25 mg (n = 46)	Palonosetron 0.25 mg - Placebo	Palonosetron 0.75 mg - Placebo	Palonosetron 2.25 mg - Placebo
0.25	-3.1	-5.6	-2.4	-0.4	-0.6	2.6	4.5
0.5	-6.1	-6.9	-6.2	-3.7	1.1	1.8	4.3
1	-7.0	-7.1	-4.4	-3.0	2.0	4.7	6.1
2	-5.3	-5.1	-4.4	-2.0	2.3	2.9	5.3
4	-3.3	-5.7	-2.9	-2.0	-0.5	2.3	3.2
6	-2.0	-0.6	-2.0	-1.3	3.3	1.8	2.5
8	-2.6	-2.9	-3.2	-1.3	1.7	1.4	3.3
10	-2.0	-2.7	-1.7	-1.3	1.1	2.1	2.5
12	-2.0	-4.2	-2.5	1.0	-0.3	1.3	4.8
14	-2.5	-5.0	0.6	0.1	-0.6	5.1	4.5
16	-1.3	-3.1	-2.8	0.7	0.3	0.5	4.0
24	-3.2	-2.5	-1.9	-2.4	2.6	3.2	2.7
26	-14.0	-15.7	-12.3	-12.6	0.4	3.7	3.4
30	-3.6	-3.1	-2.1	-0.5	2.5	3.4	5.0
36	-3.3	-6.0	-3.8	-4.0	-0.9	1.3	1.1
40	-4.9	-5.5	-4.2	-2.5	1.5	2.8	4.5
48	-5.1	-6.2	-5.1	-4.7	0.9	2.1	2.4

In addition, assay sensitivity was demonstrated by the time-matched analysis showing at least one lower bound of the mean difference of moxifloxacin and placebo after baseline correction for QTcI exceeded 5 ms. It should be noted that a multiple endpoint adjustment was not performed here.

Table 8: Assay Sensitivity Analysis of Time-Matched and Baseline Adjusted QTcI (ms) by Time Point in Day 1

Time Point (hr)	Least Square Means		Treatment Diff. Moxifloxacin - Placebo	90% Confidence Intervals Moxifloxacin - Placebo	
	Placebo (n = 42)	Moxifloxacin (n = 43)		Lower Bound	Upper Bound
0.25	-3.4	-4.5	-1.1	-3.0	0.7
0.5	-6.3	-5.4	0.9	-1.2	2.9
1	-7.4	1.1	8.4	6.2	10.7
2	-5.9	4.7	10.7	8.6	12.7
4	-3.7	5.1	8.9	6.9	10.9
6	-2.3	4.7	7.0	5.2	8.8
8	-3.2	3.7	6.9	4.9	8.9
10	-2.6	1.8	4.4	2.5	6.3
12	-2.2	1.9	4.2	2.3	6.1
14	-3.1	1.5	4.7	2.7	6.6
16	-1.6	3.6	5.2	3.1	7.2
24	-3.4	2.4	5.8	3.6	8.0

For categorical analysis, we conducted the analysis on triplicate QT/QTc without averaging the replicates at each time points (see results in Table 9). We confirmed that no subject had an absolute QTcI interval above 450 ms post treatment. There were five subjects who had an increase from baseline between 30 and 60 ms in Palonosetron 2.25 mg group and only one in placebo and Palonosetron 0.75 mg group, respectively, but no subject had an increase in QTcI from baseline of more than 60 ms.

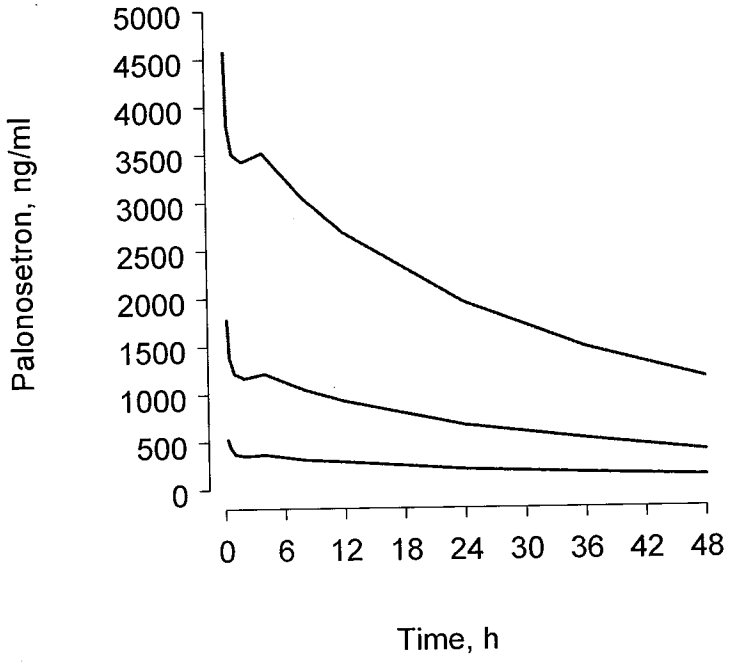
Table 9: Frequency for Delta QTc: 30~60 ms.

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Treatment A: Placebo	42	1	2.38	1512	1	0.07
Treatment B: Palonosetron 0.25 mg IV	44	0	0.00	1584	0	0.00
Treatment C: Palonosetron 0.75 mg IV	46	1	2.17	1656	1	0.06
Treatment D: Palonosetron 2.25 mg IV	46	5	10.87	1655	7	0.42
Treatment E: Moxifloxacin 400 mg	43	4	9.30	1548	8	0.52

4.2 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean palonosetron concentrations are shown in Figure 2 for the 0.25 mg, 0.75 mg and 2.5 mg dose groups. Mean concentrations obtained 15 minutes after IV dosing were 527 ng/ml, 1780 ng/ml and 4570 ng/ml for the respective dose groups.

Figure 2: Mean Concentration-Time Profiles for 0.25 mg (black), 0.75 mg (blue) and 2.25 mg (red) Dose Groups (Excludes Subject 382)



4.3 CLINICAL ASSESSMENTS

None of the adverse events identified as significant in the ICH E14 guidelines (i.e., sudden death, torsade de pointes, ventricular tachycardia, syncope, and seizures) were observed during the trial.

5 APPENDIX

5.1 TABLE OF STUDY ASSESSMENTS

EVALUATION	SCR	BASELINE		TREATMENT PERIOD																END STUDY
Hours before / after start of infusion		-36 to -24	-24 to -6 (a)	0	0.25	0.5	1	2	4	6	8	10	12	14, 16	24	28, 30	36	40	48 (c)	14 – 21 days after applications
Informed Consent	x																			
Demographics	x																			
12 lead single standard ECG	x																			x
Inclusion/Exclusion Criteria	x	x																		
Body weight	x	x																		x
Medical History	x																			
Physical Examination	x	x																		x
Vital signs (BP, PR, heart rate, body temperature)	x	x																	x	x
Prior/Concomitant Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology/Biochemistry/ Urine	x	x																		x
Serology (Hepatitis/HIV)	x																			
Drugs of Abuse	x	x																		
Alcohol breath test	x	x																		
Pregnancy test	x	x																		x
Randomization			x																	
Study drug administration				x																
Digital 12 lead ECG in triplicate			x	x (b)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Blood sampling for PK evaluations				x (b)	x	x	x	x	x		x		x		x		x		x	
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Comments	As required																			

SCR: screening
BP: blood pressure
PR: pulse rate
(a): *-23h45min, -23h30min, -23h, -22h, -20h, -18h, -16h, -14h, -12h, -10h, -8h
*(no ECG was performed at -24 h according to Amendment 01, dated 08-Jun-2005)
(b): Immediately before study drug administration (pre-dose)
(c): discharge from the clinical unit

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/s/

Stephen Grant
8/3/2007 06:38:57 PM
MEDICAL OFFICER

Joanne Zhang
8/6/2007 10:37:05 AM
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Kate L Dwyer
8/6/2007 10:39:12 AM
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Christine Garnett
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PHARMACOLOGIST

Norman Stockbridge
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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-372	Submission Date(s): April 27, 2007, Jan 14, 2008
Brand Name	Aloxi®
Generic Name	Palonosetron hydrochloride
Reviewer	PeiFan Bai, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Gastroenterology Products
Sponsor	Helsinn Healthcare
Submission Type; Code	Supplement 008, (b) (4) 010
Formulation; Strength(s)	0.075 mg/1.5 ml
Indication	Prevention of postoperative (b) (4) nausea and vomiting (PON (b) (4) for up (b) (4) (b) (4)

Table of Contents

1 Executive Summary

1.1 Recommendation

The application is acceptable from the clinical pharmacology perspective provided the labeling comments are adequately addressed by the sponsor.

1.2 Phase IV Commitments

None

1.3 Regulatory Background

Aloxi (palonosetron hydrochloride injectable) has been approved since July 25, 2003 for the prevention of chemotherapy-induced nausea and vomiting (CINV). The dose approved is 0.25 mg (free base). On April 27, 2007, Helsinn Healthcare submitted supplements 008, (b) (4) to seek the approval of intravenous palonosetron for two new indications of preventing postoperative (b) (4) nausea and vomiting (PONV (b) (4) up to (b) (4) and to add the safety data from a thorough QT/QTc study PALO-03-11 to label. For the newly submitted supplements and proposed indication, the dose is 0.075 mg (free base).

1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Product: Aloxi® for the proposed indications contains palonosetron hydrochloride (0.075 mg free base per 1.5 ml) for a single dose administration. Palonosetron is a selective 5-HT 3 receptor antagonist. The proposed new indications are prevention of postoperative (b) (4) nausea and vomiting (PONV (b) (4) up to (b) (4) (b) (4)

Pharmacokinetic characteristics: In the target population of women with abdominal and vaginal hysterectomy, the pharmacokinetic parameters of palonosetron were highly variable. The AUC_{0-24} values showed a trend of dose proportionality over the dose range of 0.3 μg/kg to 30 μg/kg. Overall, the pharmacokinetic characteristics of palonosetron in these patients were similar to those in cancer patients.

Exposure/response relationship: There is no clear exposure/response relationship. The anti-emetic effect seemed to reach a plateau at an intravenous dose of 1 μg/kg and at an oral dose of 1 μg/kg with no further increase in response at higher doses. The dose of intravenous 1 μg/kg is therefore chosen for the PONV (b) (4)

Drug-drug interactions: According to the approved label, "*In vitro* metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive CYP2D6 metabolizers." Though CYP2D6 is the primary enzyme involved in palonosetron metabolism, the sponsor did not study drug interaction with a 2D6 inhibitor such as paroxetine, quinidine, fluoxetine. In light of the fact that there was no difference in the pharmacokinetics of palonosetron between CYP2D6 extensive and poor metabolizers, it is considered acceptable that the sponsor did not conduct DDI studies concerning CYP2D6.

The sponsor submitted two drug interaction studies in S008 (b) (4) S010, as summarized below.

1. Palonosetron and dexamethasone: Both palonoseteron and dexamethasone are metabolized at least in part via the Cytochrome P450 3A4 isozyme. There was no pharmacokinetic interaction between palonosetron (intravenous 0.25 mg) and dexamethasone (intravenous 20 mg).

2. Palonosetron and aprepitant: Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4, and is primarily metabolized by CYP 3A4. Palonosetron was not an enzyme inducer or inhibitor at clinically relevant doses.

Aprepitant (three-day oral regimen of 120mg/80mg/80mg) did not affect the AUC0-∞ of palonosetron (0.25 mg, IV bolus) but did increase its Cmax by 15% with the 90% CI of bioequivalence comparison being 61.8%-157%, which is outside the bioequivalence acceptance criteria of 80% to 125%. Based on the Cmax observed in Study 2500 at the dose of 30 μg and the supratherapeutic dose of 2.5 mg ever studied clinically, there is no safety concern over the 15% increase in the Cmax of palonosetron by aprepitant (the reviewer also consulted the clinical team of Drs. Nancy Snow and Hugo E Gallo Torres for this conclusion).

QT/QTc study

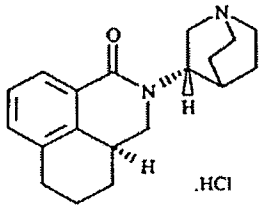
The thorough QT/QTc study (PALO-03-11) was adequately conducted with the supratherapeutic dose of 2.25 mg palonosetron and a group of 221 healthy subjects. The QT-IRT team concluded that there was no significant effect of palonosetron administration on the QT interval.

2 Question Based Review

2.1 General Attributes

2.1.1 What is the drug substance of Aloxi?

The active ingredient of Aloxi is palonosetron, which is a selective 5-HT 3 receptor antagonist.



Chemically, palonosetron hydrochloride is [3aS-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo1H-benz[*de*]isoquinoline hydrochloride].

2.1.2 What is the proposed indication of Aloxi?

The intravenous formulation of Aloxi has been approved for the indication of CINV. The active ingredient of Aloxi is palonosetron, which is a selective 5-HT 3 receptor antagonist. For the supplements submitted in this submission, the indications proposed are the prevention of PONV (b) (4) up to (b) (4)

2.1.3 What is the proposed mechanism of Aloxi?

Palonosetron is a 5-HT_3 receptor antagonist. 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex.

2.1.4 What are the proposed dosage and route of administration?

The proposed dose for PONV (b) (4) is 0.075 mg/1.5 ml for a single intravenous use.

2.1.5 What are the pharmacokinetic characteristics of palonosetron observed in the pharmacokinetic study submitted to this supplement submission?

Since Study 2500 had a larger number of subjects than study 2502 and used intravenous administration, its pharmacokinetic data are used here to illustrate the pharmacokinetic characteristics of palonosetron for the new proposed indications in the target population.

The following data are summarized from the results of Study 2500

PK parameter	0.1 µg/kg (n=4)	0.3 µg/kg (n=7)	1 µg/kg (n=5)	3 µg/kg (n=6)	30 µg/kg (n=7)
Cmax (ng/mL)	0.923(0.878)	4.28 (9.06)	1.87 (1.03)	7.89 (10.8)	29.6 (24.3)
T1/2 (hr)	38 (13.7)	91.7 (38.7)	110 (108)	51.9 (8)	53.7 (15.9)
AUC_{0-24} (ng * hr/mL)	0.9 (1.05)	6.57 (15)	3.31 (0.52)	7.64 (1.77)	80.4 (34.1)
AUC0-∞ (ng * hr/mL)	5.23 (0.38)	23.6 (38.9)	21.3 (14.8)	28.4 (6.54)	302 (141)
CL (ml/min/kg)	0.32 (0.023)	0.659 (0.34)	1.07 (0.64)	1.83 (0.38)	2.14 (1.41)
Vdß	1.07 (0.46)	5.96 (3.33)	6.68 (1.68)	8.2 (2.19)	10 (7.67)

Note: values are mean (SD)

The above data showed no dose proportionality for the AUC_{0-24} and Cmax of palonosetron, which is different from what is described in the approved label for the indication of CINV. It is stated in the approved label that "Mean maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC 0–inf) are generally dose-proportional over the dose range of 0.3–90 µg/kg in healthy subjects and in cancer patients." Since the half-life of palonosetron was more than 40 hrs and blood sampling for study 2500 was not performed long enough, the extrapolated AUC0-∞

values are unreliable. The clearance of palonosetron determined in this study changed with dose, which differs from the statement in the approved label. In the approved label, it is stated that "In healthy subjects the total body clearance of palonosetron was 160 ± 35 mL/h/kg (2.66 ml/min/kg) and renal clearance was 66.5± 18.2 mL/h/kg." and that "Palonosetron has a volume of distribution of approximately 8.3 ± 2.5 L/kg, and Mean terminal elimination half-life is approximately 40 hours". Vdß was not a constant either but increased with dose, though not dose proportionally. The half-life ranged from 38hr to 110hr with no trend of increasing with dose.

Through the Dec-28-07 letter, the Agency requested that the sponsor offer explanations for the above-mentioned inconsistency and submit a detailed analytical report for study 2500. In its Jan-14-08 amendment, the sponsor compared the pharmacokinetic results of study 2500 (PONV patients), study 2902 (healthy subjects), and study 2330 (CINV patients), and suggested there was dose proportionality for both Cmax and AUC_{0-24} if omitting the outlier, patient 1231) from the 0.3 µg/kg dose group, and the whole 0.1 µg/kg dose group (N=4) of study 2500. Omission of the 0.1 µg/kg dose group was based on the fact that plasma concentrations of palonosetron in two subjects were lower than the low detection limit of analytical methods, and that the remaining two subjects could not provide statistically meaningful data. In light of the analytical limitation, the sponsor's explanation is accepted. The recalculated AUC_{0-24} values do show a trend of dose proportionality, as shown below. Nonetheless, the recalculated Cmax values do not show dose proportionality due to the data from the 30 µg/kg dose.

Results of study 2500 with the 0.1 µg/kg group and patient 1231 from the 0.3 µg/kg group omitted

PK parameter	0.3 µg/kg (n=5)	1 µg/kg (n=5)	3 µg/kg (n=6)	30 µg/kg (n=7)
Cmax (ng/mL)	0.86 (0.54)	1.87 (1.03)	7.89 (10.8)	29.6 (24.3)
AUC_{0-24} (ng * hr/mL)	0.9 (0.17)	3.31 (0.52)	7.64 (1.77)	80.4 (34.1)
AUC0-∞ (ng * hr/mL)	6.21 (0.55)	21.3 (14.8)	28.4 (6.54)	302 (141)

Note: values are mean (SD)

2. 1.6 How is palonosetron metabolized and eliminated?

In humans, palonosetron is eliminated renally and hepatically with approximately 50% metabolized to form two primary metabolites (N-oxide-palonosetron (M9) and 6-S-hydroxy-palonosetron (M4). With negligible pharmacological activities, metabolites M9 and M4 represent approximately 13% and 11% of the intravenous palonosetron dose in urine, respectively. In vitro incubations with individual cytochrome P450 enzymes showed that CYP2D6 was the major enzyme involved in the metabolism of palonosetron, followed by CYP3A4 and CYPI A2. Palonosetron was shown to be a competitive inhibitor of these three isozymes . Nonetheless, palonosetron would have no inhibitory potential for these isozymes at the clinically relevant concentrations, in light of its inhibition constants (K_i). Induction experiments with fresh human hepatocytes demonstrated that palonosetron did not induce cytochrome P450 isozymes at clinically relevant concentrations. The above information is adopted from the approved label and the sponsor's submitted material.

2.1.6 What are the outcomes of drug interaction studies?

Drug interaction between palonosetron and dexamethasone:

The drug interaction study between palonosetron and dexamethasone showed that there was no interaction between these two drugs. The pharmacokinetic parameters of palonosetron (0.25 mg, iv) with and without dexamethasone (20 mg, iv) were bioequivalent, with the 90% CI for AUC0-t and Cmax being 85.8%-104% and 92.3%-113%, respectively. The pharmacokinetic parameters of dexamethasone (20 mg, iv) with and without palonosetron (0.25 mg, iv) were bioequivalent, with the 90% CI for AUC0-∞ and Cmax being 91.9%-105% and 102%-111%, respectively.

Mean (SD) pharmacokinetic parameters are tabulated below.

Treatments	Cmax (ng/L)	Tmax (hr)	AUC_{0-T} (ng * hr/L)	AUC0-∞ (ng * hr/L)	T1/2 (hr)
Palonosetron					
b1	463.9(93.64)	1.33 (2.13)	14473.86(4549.48)	19596 (9965.85)	42.42 (28.35)
b2	483.1(129.55)	1.30 (1.99)	13555.34(3605.06)	18241.17(5861.27)	43.8 (17.03)
M9					
b1	44.02 (17.12)	3.83 (1.88)	1218.02 (744.56)	2421.61(1224.61)	45.95 (23.46)
b2	37.87 (10.66)	18.06(51.31)	1296.51 (680.05)	2950.87(1254.07)	78.27 (75.06)
Dexamethasone					
b2	430.12(101.73)	0.25 (0)	1400.46 (347.18)	1424.26 (358.55)	3.99 (0.64)
b3	402.81(83.98)	0.25 (0.01)	1420.03 (305.1)	1441.95 (313.98)	3.98 (0.49)

b1: iv palonosetron 0.25 mg; b2: iv palonosetron 0.25 mg, then iv dexamethoasone 20mg; b3:iv dexamethasone 20 mg

ANOVA and 90% confidence intervals for log-transformed pharmacokinetic characteristics of palonosetron, M9, and dexamethasone

Analyte/Measure	Point estimate $100*b_2/b_1$ (for palonosetron) $100* b_2/b_3$ (for dexamethasone) [%]	90% confidence interval [%]
Palonosetron		
AUC_{0-t}	94.6	[85.8 ; 104.]
C_{max}	102	[92.3 ; 113]
Dexamethasone		
$AUC_{0-\infty}$	98.1	[91.9 ; 105]
C_{max}	107.	[102 ; 111]

b_1: i.v. palonosetron 0.25 mg administration only (Reference 1)
b_2: i.v. palonosetron 0.25 mg administration, then i.v. dexamethasone 20 mg administration (Test)
b_3: i.v. dexamethasone 20 mg administration only (Reference 2)

Summary: Based on the bioequivalence acceptance range, it is concluded there is no significant interaction between these two drugs.

Drug interaction between between palonosetron and aprepitant:

The drug interaction study of palonosetron and aprepitant was conduced in healthy subjects. A single dose of Palonosetron (0.25 mg, iv) was administered with and without a single 125 mg oral dose of aprepitant (EMEND®, 125 mg, oral) 30 minutes before palonosetron plus a single 80 mg oral dose of EMEND® on Days 2 and 3.

Mean (SD) pharmacokinetic parameters are tabulated below.

Cmax (ng/L)	Tmax (hr)	AUC_{0-T} (ng * hr/L)	AUC0-∞ (ng * hr/L)	T1/2 (hr)	CLp (ml/min)
A: Palonosetron alone					
2060 (1260)	0.55 (1.72)	30700 (10700)	34800 (11500)	43 (13.7)	136 (58.5)
B: Palonosetron with EMEND (aprepitant)					
2360 (2440)	1.06 (3.45)	30500 (8660)	34300 (9240)	40 (11)	130 (36.5)
90% CI					
61.8%-1.57%*	-	-	85.6%-119%*	-	-

Note: N=12; *: 90% CI (ratio of natural log-transformed for treatment B to treatment A; the Vdss (l): 442.3 (157.5) for palonosetron alone and 410.9 (95.1) for palonosetron with EMEND®.

Summary: The pharmacokinetic parameters of palonosetron (0.25 mg, iv) with or without a single 125 mg oral dose of aprepitant (EMEND®, 125 mg, oral) 30 minutes before palonosetron plus a single 80 mg oral dose of EMEND® on Days 2 and 3 were not

bioequivalent to each other with the 90 CI% for AUC0-∞ and Cmax being 85.6%-119% and 61.8%-157%, respectively. The drug interaction study between palonosetron and aprepitant showed that aprepitant did not influence the AUC0-∞ or AUC_{0-T} of palonosetron, but increased its Cmax by 15% with the 90% CI being 61.8%-157%. The adverse events observed in both treatments were similar. There was no significant effect of aprepitant on the pharmacokinetics of palonosetron. The reviewer consulted Drs. Nancy Snow and Hugo Gallo-Torres, and reached the conclusion that there would be no particular safety concern over the slight increase of Cmax by aprepitant.

Though CYP2D6 is the primary enzyme involved in palonosetron metabolism, the sponsor did not study drug interaction with a 2D6 inhibitor such as paroxetine, quinidine, fluoxetine. In light of the fact that there was no difference in the pharmacokinetics of palonosetron between CYP2D6 extensive and poor metabolizers, it is considered acceptable that the sponsor did not conduct DDI studies concerning CYP2D6.

2.1.7 What are the design features of the clinical pharmacology and clinical studies used to support claims?

For the interaction study between palonosetron and dexamethasone, the study was a phase I, open label, single-dose, single centre, randomized, three-way crossover study using healthy males and females. The wash-out period of 21 days was adequate to avoid a carry-over effect. The interaction study between palonosetron and aprepitant was a phase 1, open-label, randomized crossover study in healthy subjects. The washout period of 14 days was adequate.

For the clinical study 2500 in which the efficacy of intravenous palonosetron for PONV and PDNV was studied, the study design was a randomized, double-blind, multicenter, placebo-controlled study of parallel design. A single IV dose of palonosetron or placebo was administered at skin closure. The 24-hour postoperative observation period began at recovery, which was defined as the time when the patient became responsive to vocal commands in the post anesthesia care unit.

For the clinical study 2502 in which the efficacy of oral palonosetron in the treatment of PONV and PDNV was studied, the study design was a randomized, double-blind, multicenter, placebo-controlled dose-ranging efficacy, safety, and pharmacokinetic study of five doses of oral palonosetron. This study investigated the effect of oral palonosetron compared to placebo in the prevention of postoperative nausea and vomiting following laparoscopic procedures. This study used oral administration and the results were not used in the label of injectable palonosetron for PONV and PDNV.

The study designs of these studies are acceptable.

2.1.8 What are the characteristics of the dose-response and exposure-response relationship for efficacy?

In terms of clinical evaluations of complete response (CR), complete control (CG), and no emetic episodes (EE) for the six dose groups, the response reached a plateau at an intravenous dose of 1 μg/kg with no further increase in response at higher doses. It is

concluded that there is no clear linear exposure/response relationship. The intravenous dose of 1 µg/kg was chosen for the indication of PONV because no further increase in efficacy was observed at higher doses and this dose was well tolerated.

2.2 General Biopharmaceutics

2.2.1 Is the to-be-marketed formulation identical to the one used for the phase 3 efficacy trial?

The proposed NDA/commercial and Phase 3 clinical formulations are the same aqueous solution with the same components and compositions for an intravenous bolus administration over 10 seconds.

2.2.2 What is the formulation?

Ingredient	Formulations Used in Clinical Studies Conducted by			Commercial Formulation[c]
	Syntex		Helsinn	Helsinn
	Phase 1 (mg/ml)	Phase 2 (mg/ml)	Phase 1[a] Phase 3[b] (mg/ml)	Commercial (mg/ml)
Palonosetron HCl (calculated as Palonosetron free base)				(b) (4)
Mannitol, USP/EP				
Edetate disodium dihydrate, USP/EP				
Citric acid monohydrate, USP/EP				
Water for injection, USP/EP q.s. to				
Vial fill volume and vial size[c]				

[a] 5 ml vials containing 0.75 mg (0.15 mg/ml).
[b] 5 ml vials containing 0.25 mg (0.05 mg/ml) or 0.75 mg (0.15 mg/ml). 0.15 mg/mL used in CINV Phase 3 trials, not in PONV Phase 3 trials
[c] 5 ml vials containing 0.25 mg (0.05 mg/ml).
Source: NDA 21-377 Chemistry and Manufacturing and Controls, Section 4

(b) (4)

2.3 Analytical Section

2.3.1 What bioanalytical methods were used to assess concentrations?

Study PALO 03-05: the concentrations of palonosetron and its metabolite M9 were analyzed using a validated LC/MS/MS method. The palonosetron calibration standards used for validation ranged from (b) (4) ng/L to (b) (4) ng/L with the precision and accuracy ranging from 5.05% to 7.28% and 0.22 to -3.34%, respectively. The LLOQ was (b) (4) ng/L. The M9 calibration standards used for validation ranged from (b) ng/L to (b) (4) ng/L with the precision and accuracy ranging from 8.0% to 12.41% and -1.98 to 14.19%, respectively. The firm did not provide the regression coefficients for the standard curves of palonosetron and its metabolite M9. The regression coefficients calculated by the reviewer for both palonosetron and its metabolite M9 are 0.9999.

Study PALO 03-10: The concentrations of palonosetron, its metabolite M9, and dexamethasone were determined using validated LC/MS/MS methods. The concentrations of the calibration standards of palonosetron ranged from (b) (4) g/L to (b) (4) ng/L, with the precision and accuracy values ranging from 16.73% to 5.43% and from -1.83% to 4.2%, respectively. The palonosetron quality control was conducted over a concentration range of (b) (4) to (b) (4) ng/L, and the precision and accuracy values ranged from 8.5% to 17.04% and -1.33% to 5.24%, respectively. For quality control, the precision values were 17.04% and 15.44% for 96.77ng/L and 1608.83 ng/L, respectively

The concentrations of M9 calibration standards ranged from (b) (4) with the precision and accuracy values ranged from 6.49%% to 13.07% and from -3.56% to 2.59%, respectively. The M9 quality control was conducted over a concentration range of (b) (4) ng/L to (b) (4) ng/L with the precision and accuracy values ranging from 10.39% to 21.69% and from -4.74% to -10.23%, respectively. The quality control for dexamethasone was conducted over a range of (b) µg/L to (b) (4) g/L, with the precision and accuracy values ranging from 2.94% to 7.88% and -4.7% to 4.14%.

No analytical report for study 2500 was submitted in the April-27-07 submission. The sponsor provided a detailed analytical report in its Jan-14-08 amendment. The QC control concentrations for palonosetron was (b) (4) ng/ml, and the corresponding CV% and % recovery were 8.9% and 110%, 6% and 110%, and 8.7% and 98%, respectively. The QC concentrations for RS-17825 (its metabolite M9) was (b) (4) ng/ml, and the corresponding CV% and % recovery were 10.7% and 97%, 5.5% and 107%, and 8.0% and 103%, respectively. The QC results are acceptable.

2.6.2 Are the analytical assay methods adequately validated?

In general the analytical assay methods are acceptable.

Study PALO 03-10: For calibration, the 16.73% precision value for (b) (4) ng/L of palonosetron is less satisfactory. For quality control, the precision values at (b) (4) ng/L and (b) (4) ng/L were greater than 15% and are deemed less satisfactory. Furthermore, the analytical report did not include the regression analyses of palonosetron and M9 calibration standards.

Study 2500 (Jan-14-08 amendment): The QC control concentrations for palonosetron was (b) (4) ng/ml, and the corresponding CV% and % recovery were 8.9% and 110%, 6% and 110%, and 8.7% and 98%, respectively. The QC concentrations for RS-17825 (its metabolite M9) was (b) (4) ng/ml, and the corresponding CV% and % recovery were 10.7% and 97%, 5.5% and 107%, and 8.0% and 103%, respectively. The QC results are acceptable.

3 Detailed Labeling Recommendations

(The firm's proposed labeling has been incorporated below)

Section 7 Drug interaction

(b) (4)

This statement should be changed to "Coadministration of 0.25 mg IV palonosetron and 20 mg IV dexamethasone in healthy subjects revealed no pharmacokinetic drug-interactions between palonosetron and dexamethasone."

(b) (4)

This statement should be changed to "In an interaction study in healthy subjects, palonosetron 0.25 mg (IV bolus) was administered on day 1 and oral aprepitant for 3 days (120 mg/80 mg/80mg), the pharmacokinetics of palonosetron was not significantly altered (AUC: no change, Cmax: 15% increase) (b) (4)

Section 12.3 Pharmacokinetics

In the firm's proposed label, it is stated that (b) (4)

(b) (4)

(b) (4)

This statement should be revised to "After intravenous dosing of palonosetron in patients undergoing abdominal and vaginal hysterectomy, the phamacokinetic characteristics of palonosetron were similar to those observed in cancer patients"

8 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 21-372
SDOB/SOD

4.2 Individual Study Reviews

Please see appendix 4.2.1

4.3 Cover sheet and OCP Filing/Review Form

4.4 Attendees at my briefing which took place

4.5 Appendix 1 Individual study reviews

Review of Study 2500

Title: A dose ranging safety and efficacy comparision of four dose levels of intravenous RS-25259 to placebo in the prevention of postoperative nausea and vomiting following abdominal and viginal hysterectomy.

Objectives:

1. Assess the antiemetic dose-response effectiveness of four dose levels of IV palonosetron in the prevention of nausea and vomiting following abdominal and vaginal hysterectomy. The proportion of complete responders in each palonosetron dose group was compared with the placebo control group. A complete responder was defined as a patient with no emetic episodes and no rescue antiemetic therapy for 24 hours after recovery from anesthesia.

2. Assess the relative safety of single IV doses of palonosetron as compared with placebo based upon standard safety measurements.

3. Determine the pharmacokinetics of single IV doses of palonosetron for each treatment group.

This was a randomized, double-blind, multicenter, placebo-controlled study of parallel design. A single IV dose of palonosetron or placebo was administered at skin closure. The 24-hour postoperative observation period began at recovery, which was defined as the time when the patient became responsive to vocal commands in the post anesthesia care unit. A study nurse/coordinator monitored patients for nausea and vomiting for at least the first 2 hours. Subsequently, patients or nurses completed the nausea and vomiting questionnaire at regular intervals until 24 hours post recovery.

The study population consisted of 381 women between the ages of 24 and 80 who were scheduled for abdominal or vaginal hysterectomy requiring balanced general anesthesia, including N20 plus an opiate.

The primary efficacy variable was the proportion of complete responders, that is, the proportion of patients who did not experience a single emetic episode and did not receive rescue medication during the 24-hour postoperative observation period. Secondary efficacy variables included the time to the first emetic episode, nausea ratings on the verbal categorical and visual analog scales, the proportion of patients who did not experience an emetic episode during the first 4 hours post surgery, the proportion of patients requiring rescue antiemetic therapy during the 24-hour postoperative period, and time to rescue.

Formulation studied: Palonosetron was provided as 500 μg/ml in 5-ml vials. The formulation number was F25259-006.

Inclusion and exclusion criteria: acceptable.

Efficacy Results

Summary of Patients' Responses for 24 Hours After Recovery (Evaluable Patients)						
	Placebo (n = 62)	0.1 µg/kg (n = 47)	0.3 µg/kg (n = 67)	1 µg/kg (n = 62)	3 µg/kg (n = 67)	30 µg/kg (n = 67)
% with CR	19%	34%	34%	44%	30%	45%
p-value[a]	--	--	0.051	0.004	0.174	0.002
% with CC	19%	34%	33%	44%	30%	45%
p-value[a]	--	--	0.075	0.004	0.174	0.002
% no EE	47%	55%	60%	73%	61%	76%
p-value[a]	--	--	0.137	0.003	0.101	< 0.001

[a] p-value for treatment effect versus placebo

Note: CR: complete response (no emetic episode and without rescue antiemetic therapy); CC: complete control (complete response and only mild nausea or no nausea); EE: no emetic episodes.

The sponsor concluded that "palonosetron reaches a plateau with respect to clinical response at a dose of 1 µg/kg. At this dose, it was significantly more effective than placebo with respect to the control of both nausea and vomiting following abdominal and vaginal hysterectomy and was well tolerate." The sponsor indicated that the long half-life of palonosetron (38-110 hr) support single-dose administration for postoperative nausea and vomiting.

Reviewer's comments: For complete response, there was no further increase in efficacy as the dose increased from 0.1 µg/kg to 30 µg/kg; likewise for complete control. As for no emetic episodes, there was no further increase in efficacy as the dose increased from 0.3 µg/kg to 30 µg/kg but there was a slight increase in efficacy when the dose increased from 0.1 µg/kg to 0.3 µg/kg.

Pharmacokinetic results

A total of 35 patients participated in the pharmacokinetic portion of this study. All were dosed at the same investigational site. Six of these patients were given placebo and therefore had no pharmacokinetic data to be presented. Of the 29 patients in the pharmacokinetic study who were given active drug, 4, 7, 5, 6, and 7 patients were dosed at the 0.1-,0.3-,1-,3-, and 30-µg/kg dose levels, respectively.

Summary of Mean RS-25259 Pharmacokinetic Parameters						
RS-25259 Parameter	Mean (± SD)					
	Placebo (n=6)	0.1 µg/kg (n=4)	0.3 µg/kg (n=7)	1 µg/kg (n=5)	3 µg/kg (n=6)	30 µg/kg (n=7)
C_{max} (ng/mL)	--	0.923 (0.878)	4.28 (9.06)	1.87 (1.03)	7.89 (10.8)	29.6 (24.3)
T_{max} (hr)for all five dose levels	--	0.113 (0.149)	0.0452 (0.0550)	0.0333 (0.0204)	0.0306 (0.0267)	0.0190 (0.0063)
$t_{½}$ (hr)	--	38.0 (13.7)	91.7 (38.7)	110 (108)	51.9 (8.00)	53.7 (15.9)
AUC_{0-24} (hr) (ng·hr/mL)	--	0.900 (1.05)	6.57 (15.0)	3.31 (0.524)	7.64 (1.77)	80.4 (34.1)
Total AUC (ng·hr/mL)	--	5.23 (0.378)	23.6 (38.9)	21.3 (14.8)	28.4 (6.54)	302 (141)
Cl (mL/min/kg)	--	0.320 (0.0232)	0.659 (0.344)	1.07 (0.638)	1.83 (0.378)	2.14 (1.41)
$V_{dβ}$ (L/kg)	--	1.07 (0.456)	5.96 (3.33)	6.68 (1.68)	8.20 (2.19)	10.0 (7.67)

Summary of Mean RS-17825 Pharmacokinetic Parameters						
RS-17825 Parameter	Mean (±SD)					
	Placebo (n=6)	0.1 µg/kg (n=4)	0.3 µg/kg (n=7)	1 µg/kg (n=5)	3 µg/kg (n=6)	30 µg/kg (n=7)
C_{max} (ng/mL)	--	0.0665[a] (--)	0.0625[a] (--)	0.00[b] (--)	0.00[b] (--)	0.179 (0.0728)
T_{max} (hr)	--	168[a] (--)	1.93[a] (--)	NC	NC	9.93 (16.6)
Apparent $t_{½}$ (hr)	--	NC	NC	NC	NC	25.1 (9.38)
AUC_{0-24} (hr) (ng·hr/mL)	--	NC	0.565[a] (--)	NC	NC	2.54 (1.28)
AUC_{tot} (ng·hr/mL)	--	NC	NC	NC	NC	6.34 (0.750)
AUC Ratio (RS-17825/ RS-25259)	--	NC	NC	NC	NC	0.0191 (0.0052)

[a] Calculable for only 1 patient

[b] All plasma concentrations were BQL at this dose level

NC = Not calculable because of BQL values

Reviewer's comments: The data shown above do not demonstrate a linear dose proportionality for the AUC and Cmax of palonosetron, which is different from what is described in the approved label for the indication of CINV. It is stated in the approved label that "Mean maximum plasma concentration (C max) and area under the concentration-time curve (AUC 0–inf) are generally dose-proportional over the dose range of 0.3–90 μg/kg in healthy subjects and in cancer patients." The inconsistent results may be due to the poor quality of pharmacokinetic study in Study 2500.

Through the Dec-28-07 letter, the Agency requested that the sponsor offer explanations for the above-mentioned inconsistency and submit a detailed analytical report for study 2500. In its Jan-14-08 amendment, the sponsor compared the pharmacokinetic results of study 2500 (PONV patients), study 2902 (healthy subjects), and study 2330 (CINV patients), and suggested there was dose proportionality for both Cmax and AUC_{0-24} if omitting the outlier, patient 1231) from the 0.3 μg/kg dose group, and the whole 0.1 μg/kg dose group (N=4) of study 2500. Omission of the 0.1 μg/kg dose group was based on the fact that plasma concentrations of palonosetron in two subjects were lower than the low detection limit of analytical methods, and that the remaining two subjects could not provide statistically meaningful data. In light of the analytical limitation, the sponsor's explanation is accepted. The recalculated AUC_{0-24} values do show a trend of dose proportionality, as shown below. Nonetheless, the recalculated Cmax values do not show dose proportionality due to the data from the 30 μg/kg dose.

Results of study 2500 with the 0.1 μg/kg group and patient 1231 from the 0.3 μg/kg group omitted

PK parameter	0.3 μg/kg (n=5)	1 μg/kg (n=5)	3 μg/kg (n=6)	30 μg/kg (n=7)
Cmax (ng/mL)	0.86 (0.54)	1.87 (1.03)	7.89 (10.8)	29.6 (24.3)
AUC_{0-24} (ng * hr/mL)	0.9 (0.17)	3.31 (0.52)	7.64 (1.77)	80.4 (34.1)
$AUC0-\infty$ (ng * hr/mL)	6.21 (0.55)	21.3 (14.8)	28.4 (6.54)	302 (141)

Note: values are mean (SD)

Review of Study 2502

Title of Study: A Dose-Ranging Safety and Efficacy Comparison of Four Dose Levels of Oral RS. 25259 to Placebo in the Prevention of Postoperative Nausea and Vomiting Following Laparoscopic Procedures. This study was completed in 1995.

Objectives:

1. Assess the antiemetic dose-response effectiveness of four dose levels of oral palonosetron in the prevention of nausea and vomiting following laparoscopic surgical procedures. The proportion of complete responders in each palonosetron dose group was compared with the placebo control group. A complete responder was a patient with no emetic episodes and no rescue therapy for 24 hours postoperatively.

2. Assess the relative safety of single oral doses of palonosetron as compared with placebo, based upon standard safety measurements.

3. Determine the pharmacokinetics of single oral doses of palonosetron for each treatment group. (Pharmacokinetic data were collected at one investigational site only.)

Methodology: The study population consisted of 43 men and 308 women aged 19-75 years who were scheduled for elective laparoscopic surgical procedures requiring balanced general anesthesia with N20 (nitric oxide) plus an opiate. This was a randomized, double-blind, multicenter, placebo-controlled dose-ranging efficacy, safety, and pharmacokinetic study of five doses of oral palonosetron. The treatments were 0.1, 1.0, 3.0, 10.0, or 30.0 µg/kg of palonosetron or placebo. Patients were randomized to receive either study drug or placebo.

Formulation: Palonosetron was provided as 500µg/ml in 5-ml vials. The formulation number was No. F25259-006, and the same as the one used in study 2500.

Patients were randomly assigned to one of five treatments. Patients received a single oral dose of palonosetron or placebo. Patients were assigned a patient number from one of three series of patient numbers according to their status as defined by the stratification factor history of PONV (previous surgery with at least one episode of nausea or vomiting, previous surgery with no episodes of nausea or vomiting, or no previous general anesthesia) and then randomized with equal probabilities to one of the palonosetron dose levels or placebo. The study had 57 patients for the placebo group, and 47, 30, 57, 54, and 49 for the palonosetron dose group of 0.1 µg/kg, 1.0 µg/kg, 3 µg/kg, 10.0 µg/kg, and 30.0 µg/kg, respectively.

Blood samples for pharmacokinetic analysis ere taken from patients at one investigational site before dosing and at various times up to 168 ours after dosing; the plasma portion was assayed for palonosetron and RS-17825 (the N-oxide metabolite) concentrations, for which pharmacokinetic parameters were computed.

Inclusion and exclusion criteria: acceptable.

Efficacy Results

The following table summarizes and compares complete response (CR), complete control (CG), and no emetic episodes (EE) for the six dose groups.

Summary of Patients' Responses for 24 Hours After Recovery (Evaluable Patients)						
	Placebo (n = 57)	0.3 µg/kg (n = 30)	1.0 µg/kg (n = 57)	3.0 µg/kg (n = 54)	10 µg/kg (n = 49)	30 µg/kg (n = 62)
% with CR	33%	37%	58%	52%	59%	53%
p-value*			0.013	0.059	0.009	0.018
% with CC	33%	37%	58%	52%	57%	51%
p-value*			0.013	0.059	0.016	0.038
% no EE	40%	50%	67%	63%	71%	65%
p-value*			0.007	0.019	0.001	0.008

* p-value for treatment effect versus placebo

Note: CR: complete response (no emetic episode and without rescue antiemetic therapy); CC: complete control (complete response and only mild nausea or no nausea); EE: no emetic episodes.

Reviewer's comments: For complete response, there was no further increase in efficacy as the dose increased from 1 µg/kg to 30 µg/kg; likewise for complete control and no emetic episodes. The sponsor stated that "palonosetron reaches a plateau with respect to clinical response at a dose of 1 µglkg. At this dose, palonosetron was significantly more effective than placebo with respect to the control of both nausea and vomiting following various emetogenic laparoscopic surgical procedures, and was well tolerated."

Pharmacokinetic results:

Only 7 patients provided pharmacokinetic data.

Group	Cmax (ng/mL)	Tmax (hr)	AUC_{0-24} (ng * hr/mL)	AUC0-∞ (ng * hr/mL)	T1/2 (hr)
Group A (n=1) 0.3 µg/kg	0.028	31	0.42	-	-
Group B (n=1) 1.0 µg/kg	0.29	2.98 (1.44)	17.7 (7.69)	23.8 (14.2)	68.3 (44.2)
Group C (n=2) 3 µg/kg	0.246	2.97	18.6	23.3	78
Group D (n=1) 10 µg/kg	2.33 (0.96)	2.5 (0.71)	115	149	68.7 (14.6)
Group E (n=1) 30 µg/kg	8.08	2.67	459	509	47

Note: Mean (SD). For the majority of data, the firm did not provide SD due to only 1 subject was involved.

The firm's summary and conclusions: Because only 7 patients provided pharmacokinetic data, it was not possible to draw any conclusions about the pharmacokinetics or dose proportionality. In this small sampling of patients, individual

values for half-life ranged from 37.0 to 99.5 hours over the 0.3-30.0 µg/kg range of doses. Tmax generally occurred at between 2 and 4 hours, and the largest palonosetron plasma concentration observed was (b) ng/mLat the 30.0 µglkg dose level. Plasma concentrations of RS-17825 were not measurable in most patients, and therefore, no pharmacokinetic parameters were computed for RS-17825.

Reviewer's comments: In this study, palonosetron was administered orally. The Cmax values from this study are significantly lower than those reported for Study 2500 while the AUC_{0-24} and AUC0-∞ values are significantly higher than those reported for Study 2500. At doses of 1.0 µg/kg and 3.0 µg/kg, the Cmax and AUC values observed in this study are similar, while in Study 2500, the Cmax and AUC values obtained from the dose of 3.0 µg/kg are higher than those observed from the dose of 1.0 µg/kg.

Review of study PALO-03-05

Title of study: Phase 1, open-label, randomized crossover study in healthy subjects of determine the pharmacokinetics and safety of palonosetron IV coadministration with EMEND.

Rationale: Aprepitant is an antiemetic agent indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Aprepitant, also used in combination with 5-HT3 inhibitors, is an inhibitor and an inducer of CYP3A4, like some commonly used anesthetics (both fentanyl and propofol inhibit CYP3A4). CYP3A4 is a minor metabolic pathway for the metabolism of palonosetron. Therefore, the potential for interaction between aprepitant and palonosetron is of both clinical and metabolic importance.

Objective: To evaluate the pharmacokinetic (PK) and safety of single doses of palonosetron 0.25 mg administered intravenously (IV) in healthy subjects with concomitant administration of EMEND.

Palonosetron hydrochloride 0.25 mg, administered as a 10-second bolus into a peripheral vein (0.05 mg palonosetron per ml.), Lot number HP A003.
EMEND® (aprepitant) provided in tri-fold packs containing one 125 mg capsule and two 80 mg capsules, administered orally as a single 125 mg (Day 1) or 80 mg dose (Days 2 and 3), Lot number N7874.

Study design: an open label study

Demographic: Twelve subjects, 7 males and 5 females, were enrolled and completed the study. Overall mean age was 29.9 years (range 19 to 45). The study population was 75% white, 16.7% Hispanic, and 8.3% black.

Treatment A: a single 0.25 mg dose of iv palol1osetron on Day 1;
Treatment B: a single 125 mg oral dose of EMEND® followed 30 minutes later by a single 0.25 mg dose of IV palonosetron, and then a single 80 mg oral dose of EMEND® on Days 2 and 3. Meals were served 4.5 hrs after dosing. There is no description about whether the drug was dosed in fasted or fed state.

Washout Period: a 14-day washout period occurred between the subject's first treatment and the initiation of the second treatment.

In each treatment period, 5-mL blood samples were collected to evaluate PK profiles of palonosetron and its metabolite (M9) on Days 1 and 15 prior to any dosing; at 1, 3, 5, 15, 30 minutes, and 1, 2, 4, 6, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose. Plasma samples were assayed for palonosetron and metabolite M9 using a validated LCIMSIMS method.

Concomitant medication: subjects 4, 5, and 12 used hormonal contraceptives during the study. The AUC values of these subjects in both sequences did not differ much from those of other subjects.

Inclusion and exclusion criteria: acceptable.

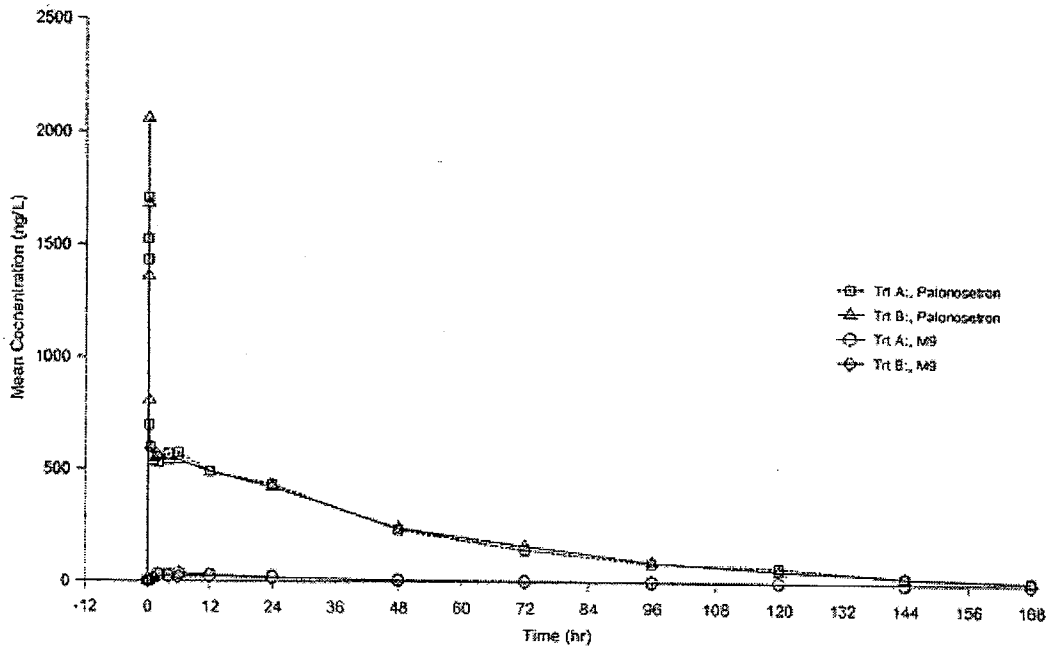
Results:

The mean (SD) of pharmacokinetic parameters.

Cmax (ng/L)	Tmax (hr)	AUC_{0-T} (ng * hr/L)	AUC0-∞ (ng * hr/L)	T1/2 (hr)	CLp (ml/min)
A: Palonosetron alone					
2060 (1260)	0.55 (1.72)	30700 (10700)	34800 (11500)	43 (13.7)	136 (58.5)
B: Palonosetron with EMEND (aprepitant)					
2360 (2440)	1.06 (3.45)	30500 (8660)	34300 (9240)	40 (11)	130 (36.5)
90% CI					
61.8%-1.57%*	-	-	85.6%-119%*	-	-

Note: N=12; *: 90% CI (ratio of natural log-transformed for treatment B to treatment A; the Vdss (l): 442.3 (157.5) for palonosetron alone and 410.9 (95.1) for palonosetron with EMEND®.

Mean plasma concentrations of palonosetron and M9 after administration of IV palonosetron alone or with the coadministration of EMEND in healthy subjects (n=12)



Reviewer's Comments: The recommended dose for EMEND® (Aprepitant) is 125 mg orally 1 hr prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3. Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. Tmax of aprepitant is approximately 3 hrs and the AUC0-∞ was 26% greater than dose proportional between 80-mg and 125-mg single dose administered in the fed state.

According to the firm's submission, aprepitant is primarily metabolized by CYP 3A4 with minor metabolism by CYP1A2 and CYP2C19. Briefly, palonosetron is approximately equally eliminated via renal and hepatic mechanisms. In vitro data showed that palonosetron was not an enzyme inducer or inhibitor at clinically relevant doses, Specific metabolic pathways of elimination involve CYP2D6 as the primary isozyme and CYP3A4 and CYP 1 A2 isozymes as secondary. Clinical studies in subjects known to be poor versus extensive metabollzers of CYP2D6 substrates did not reveal any differences in PK parameters between the populations (PALO-99-39).

In terms of AUC0-∞, treatment A and treatment B are bioequivalent. In terms of Cmax, treatment A and treatment B were not bioequivalent. That is, aprepitant did not affect the AUC of palonosetron but increased Cmax b 15%.

Review of Study PALO-03-10

Title: Evaluation of Pharacokinetic Interaction between Palonosetron (0.25 mg i.v.) and Dexamethasone (20 mg i.v.): A Randomized Three-way Crossover Study in Healthy Males and Females. Phase I, open label, single-dose, single centre, randomized, three-way crossover study.

Rationale: Palonosetron and dexamethasone are routinely used together in the treatment of CINV. Both palonoseteron and dexamethasone are metabolized at least in part via the Cytochrome P450 3A4 isozyme. In humans, palonosetron is eliminated by renal and hepatic routes with approximately 50% metabolized to form two primary metabolites (N-oxide-palonosetron (M9) and 6-S-hydroxy-palonosetron (M4)). Metabolite M9 and M4 represent in urine approximately 13% and 11% of the intravenous palonosetron dose, respectively. These metabolites have negligible pharmacologic activity.

Primary objective:
To assess the effects of dexamethasone on the pharmacokinetics of palonosetron and its main metabolite M9 in healthy male and female volunteers.

Secondary objectives:
To assess the effects of palonosetron on the pharmacokinetics of dexamethasone in healthy male and female volunteers.

To evaluate safety and tolerabilty of palonosetron in healthy male and female subjects with and without concomitant administration of dexamethasone.

Study design: It is a phase I open label study of an open, three-treatment (b1, b2, b3), three-period, six-sequence cross-over design with a wash-out period of at least 21 days between each study period). The study involved 18 healthy subjects (9 males and 9 females) aged 18-45.

Treatment b1: i.v. palonosetron 0.25 mg administration only (reference 1).

Treatment b2: i.v. palonosetron 0.25 mg administration, then (following an appropriate rinse of the canula with saline), i.v. dexamethasone 20 mg administration (test).

Treatment b3: i.v. dexamethasone 20 mg administration only (reference 2).

Blood sampling:

Treatment b1: predose, 0.25, 0.5, 1,2,4,6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192,216, and 240h post administration. (19 samples).

Treatment b2: predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, 96, 120, 144, 168, 192,216, and 240 h post administration. (22 samples).

Treatment b3: predose, 0.25, 0.5,1, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 48 h post administration. (14 samples).

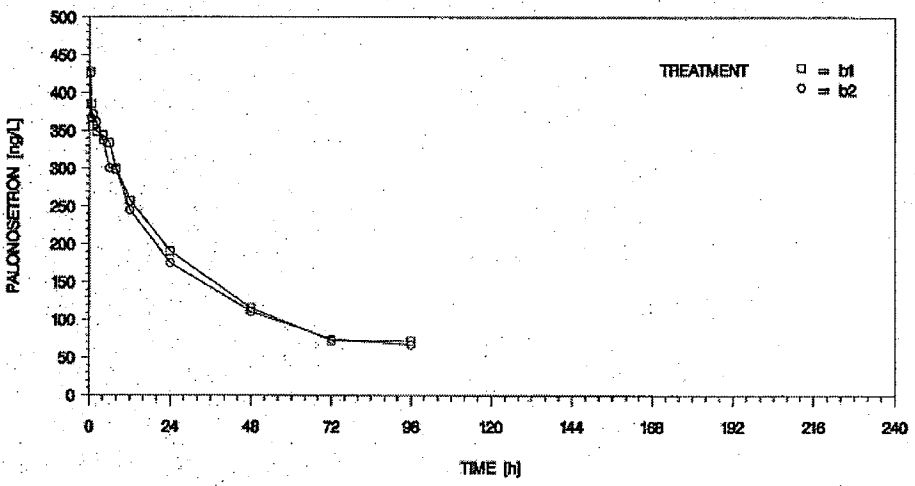
Subject 4 did not participate in the study periods 2 and 3. Therefore, only 17 subjects completed the study. There were only 17 subjects in the pharmacokinetic analysis.

Inclusion and exclusion criteria: acceptable.

Prior and concomitant medication: In the study plan, it was indicated that prior or concomitant medication during the study will not be permitted. There is no mention of concomitant medication in the final study report.

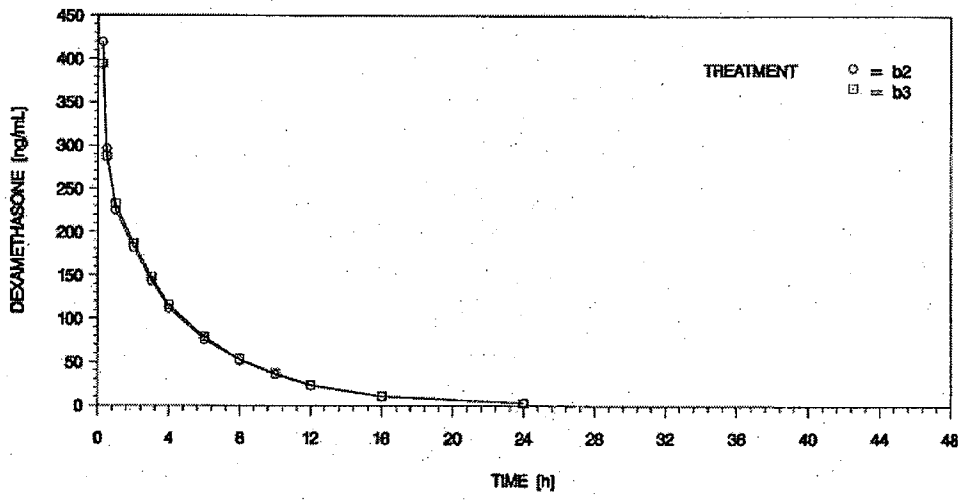
Results:

Geometric mean concentrations of palonosetron [ng/L] versus time [h] (n=17)



Treatment b_1: i.v. palonosetron 0.25 mg (reference 1)
Treatment b_2: i.v. palonosetron 0.25 mg, then i.v. dexamethasone 20 mg (test)

Geometric mean concentrations of dexamethasone [ng/mL] versus time [h] (n=17)



Treatment b_2: i.v. palonosetron 0.25 mg, then i.v. dexamethasone 20 mg (test)
Treatment b_3: i.v. dexamethasone 20 mg (reference 2)

The mean (SD) of pharmacokinetic parameters.

	Cmax	Tmax	AUC_{0-T}	AUC0-∞	T1/2

period	(ng/L)	(hr)	(ng * hr/L)	(ng * hr/L)	(hr)
Palonosetron					
b1	463.9(93.64)	1.33 (2.13)	14473.86(4549.48)	19596 (9965.85)	42.42 (28.35)
b2	483.1(129.55)	1.30 (1.99)	13555.34(3605.06)	18241.17(5861.27)	43.8 (17.03)
M9					
b1	44.02 (17.12)	3.83 (1.88)	1218.02 (744.56)	2421.61(1224.61)	45.95 (23.46)
b2	37.87 (10.66)	18.06(51.31)	1296.51 (680.05)	2950.87(1254.07)	78.27 (75.06)
Dexamethasone					
b2	430.12(101.73)	0.25 (0)	1400.46 (347.18)	1424.26 (358.55)	3.99 (0.64)
b3	402.81(83.98)	0.25 (0.01)	1420.03 (305.1)	1441.95 (313.98)	3.98 (0.49)

b1: iv palonosetron 0.25 mg; b2: iv palonosetron 0.25 mg, then iv dexamethoasone 20mg; b3:iv dexamethasone 20 mg

ANOVA and 90% confidence intervals for log-transformed pharmacokinetic characteristics of palonosetron, M9, and dexamethasone

Analyte/Measure	**Point estimate** $100*b_2/b_1$ **(for palonosetron)** $100* b_2/b_3$ **(for dexamethasone)** [%]	**90% confidence interval** [%]
Palonosetron		
AUC_{0-t}	94.6	[85.8 ; 104.]
C_{max}	102	[92.3 ; 113]
Dexamethasone		
$AUC_{0-\infty}$	98.1	[91.9 ; 105]
C_{max}	107.	[102 ; 111]

b_1: i.v. palonosetron 0.25 mg administration only (Reference 1)
b_2: i.v. palonosetron 0.25 mg administration, then i.v. dexamethasone 20 mg administration (Test)
b_3: i.v. dexamethasone 20 mg administration only (Reference 2)

Reviewer's Comments: With coadministration of dexamethasone, the AUC of M9 decreased slightly while the AUC of palonosetron increased slightly. The Tmax and T1/2 of M9 in the presence of dexamethasone increased substantially. It seemed that the production of M9 was delayed and decreased resulting in lower Cmax and longer Tmax while the elimination of M9 was somewhat reduced as well. Consequently, the net

result is slightly higher AUC values. The firm indicated that M9 data were erratic, possibly due to a low palonosetron dose. The 90% CI values for AUC and Cmax of palonosetron and dexamethasone are all within the bioequivalence acceptance range. It is concluded there is no interaction between these two drugs, which would cause in-equivalence of exposure to either drug when both drugs are administered simultaneously.

4.6 Appendix 2. Jan-14-08 amendment review

Due to the PK results of study 2500 are not consistent with the statement in the approved label in that the former results did not show dose proportionality for both Cmax and AUC as stated in the approved label. In response to the Agency's Dec-28-07 request for an explanation of inconsistent PK results and for detailed analytical report for study 2500, the sponsor submitted an amendment on Jan 14, 2008.

FDA Request #1. Please provide the complete analytical study report. If the report has been submitted, please indicate the location of the report in the submission (V olume# and Page#).

Reviewer's review and comment on the sponsor's response. The sponsor did provide detailed analytical reports in the Jan-14-08 amendment. The QC control concentrations for RS-25259 was (b) (4) and the corresponding CV% and % recovery were 8.9% and 110%, 6% and 110%, and 8.7% and 98%, respectively. The QC concentrations for RS-17825 was (b) (4) and the corresponding CV% and % recovery were 10.7% and 97%, 5.5% and 107%, and 8.0% and 103%, respectively. The QC results are acceptable.

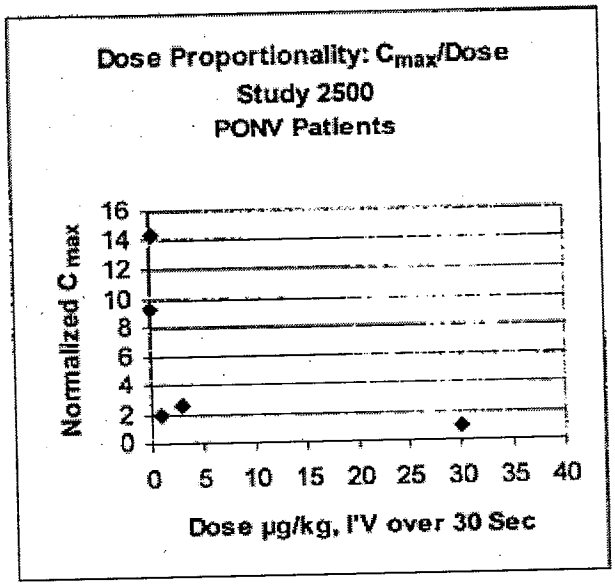
FDA Request #2. Explain the PK inconsistency between what is observed in study 2500 and the statement in the approved labeL. The approved label states that "Mean maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC O-inr) are generally dose-proportional over the dose range 0.3-90 mcglkg in healthy subjects and in cancer patients." No dose proportionality is observed in Study 2500 which is different from the statements in the approved label.

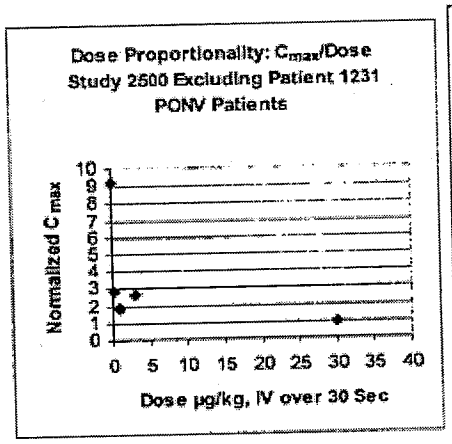
Reviewer's review and commentson the sponsor's response.

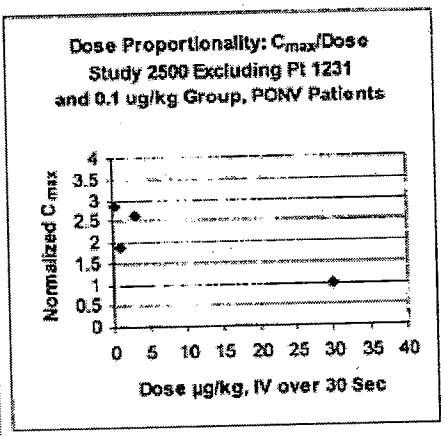
The sponsor tabulated the PK results of study 2500 (PONV patients), study 2092 (healthy subjects) and study 2330 (cancer patients, CINV) for comparison. Furthermore, the sponsor submitted 36 figures showing the relationship of dose normalized Cmax, AUClast, AUC0-24, AUCinf from all three studies. The sponsor discussed the differences between these three studies: 1) subject populations as listed above, 2) administration (Administration ofpalonosetron was via a 5- minute iv infusion in study 2092, whereas palonosetron was given via a 30 second iv bolus in studies 2500 and 2330), 3) analytical methods (study 2092 employed an early HPLC (b)assay, while studies 2500 and 2330 utilized an LC/MS method differences), 4) slightly different PK sampling times.

Dose Proportionality for Cmax. The sponsor argued that generally the same values across the doses evaluated with the exception of the two lowest dose groups, 0.1 and 0.3 μg/kg, in study 2500 (PONV patients). Study 2500 dose-normalized Cmax values appear spuriously high in the 0.3 pg/kg dose group due to a profound outlier (Patient #1231) and in the 0.1 μg/kg group (n=4, study 2500) probably due to the extreme range of Cmax values observed (0.0667 to 1.94 ng/mL, a 29-fold range. The sponsor suggested that there was dose proportionality for Cmax if omitting Pt #1231 and the 0.1 μg/kg dose group for study 2500, as shown below.

The sponsor noted that study 2092 dose-normalized Cmax values are somewhat lower than observed in studies 2500 and 2330 since in study 2092 palonosetron was administered by iv infusion over 5 minutes and not by iv bolus over 30 seconds as in studies 2500 and 2330. Overall, the collective PK data from studies 2500, 2092 and 2330 illustrate that Cmax for IV palonosetron is generally dose-proportional over the dose range of 0.3-90 pg/kg, with some variability and outliers.



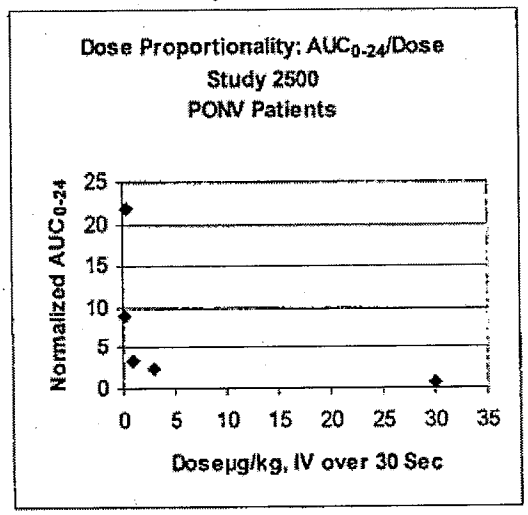


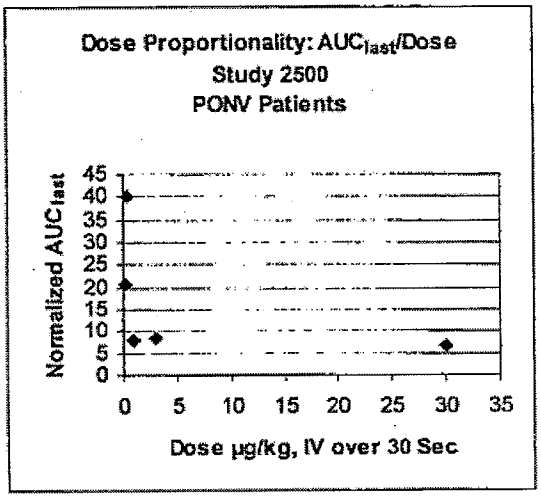


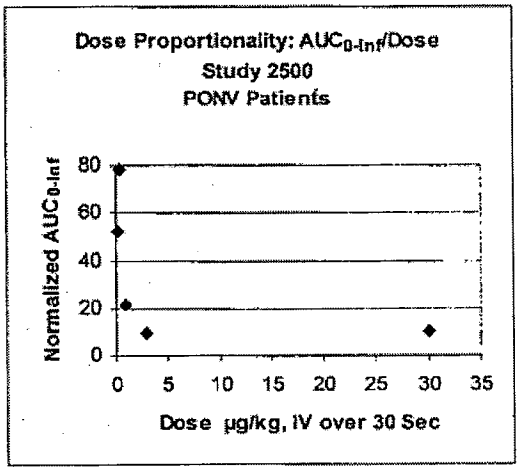
Dose Proportionality for Systemic Exposure (AUC).

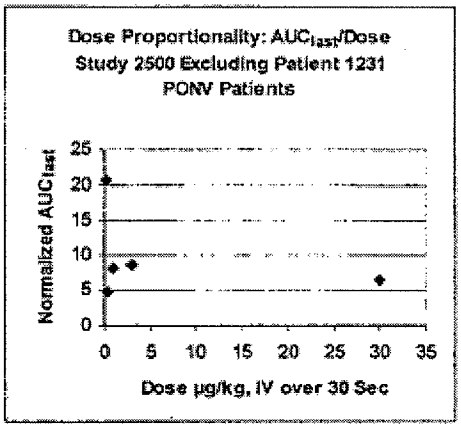
The sponsor argued that there is general a dose-proportionality with the exception of the 0.1 µg/kg group in Study 2500. Once again, the sponsor suggested omitting the profound outlier patient 1231. Furthermore, the 0.1 µg/kg dose group in study 2500. This latter group (n=4) received a very low dose, two (#230 and #727) of these 4 patients had plasma palonosetron levels less than the lower limit of quantitation (20 pg/mL) for all P K blood sampling times ≥6 hours postdose, i.e., the AUCO-24 was spuriously low for these two patients due to the low dose and the limit of quantitation (LOQ, 20 pg/mL) of the assay resulting in spuriously elevated dose

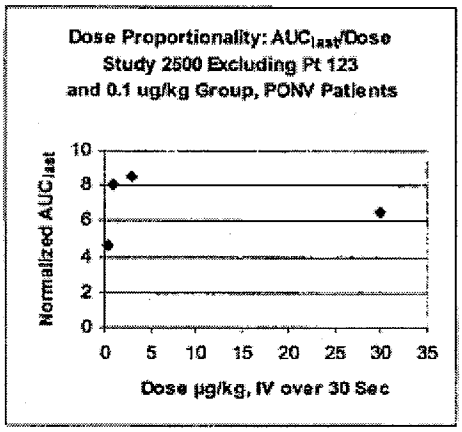
normalized dot-plot data points. With two remaining patients (#734 and #1228) in the 0.1 μg/kg dose group for A UC calculation (study 2500), this sample size is considered insuffcient to adequately characterize AUCO-24 for the 0.1 μg/kg dose particularly for this drug which is known to have substantial between-subject variance in P K parameters. The above explanation of the dose-normalized A UCO-24 data is also applicable to the AUClast and AUCo_infdot-plots in Figures 19-36 (Appendix #2) for studies 2500, 2092 and 2300. AUCo-24, AUClasl and AUCO-inf are also considered generally dose proportional over the 0.3-90 μg/kg dose range, with some outliers. Sponsor concluded that mean Cmax and A UC values are generally dose-proportional over the dose range of 0.3-90 pg/kg in healthy subjects, cancer patients and in post-operative patients.











Reviewer's comments: Though the sponsor pointed that there is dose proportionality for Cmax and AUC by omitting the outlier and the low dose group, such practice of selectively omitting some data in order to conclude a PK relationship is generally not allowed. Considering the number of subjects in study 2902 (n=60 with 6 for each dose cohort) and in study 2330 (N=37 with 5-12 for each dose cohort) and the consistency between these studies, the sponsor's explanation and PK analyses of omitting subject 1231 and the low dose group (0.1 µg/kg) were acceptable.

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/s/

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