CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-372

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-372	Submission Date: 09/27/02
Brand Name:	Aloxi
Generic Name:	Palonosetron Hydrochloride
Reviewers:	Sue-Chih Lee, Ph.D.
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Team Leader:	Suresh Doddapaneni, Ph.D.
OCPB Division:	Division of Pharmaceutical Evaluation II
OND Division:	Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Sponsor:	Helsinn Healthcare SA (Switzerland)
Relevant IND(s):	[redacted]
Submission Type; Code:	NME, 1S
Formulation; Strength(s):	IV Injection, 0.25 mg/5 mL
Dosing regimen:	Single 0.25 mg dose, administered 30 minutes prior to chemotherapy
Proposed Indication:	Prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer therapy

1. EXECUTIVE SUMMARY

Palonosetron is a novel 5-HT_3 receptor antagonist. The sponsor is seeking approval of single IV dose of palonosetron hydrochloride 0.25 mg for the prevention of acute and delayed nausea and vomiting associated with emetogenic cancer therapy, including highly emetogenic chemotherapy. To evaluate the potential QT effect of palonosetron following IV administration, the sponsor analyzed 12-lead ECG data collected from Phase 3 trials in which palonosetron was studied at two dose levels (0.25 mg and 0.75 mg). A subset of the patients also received Holter monitoring. Based on the overall QT data and cardiac safety profiles, the QT effect of palonosetron appears to be similar to the approved comparator drugs (dolasetron and ondansetron) used in the trials. Palonosetron is eliminated through both renal excretion and metabolic pathways with the latter mediated via multiple CYP isozymes. *In vitro* studies indicated that it does not inhibit or induce the activity of many CYP isozymes at the therapeutic concentrations. Therefore, the potential for drug interactions with palonosetron is low. No dosage adjustment is necessary based on age (18 yrs and up) or gender, nor is it necessary for any degree of

renal or hepatic impairment. Safety and efficacy in pediatric patients have not been established.

1.1 RECOMMENDATION

From the standpoint of the Office of Clinical Pharmacology and Biopharmaceutics, the Human Pharmacokinetics and Biopharmaceutics section of the application is acceptable provided that a satisfactory agreement is reached between the Agency and the sponsor regarding the language in the package insert.

/S/

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3. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

3.1 Pharmacokinetics

3.1.1 Dose Proportionality

In a Phase 1 study, healthy subjects received a single IV dose of palonosetron. Both C_{max} and AUC were found to be approximately dose proportional over the dose range of 0.3-90 • g/kg.

3.1.2 Distribution

Following single IV administration to healthy volunteers, plasma palonosetron concentration exhibited a biphasic decline. The mean volume of distribution (V_z) was

8.34±2.45 L/kg. Protein binding in human plasma was constant over the concentration range of 5-412 ng/mL and averaged approximately 62%.

3.1.3 Metabolism

In vitro studies suggested that metabolism of palonosetron is mediated primarily via CYP2D6 followed by CYP3A4 and CYP1A2. The major metabolites are an N-oxide metabolite (M9; 12.5% of the administered dose) and a hydroxy metabolite (M4; 10.9% of the administered dose). The metabolites had negligible pharmacological activities.

3.1.4 Elimination

Both renal excretion and hepatic metabolism play important roles in the elimination of palonosetron. Following single IV administration of ^{14}C-palonosetron hydrochloride 10 • g/kg (0.7 mg/70 kg), renal clearance amounted to 42% of the total clearance while approximately 50% of the administered dose was metabolized. The mean terminal half-life based on a Phase 1 study was 37.4±14.2 hrs.

3.1.5 Special Populations

Age/Gender/Race

The disposition of palonosetron seemed to be similar between males and females after I.V. administration of a single dose of palonosetron to 6 healthy subjects (3 males and 3 females) in a mass balance study. A population PK analysis was performed using data obtained from the Phase III trials in which palonosetron was studied at two dose levels (0.25 mg and 0.75 mg). Age, gender and race were not found to be significant covariates for clearance. However, the final model yielded a high intersubject variability (88.8%) in clearance. Since analysis of the Phase III trial data did not reveal any subgroup with significant differences in the safety profiles, no dosage adjustment based on age or gender is considered necessary. It should be noted that Blacks were poorly represented in the Phase III trials. Hence, no conclusion can be made about PK in Blacks compared to Caucasians.

Renal insufficiency

Mean values of the primary PK parameters for palonosetron in patients with mild to moderate renal impairment were similar to those of healthy subjects. In patients with severe renal impairment, the mean $AUC_{0-\infty}$ increased by around 30% compared to healthy subjects. No dosage adjustment is recommended for patients with any degree of renal impairment.

Hepatic insufficiency

The mean values of C_{max} and AUC for palonosetron and the M9 metabolite were significantly reduced in patients with moderate and severe hepatic impairment relative to those of healthy subjects. Albeit the apparent half-life of palonosetron is prolonged by 50% in patients with moderate and severe hepatic impairment, dosage adjustment is not necessary as palonosetron will be administered as a single dose in the clinical setting.

3.2 Drug-Drug Interactions

Palonosetron was eliminated from the body by both renal excretion and metabolic pathways. *In vitro* studies showed that metabolism of palonosetron is mediated via multiple CYP enzymes. Further *in vitro* studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A (CYP2C19 was not investigated) and does not induce the activity of CYP1A2, CYP2D6 or CYP3A. Therefore, the potential of drug interactions with palonosetron is low.
An *in vivo* pharmacokinetic study showed that single dose palonosetron (0.75 mg I.V.) did not interact with metoclopramide (10 mg Q 6 hrs dosed to steady state). It should be noted that the metoclopramide dose used in this study is lower than that recommended for prevention of chemotherapy-associated nausea and vomiting.

3.3 QT-Related Studies

—— .. in the synthesis of palonosetron and is suspected of being cardiotoxic. *In vitro* (human hepatic microsomes, cryopreserved hepatocytes and fresh liver slices) and *in vivo* studies were carried out to determine whether .—— is a metabolite of palonosetron. At a detection limit of 10 ng/L for —— and 500 ng/L for —— (metabolite of . —— , in plasma and approximately 10-times greater in urine, neither compound could be detected following a 0.75 mg IV dose. *In vitro* studies did not detect any formation of . —— . However, the sensitivity of the studies was unclear. No further information was requested because the QT data and cardiac safety profiles reflected the overall effect following IV administration of palonosetron, including the effect of —— , if any was formed in vivo .

The sponsor conducted a QT analysis using data collected from 12-lead ECG in Phase III trials and indicated that no relationship between palonosetron exposure and QTc or heart rate was found. However, the information that can be derived from this analysis is limited because of the study design. Separate analysis based on 12-lead ECG data, Holter data and cardiac safety profiles were reviewed and found to be comparable to the approved comparator drugs (ondansetron and dolasetron) by Dr. Narayan Nair, Medical Officer of HFD-180.

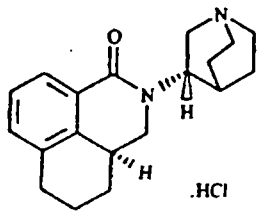
4. QUESTION BASED REVIEW

4.1 General Attributes

4.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

The structure and physico-chemical properties of palonosetron hydrochloride are given below:

Empirical formula: $C_{19}H_{24}N_2O \cdot HCl$ Molecular weight: 332.87



Chemical name:	(3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline hydrochloride
Structure:	exist as a single stereoisomer, the (S,S)-isomer
Solubility:	freely soluble in water; slightly soluble in ethanol

The components and composition of the to-be-marketed formulation are shown below:

Table: Formulation of palonsetron HCl IV injection

Ingredient	mg/mL [a]	Function
Palonosetron HCl	0.05[b]	Active
Mannitol, USP/EP	41.5	Tonicifying agent
Edetate Disodium Dihydrate, USP/EP		Chelating agent
Tri Sodium Citrate Dihydrate, USP/EP		Buffering agent
Citric Acid Monohydrate, USP/EP		Buffering agent
1N NaOH and/or HCl Solution, NF/EP	pH 5.0 ± 0.5	For pH adjustment
Water for Injection, USP/EP	qs ad 1.0 mL	Vehicle

[a] 5 mL vials containing 0.25 mg (0.05 mg/mL).

[b] Calculated as palonosetron free base.

[c]

4.1.2 What is the proposed mechanism of action?

Palonosetron is a potent and highly selective 5-HT_3 receptor antagonist. Certain cancer chemotherapy agents such as cisplatin are associated with a high incidence of nausea and vomiting. 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing

serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex.

4.2 General Clinical Pharmacology

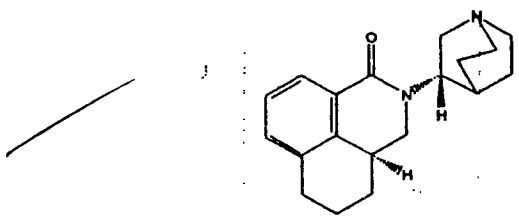
4.2.1 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

For efficacy assessment in clinical trials, the primary endpoint was the proportion of patients with a complete antiemetic response (no vomiting, retching or rescue medication) for 24 hours after emetogenic chemotherapy in chemotherapy-naive cancer patients. The secondary efficacy variables include among other measures time to the first emetic episode, and time to administration of rescue therapy.

4.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The concentrations of palonosetron and its major metabolite, M9, in plasma and urine samples were determined by validated analytical methods. M9 has low activity as a 5-HT_3 receptor antagonist and present in plasma at low concentrations, determination of its concentrations in the biological fluids was at the end considered to be not crucial.

A suspected compound, exists as a related impurity of the drug substance. Efforts were made to determine the potential of its formation in vivo. A method was used to detect the presence of and its metabolite in human plasma and urine samples (detection limit: ~10 ng/L (plasma) and 100 ng/L (urine) for and ~500 ng/L (plasma) and 2000 ng/L (urine) for). There was no indication of formation following single IV dose administration of palonosetron 0.75 mg.

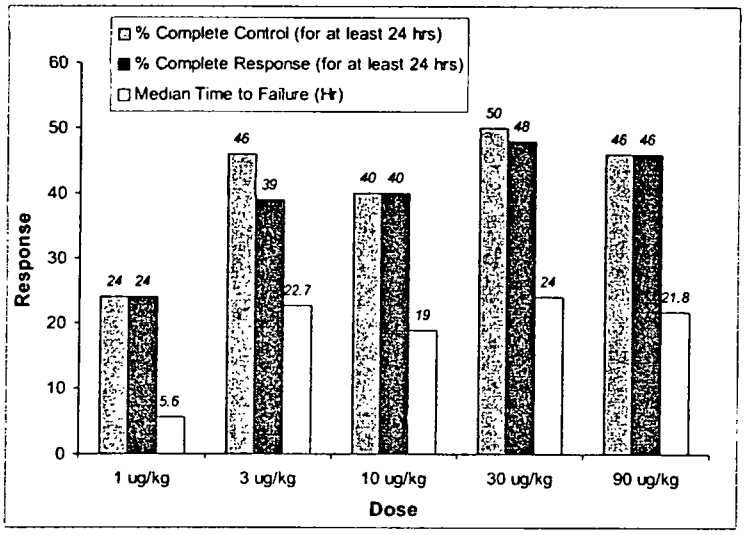


Paonosetron

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

4.2.3.1 Efficacy

A Phase II dose ranging study was conducted in chemotherapy-naive cancer patients receiving highly emetogenic chemotherapy. Single IV dose of palonosetron was administered to patients 30 minutes before chemotherapy. The figure below shows the dose-response relationship in terms of three key response variables. The dose levels of 3, 10, 30 and 90 • g/kg, were approximately equally effective as compared with the combined results from a cohort of 0.3 and 1 • g/kg in suppressing chemotherapy-induced emesis for 24 hours. No apparent dose-response relationship was found for adverse events in this trial. Based on the results, the dose levels of 0.25 mg (~3.6 • g/kg) and 0.75 mg (~10.7 • g/kg) were studied in the Phase III trials.



[1]Complete control: free from emetic episodes and requiring no rescue medication
[2]Complete response: free from emetic episodes and rescue medication who experienced only mild or no nausea.
[3]Median time to failure (first emetic episode or rescue medication)

4.2.3.2 Safety:

4.2.3.2.1 Adverse events:

According to Dr. Narayan Nair, Medical Officer of HFD-180, no clear dose response relationship for adverse event rate can be derived from the available clinical data.
Dr. Nair shared, among other information from his review, the following summary tables of adverse event rate observed in the integrated Phase I-III or Phase II/III trials:

- All adverse events by System Organ Class (Phase I-III)
- Serious adverse events (Phase I-III)

- Selected cardiovascular adverse events (Phase II/III)

Table: All adverse events (AE) in all integrated Phase I-III trials by number and percent of subjects

SOC	Palonosetron										Active Comparators						Placebo	
	< 0.25 mg (n = 341)		0.25 mg (n = 841)		0.75 mg (n =819)		> 0.75 mg (n = 347)		Total (n = 2348)		Onda 32 mg (n = 410)		Dola 100 mg (n = 194)		Total (n = 604)		(n = 173)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
No AE	105	31	245	29	213	24	92	27	655	28	127	31	45	23	172	28	67	39
Any AE	236	69	596	71	606	76	255	73	1693	72	283	69	149	77	432	72	106	61
Blood	20	6	129	15	150	18	18	5	317	14	92	22	49	25	141	23	4	2
Cardiac	11	3	46	5	50	6	17	5	124	5	28	7	8	4	36	6	5	3
Ear	3	1	17	2	10	1	5	1	35	1	5	1	2	1	7	1	0	0
Endocrine	1	<1	2	<1	0	0	4	<1	0	0	0	0	0	0	0	0	0	0
Eye	4	1	8	1	8	1	3	1	23	1	4	1	0	0	4	1	1	1
Gastrointestinal	105	31	223	27	246	30	134	39	708	30	83	20	58	30	141	23	43	25
General	56	16	171	20	181	22	72	21	480	20	86	21	47	24	133	22	23	13
Hepatic	1	<1	5	1	10	1	0	0	16	1	6	1	1	1	7	1	1	1
Immune system	0	0	1	<1	4	<1	0	0	5	<1	1	<1	0	0	1	<1	0	0
Infection	34	10	62	7	65	8	31	9	192	8	18	4	18	9	36	6	14	8
Injury/Poisoning	2	1	5	1	4	<1	6	2	17	1	1	<1	0	0	1	<1	1	1
Investigational	16	5	92	11	114	14	27	8	249	11	56	14	21	11	77	13	13	8

Onda = Ondansetron, Dola = Dolasetron

Table: Serious adverse events (SAE) in all integrated Phase I-III trials by number and percent of subjects for various dose levels of palonosetron, active comparators and placebo

	Palonosetron (mg)					Active Comparators			Placebo
	< 0.25 n (%)	0.25 n (%)	0.75 n (%)	> 0.75 n (%)	Total	Onda n (%)	Dola n (%)	Com-bined	n (%)
No SAE	321(94)	800 (95)	773(94)	319 (92)	2213 (94)	389 (95)	185 (95)	574 (95)	168 (97)
Any SAE	20 (6)	41 (5)	46 (6)	28 (8)	135 (6)	21 (5)	9 (5)	30 (5)	5 (3)

Onda = Ondansetron; Dola = Dolasetron.

The following table shows the rate of selected cardiac adverse events of interest, which was 13%, 9%, 10%, and 16% for palonosetron at the dose levels of <0.25 mg, 0.25mg, 0.75 mg and >0.75 mg, respectively.

Table: Selected cardiac adverse events of interest in pivotal Phase II/III trials

	Palonosetron										Active Comparators					
	< 0.25 mg (n = 31)		0.25 mg (n = 633)		0.75 mg (n = 635)		> 0.75 mg (n = 77)		Total (n = 1376)		Ondansetron 32 mg (n = 410)		Dolasetron 100 mg (n = 194)		Combined (n = 604)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
No selected cardiac AE of interest	27	87	576	91	571	90	65	84	1239	90	357	87	183	94	540	89
Any selected cardiac AE of interest	4	13	57	9	62	10	12	16	135	10	53	13	11	6	64	11

4.2.3.2.2. QT interval:

Concentration-QT relationship:

The sponsor conducted an analysis using data collected from 12-lead ECG in Phase III trials and indicated that no relationship between palonosetron exposure and QTc or heart rate was found. This analysis did not examine the changes in heart rate or QTc (instead of heart rate or QTc itself) in relation to palonosetron exposure. However, a further inspection of the data by Dr. He Sun, Pharmacometrics Specialist of DPEII, did not reveal any apparent QTc change from baseline following administration of palonosetron at the ECG measurement time points.

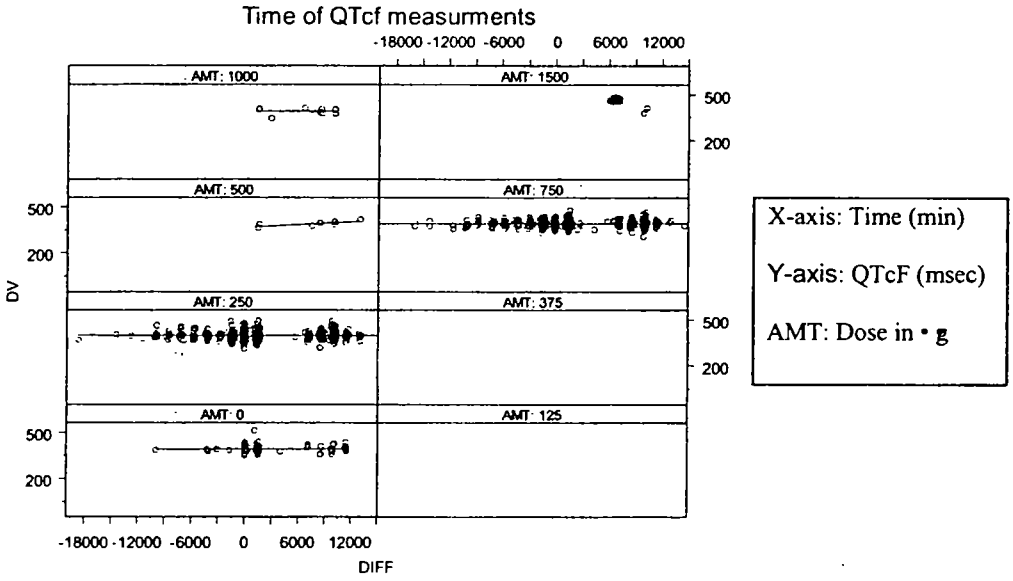


Figure: QT_CF versus Time by Dose

It should be noted that the information that can be derived from this study is limited because 12-lead ECG measurements were not performed frequently following the IV administration of palonosetron. Most patients had ECG measurements at pre-dose, 24 hr postdose and on Day 6-8. Although some patients had a measurement at 15 minutes postdose, it is not sufficient to capture the maximum QTc change since C_{max} and E_{max} do not necessarily coincide.

In addition to EKG measurements, 159 patients (0.25 mg dose: 57 patients; 0.75 mg dose: 102 patients) randomized to palonosetron 0.25 mg or 0.75 mg in the Phase III trials received Holter monitoring. These data were not subject to the above analysis.

All cardiac safety data from Phase I-III trials were reviewed by Dr. Narayan Nair. Based on his review, the cardiac adverse event profile for palonosetron appears similar to that of other drugs in this class although there seems to be more subjects with tachycardia in the palonosetron group versus comparator (ondansetron and dolasetron) arms (1% vs. 0.5%). The following is information excerpted from Dr. Nair's review:

"ECG Data:

In the Phase III trials, the mean change from baseline QTc ranged from -1 to +3 msec without any dose trends and without any case of major change from baseline. When all the Phase 3 ECG data was pooled, the effect on the QTc parameter by Bazett or Fridericia correction was 2 msec at both palonosetron doses. In the comparator arms the QTc mean changes from baseline were larger (4-5 msec). There were several cases of new absolute QTcB or QTcF >500 msec but these were equally distributed in all treatment arms.

Table: Number and percentage of patients with postdose changes in QTc based on the ECG measurements in the Phase III trials

	Palonosetron 0.25 mg (N = 605) Nt = 594		Palonosetron 0.75 mg (N = 610) Nt = 601		Ondansetron 32 mg (N = 410) Nt = 404		Dolasetron 100 mg (N = 194) Nt = 192	
	n	%	n	%	n	%	n	%
QTcB 30 to 60 msec	41	6	54	9	41	10	13	6
QTcB > 60 msec	5	0	3	0	7	1	2	1
QTcB > 500 msec	1	0	0	0	1	0	1	0
QTcF 30 to 60 msec	27	4	31	5	32	7	11	5
QTcF > 60 msec	5	0	2	0	4	1	1	0
QTcF > 500 msec	0	0	0	0	0	0	1	0

N= Number of patients in specific group.
Nt= Total Number of patients with ECG parameter.
n = Number of patients with changes
% = Percentage of patients with changes.
QTcF = QT interval corrected by Fridericia formula.
QTcB = QT interval corrected by Bazett formula.
msec = Milliseconds
Source: Expert Report PALO-02-04, Appendix A.

Holter Data:

A subset of patients in the Phase 3 trials underwent Holter monitoring. Evaluable Holters in 193 subjects were obtained from 2-hours before dosing to 22-hours after dosing. Individual infrequent cases of Mobitz Type H block, sinus pauses, and occasional runs of nonsustained ventricular tachycardia were identified, however no difference in treatment groups was seen. No clinically relevant difference seen between palonosetron at two different doses compared to ondansetron and dolasetron."

4.2.3.1 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Palonosetron PK was found to be approximately dose proportional following single IV dose administration (over 5 min.) for the dose range of 1-90 • g/kg. Dose proportionality upon multiple dosing was not studied since the drug product is intended for single dose administration. (Note: In later studies, palonosetron was administered over 30 seconds. This is the way palonosetron will be administered in clinical use conditions.)

4.2.4 How does the PK of palonosetron in healthy volunteers compare to that in patients?

4.2.4.1 What are the basic PK parameters?

The PK parameter values for palonosetron following single IV dose of 3 • g/kg and 10 • g/kg in healthy subjects in a Phase I study and in chemotherapy-naive patients undergoing chemotherapy in a Phase II trial are listed in the table below. Both C_{max} and T_{max} were highly variable in patients compared to healthy volunteers. It should be noted that the two studies differed in time period of IV dosing and sampling schemes. In the study in healthy subjects, palonosetron was administered over 5 minutes and the first sample was collected at 5 minutes post dose. In the Phase II trial in patients, palonosetron was administered over 30 seconds and the first sample was collected at 1 min postdose. Mean AUC value was comparable between healthy subjects and patients receiving chemotherapy, however, the intersubject variability was greater in patients.

Dose (• g/kg)	Cmax[1] (ng/mL)	Tmax (hr)	$AUC_{0-\infty}$ (ng.h/mL)	T1/2 (hr)	CL (mL/min/kg)	Vz (L/kg)
Healthy Volunteers (Phase I Study)						
3.0[1]	0.92 ± 0.25	0.083 ± 0.0	29.8 ± 9.02	47.2 ± 14.7	1.81 ± 0.55	6.88 ± 0.87
10	3.53 ± 1.44	0.090± 0.024	65.7 ± 14.5	35.0 ± 8.8	2.66 ± 0.61	7.83 ± 1.81
Patients (Phase II Trial)						
3.0[1]	5.63±5.48	0.144±0.196	35.8±20.9	56.4±5.81	1.66±0.59	7.91±2.53
10	13.0±20.0	0.827±1.51	81.8±23.9	49.8±14.4	2.23±0.83	9.56±4.21

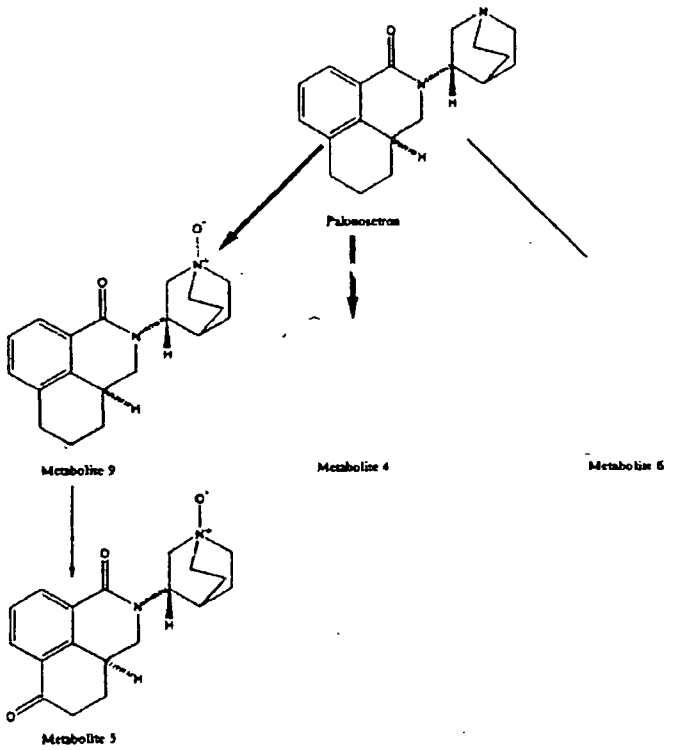
[1]Equivalent to 0.21 mg/70 kg (close to the proposed clinical dose of 0.25 mg)

4.2.4.2 Does mass balance study suggest the major route of elimination is renal or hepatic?

Following single dose administration of I.V. radiolabeled palonosetron, 79.9% of the administered dose was recovered in urine over a 144-hr period with 39.3% of the recovered dose being intact drug. Overall, renal clearance amounted to 42% of the total systemic clearance. Around 50% of the palonosetron dose was metabolized in humans with the major metabolites being an N-oxide metabolite (M9; accounts for 12.5% of the dose) and a hydroxy metabolite (M4; accounts for 10.9% of the dose).

Both renal and hepatic systems play important roles in the clearance of palonosetron. The proposed metabolic pathway is shown below:

Figure: Metabolic pathways of palonosetron



Bold arrows indicate major pathways

4.3 Intrinsic Factors

4.3.1	**What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamic? What dosage adjustments, if any, are recommended for each of these subgroups**

4.3.1.1 Age/Gender/Race

A population PK analysis was performed using data obtained from the Phase III trials. Age, gender and race were not found to be significant covariates for clearance. However, the final analysis yielded a low population mean of clearance estimate (less than half of the mean value found in the Phase II trial) with a high intersubject variability (88.8%) in

clearance. The sponsor did not explain why. Since analysis of the Phase III trial data did not reveal any subgroup with significant differences in the safety profiles, no dosage adjustment based on age or gender is necessary. It should be noted that Blacks were poorly represented in the Phase III trials. Hence, no conclusion can be made about PK in Blacks compared to Caucasians.

4.3.1.2 Renal impairment

Mean values of the primary PK parameters for palonosetron in patients with mild to moderate renal impairment were similar to those of healthy subjects. In patients with severe renal impairment, the mean $AUC_{0-\infty}$ increased by around 30% compared to healthy subjects. In addition, C_{max} and $AUC_{0-\infty}$ of M9, the major metabolite of palonosetron, increased by 1.5 to 2-fold and 3 to 4-fold, respectively, in severe renal impairment. Dosage adjustment for palonosetron is not necessary in patients with severe renal impairment.

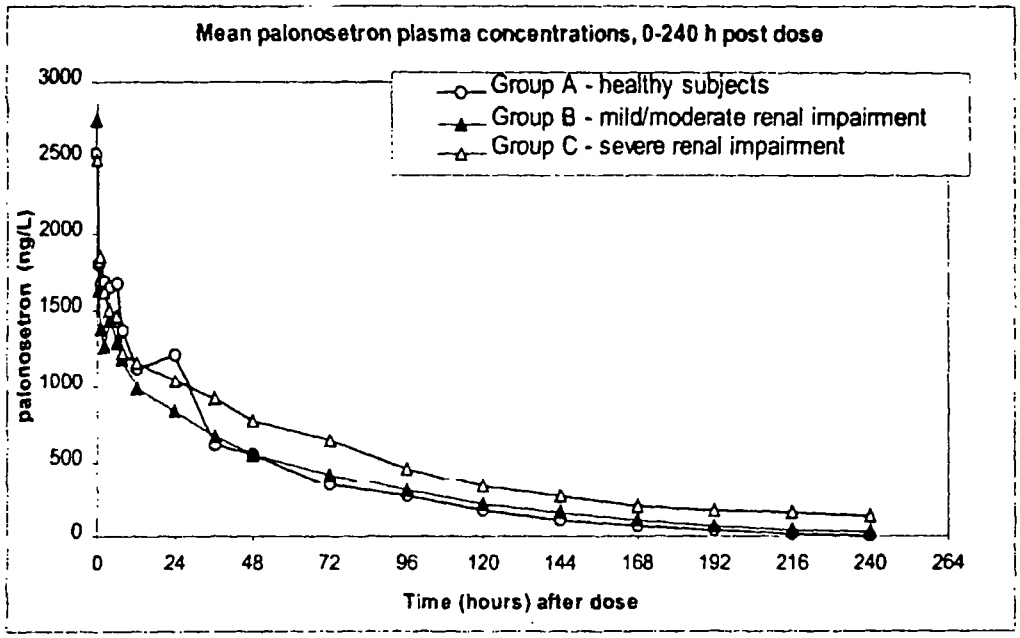


Figure: Mean palonosetron plasma concentration-time profile in subjects with varying grades of renal impairment.

4.3.1.3 Hepatic impairment

The mean values of C_{max} and AUC for palonosetron in patients with mild to severe hepatic impairment were significantly reduced relative to those of healthy subjects. The mean values of C_{max} and AUC for the M9 metabolite were significantly reduced in patients with moderate to severe hepatic impairment relative to those of healthy subjects. This has been attributed to the combination of a reduction in the metabolic pathway in hepatic impairment with an increase in the volume of distribution, altogether resulting in a net reduction in palonosetron and M9 plasma concentrations. In addition, the apparent

half-life of palonosetron was significantly prolonged in patients with moderate to severe hepatic impairment compared to that of healthy subjects.

Despite a prolongation in the apparent half-life of palonosetron by 50% in patients with moderate and severe hepatic impairment, dosage adjustment is not necessary as palonosetron will be administered as a single dose in the clinical setting.

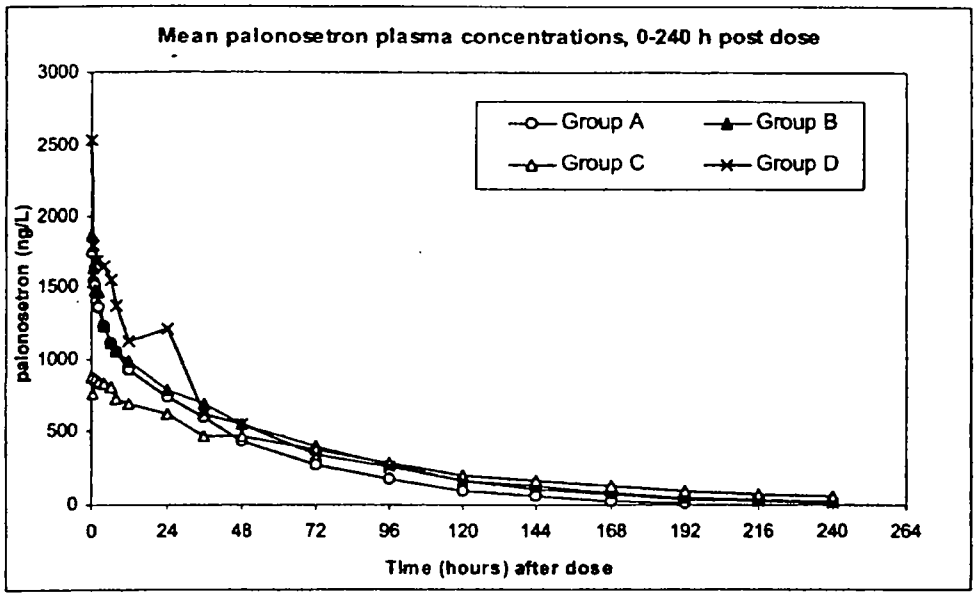


Fig.2. Mean palonosetron plasma conc.-time profile in subjects with varying grades of hepatic impairment.

4.3.1.4 CYP2D6 Poor metabolizers

Palonosetron PK parameter values following single IV dose of 0.75 mg were compared between CYP2D6 extensive (n=3) and poor metabolizers (n=3). There is no indication that CYP2D6 poor metabolizers had higher exposure to or longer half-life of palonosetron.

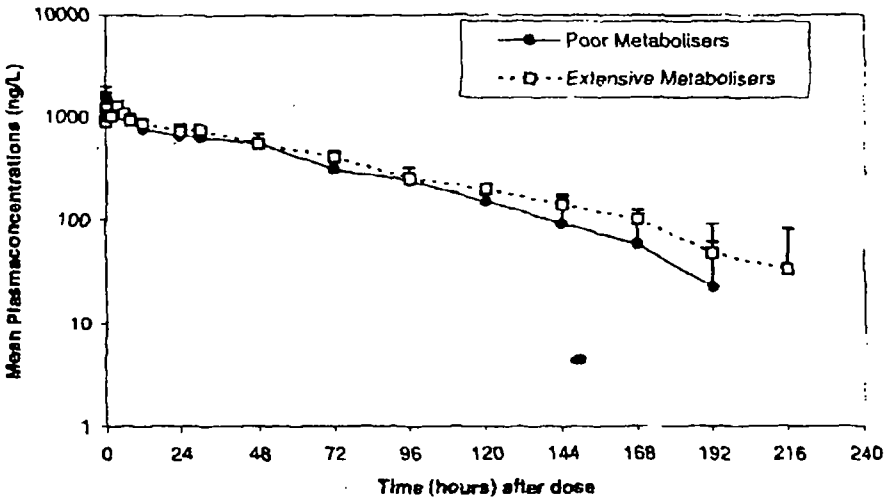


Figure: Mean plasma palonosetron concentrations following single IV injection of 0.75 mg palonosetron HCl in extensive and poor metabolizers of CYP2D6 substrates

4.4 Extrinsic Factors

4.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

At this time, there are no known factors that influences exposure or response of palonosetron.

4.4.2 Drug-Drug Interactions

4.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

In *in vitro* studies using cDNA-expressed CYP enzymes, CYP2D6 was identified as the major enzyme for the metabolism of palonosetron with other enzymes (CYP1A1, CYP1A2 and CYP3A4) playing a lesser role. In a correlation analysis using human microsomes, CYP2D6 was identified as the major enzyme for the metabolism of palonosetron, followed by CYP3A4. The correlation coefficient for CYP2D6 was 0.58 for the M9 formation, and 0.74 for the formation of the other two polar metabolites. The potential for drug-drug interactions causing significant increase in palonosetron concentrations is low. This is because metabolism accounts for only 50% of the total clearance of palonosetron, and multiple CYP enzymes appear to be involved in the metabolism of palonosetron.

The inhibitory potential of palonosetron and its metabolite M9 on the activity of human liver microsomal CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, CYP3A

was investigated. At the therapeutic concentrations, either palonosetron or M9 is not an inhibitor of these enzymes. CYP2C19 was not studied.

The induction potential of palonosetron and M9 on the enzymatic activities catalyzed by CYP1A2, CYP2D6, and CYP3A were studied using fresh isolated human hepatocytes. At the therapeutic concentrations, either palonosetron or M9 does not induce the acitivity of these enzymes.

4.4.2.2 Is the drug a substrate and/or inhibitor of P-glycoprotein transport process?

The sponsor did not conduct any studies related to P-gp transporters.

4.4.2.3 What interaction data are available? What is the impact?

Metoclopramide was given concomitantly with palonosetron in a Phase I study. Administration of multiple oral doses of metoclopramide 10 mg Q.I.D. does not have a significant effect on the pharmacokinetics of a single I.V. dose of 0.75 mg palonosetron. Also, a single I.V. dose of 0.75 mg palonosetron does not have a relevant effect on the steady-state pharmacokinetics of metoclopramide (10 mg Q 6 hrs). It should be noted that the metoclopramide dose used in this study is lower than the dose recommended for the prevention of chemotherapy-associated nausea and vomiting. On the other hand, the palonosetron dose used was higher than that proposed by the sponsor.

There is no need for dosage adjustment of metoclopramide when administered concomitantly with palonosetron.

4.5 General Biopharmaceutics

4.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparable exposure?

The to-be-marketed formulation was used in the Phase 3 trials. The formulation used in the Phase 2 dose ranging study was different. However, both formulations were solutions with palonosetron hydrochloride completely dissolved in the formulation. Thus, there is no bicequivalence issue.

4.6 Analytical Section

4.6.1 Which moieties have been selected for analysis and why?

The concentrations of palonosetron and its major metabolite, M9, in plasma and urine samples were determined by validated analytical methods. M9 is a major metabolite of palonosetron. It has low activity (at least 100 times lower than palonosetron) as a 5-HT_3 receptor antagonist and is present in plasma at low concentrations.

A suspected compound, exists as a related impurity of the drug substance. Efforts were made to determine the potential of its formation in vivo. A method was used to detect the presence of and its metabolite in human plasma and urine samples (detection limit: ~10 ng/L (plasma) and 100 ng/L (urine) for and ~500 ng/L (plasma) and 2000 ng/L (urine) for . There was no indication of formation following single IV dose administration of palonosetron 0.75 mg.

4.6.2 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total palonosetron or M9 was measured. Plasma protein binding for palonosetron was constant over the concentration range of 5.15-412 ng/mL.

4.6.3 What analytical methods are used to assess concentrations?

Three analytical methods have been utilized to measure palonosetron and M9 in plasma samples during the development of palonosetron.

(1) Method for Determination of Palonosetron and M9 (JAR B-1009)
This method was used to measure palonosetron in plasma in Studies 2092. The validation results are given below.

Parameter	Palonosetron	M9
Linearity		
Precision (%CV)	< 15% (except one out of the 4 runs at the lowest conc.: 25.7%)	≤ 15.7%
Accuracy (% bias)	< 20%	< 20%
Stability (-20°C for > 6 wks)		
Selectivity		

(2) Method for Assay of Palonosetron (RS-25259) and M9 (RS-17825) (IAR-B-1058)

Parameter	Palonosetron	M9
Linearity		
Precision (%CV)	≤ 19.3%	≤ 25%
Accuracy	≤ 20% (except for the lowest conc of 20 ng/L: <40%)	≤ 15%
Stability (24h at RT)		
Selectivity	Information not provided.	

(3) Method for Determination of Palonosetron and M9 (PALO-99-09; July 2001)
The method was developed and validated by
The assay was used to quantitate plasma palonosetron and M9 concentrations in studies

PALO-99-03, PALO-99-04, and PALO-99-05 for the population PK analysis. The method can be used to detect [redacted] in human plasma. No interference was observed for [redacted] There are interference peaks mimicing a [redacted] concentration of about 500-1000 ng/L.

Parameter	Palonosetron	M9
Detection Limit	~ 5 ng/L	~ 5 ng/L
Linearity	[redacted]	
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.

B. Urine samples

The method of analysis for urine samples developed by Syntex and [redacted] were similar to the methods for plasma samples described above with some modifications. Studies 0101 and 0100 utilized the [redacted] method. The [redacted] assay was employed in the Helsinn-sponsored trials PALO-99-33, PALO-99-34, PALO-99-35 and PALO-99-51.

Table: Validation results for the [redacted] Method for assay of urine samples

Parameter	Palonosetron	M9
Linearity	[redacted]	
Precision (%CV)	< 5%	< 10.3%
Accuracy (%bias)	< 21%	< 11%
Stability (-20°C for > 55 days; freeze/thaw, 24h at RT, 60h in autosampler)	[redacted]	
Selectivity	No interference observed in blank plasma samples	No interference found in blank plasma samples

Table: Validation results for the [redacted] Method* for assay of urine samples

Parameter	Palonosetron	M9
Detection Limit	~ 50 ng/L	~ 200 ng/L
Linearity	[redacted]	
Precision (%CV)	≤ 12.6%	≤16.47%
Accuracy (%bias)	≤11.3%	≤8.97%
Stability (freeze/thaw, 24h at RT, 60h in autosampler)	Mean: 92.55-105.18%	Mean: 74.07**-100.43%
Selectivity	No interference observed in blank plasma samples	No interference found in blank plasma samples

*The method could be used to detect [redacted] in human urine.

**Low assay was found for samples with low M9 concentrations (658 and 976 ng/L, respectively). For samples containing higher M9 concentrations, the decrease in M9 concentration in the stability testing was ≤11.04%.

15 pages redacted from this section of the approval package consisted of draft labeling

6. APPENDICES

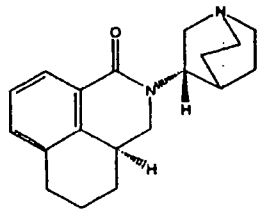
6.1 Individual Study Review

IN VITRO METABOLISM

Study #PALO-02-01:
The metabolism of ^{14}C-palonosetron in human hepatic microsomes, cryopreserved hepatocytes and fresh liver slices – Investigation of the conversion of ^{14}C-palonosetron to ——

Background:

—— is a compound with 5-HT_3 receptor antagonist activity and is a suspected This study was designed to investigate the potential of in vivo conversion of palonosetron to —— using three in vitro test systems – microsomes , cryopreserved hepatocytes and fresh liver slices. Microsomes were prepared from 6 human liver samples, freshly prepared human liver slices were obtained from 2 donors and cryopreserved human hepatocytes were pooled from 6 donors. The radiochemical purity of ^{14}C-palonosetron was 92.10%.



—— Paonosetron

Incubation of ^{14}C-Palonosetron with Human Hepatic Microsomes:

Cytochrome P450 isozyme activities in the pooled microsomal preparation were confirmed using probe substrates as indicated in the table below.

Table: CYP activities of the pooled microsomal preparation

CYP Isozyme	1A2	2C9	2C19	2D6	3A4
Probe Substrate	ethoxyresorufin	Tobutamide	S-Mephenytoin	Bufuralol	Testosterone
Reaction	O-deethylation	4-hydroxylation	4'-hydroxylation	1'-hydroxylation	6β-hydroxylation
CYP Activity[1]	18.13	144.8	43.50	55.86	632.5

[1]pmol/min/mg protein

^{14}C-Palonosetron —— was incubated with microsomal protein —— in a potassium phosphate buffer —— in a shaking water bath. After pre-incubation, reactions were initiated by the addition of a standard NADPH-generating system. In control incubations the NADPH-generating system was omitted. Incubations were terminated after 5, 15, 30 or 60 min by addition of ice-cold acetonitrile. The sample was centrifuged at 8000 g for 10 min and the resultant supernatant was removed for liquid scintillation counting (LSC) and —— analysis.

Results

Using an [redacted] method [redacted] was found to be resolved from palonosetron. The lower quantitation limit for [redacted] ng/mL, which is equivalent to a [redacted]% conversion of palonosetron at a substrate concentration of 100 • M. Following incubation of palonosetron (5 or 100 • M) with human liver microsomes in the presence of NADPH there was no evidence of [redacted] formation.

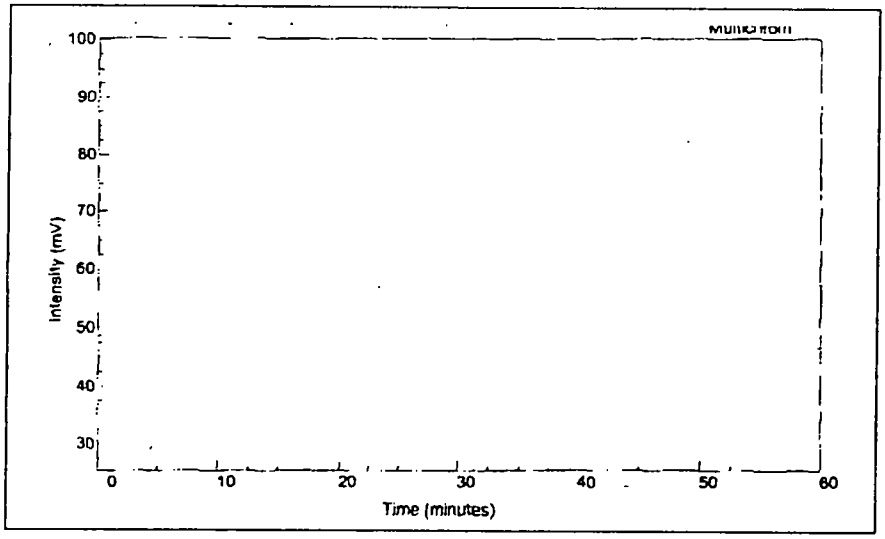


Figure: [redacted] showing resolution of authentic standards of palonosetron and

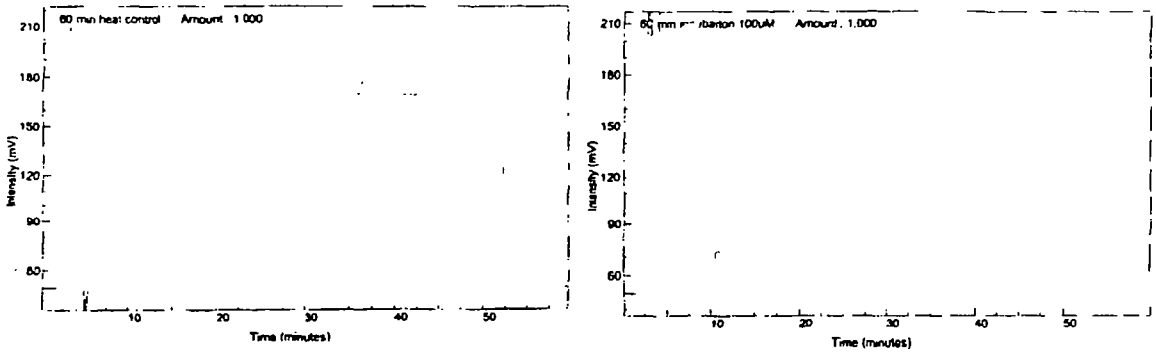


Figure: [redacted] of samples obtained following incubation of C-palonosetron (100 • M) with pooled human liver microsomes in the absence (left panel) and presence (right panel) of NADPH for 60 min.

Reviewer's note:

1. [redacted] does not appear to separate [redacted] from palonosetron. Therefore, it is not useful for the purpose of this study.
2. The [redacted] (e.g., Figure 7 on page 56) should be magnified so that trace [redacted] can be observed if formed.

3. Based on the intensity at peak — as shown in the chromatograms, little palonosetron is metabolized in 60 minutes under the experimental conditions used.

Incubation of ^{14}C-Palonosetron with Cryopreserved Human Hepatocytes:

Cryopreserved hepatocytes from 6 individual donors were thawed and the viability of each thawed preparation was determined by trypan blue exclusion. The cells were then proportionately pooled. Incubations, which were performed — contained ^{14}C-palonosetron —) and hepatocytes — in a tissue culture medium (Dulbeccos Modified Earle's Medium, DMEM). In control incubations the hepatocytes were omitted. Incubations were terminated after 0.5, 1, 3 or 6 h by addition of ice-cold methanol to each well. In parallel incubations the metabolic competence of the pooled hepatocyte preparation was determined by incubation of ^{14}C-7-ethoxycoumarin (100 • M) under identical conditions to those described for ^{14}C-Palonosetron.

Results

The metabolic competence of the cryopreserved human hepatocytes was confirmed by assessing the rate of metabolism of ^{14}C-ethoxycoumarin over a 6h incubation period. Following incubation of ^{14}C-Palonosetron, there was no evidence of formation of ——— 'see figures below).

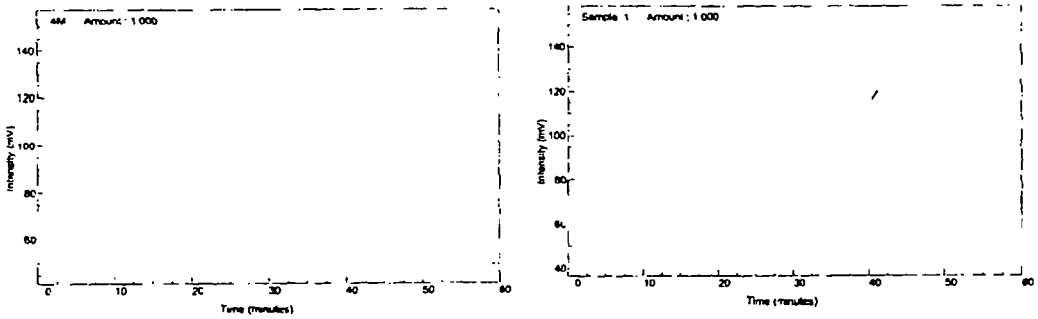


Figure: ——— of samples obtained following incubation of ^{14}C-Palonosetron (100 • M) with cryopreserved human hepatocytes (Left panel) and DMEM (right panel) for 6 h

Reviewer's note:

Again, based on the intensity at peak — as shown in the chromatograms, little palonosetron is metabolized in 60 minutes under the experimental conditions used.

Incubation of ^{14}C-Palonosetron with Human Liver Slices:

Freshly prepared liver slices from a single male and a single female donor were used in this study. Incubations, which were performed — — ^{14}C-palonosetron —), liver slices (2 slices per well) in a final volume of 250 • Ł tissue culture medium (DMEM). In control incubations the

slices were omitted. After 0.5, 1, 3 or 6 h the media was removed from the well and aliquots taken for [redacted] analysis.
In parallel incubations the metabolic competence of the liver slices was determined by incubation of ^{14}C-7-ethoxycoumarin (100 • M) under identical conditions to those described for ^{14}C-palonosetron.

Results

The metabolic competence as assessed by the rate of metabolism of ^{14}C-7-ethoxycoumarin over a 6 h incubation period indicated that liver slices from the female donor had higher metabolic activities compared to the male liver slices. Following incubation of ^{14}C-palonosetron (5 • M or 100 • M) in either the male or female liver slices, no formation of [redacted] was detected. Results using liver slices from the female donor are shown in the figures below.

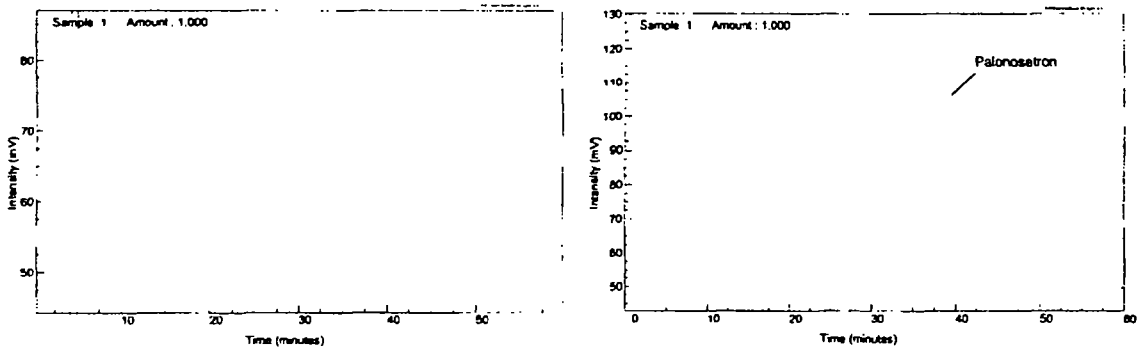


Figure: [redacted] of samples obtained following incubation of ^{14}C-palonosetron (100 • M) with female human liver slices (left panel) and DMEM (right panel) for 6 hours.

[redacted] Analysis:

The sponsor performed [redacted] analysis to determine the [redacted] content in ^{14}C-Palonosetron standard and post incubation supernatants. In all the samples tested, [redacted] content was comparable to the ^{14}C-Palonosetron standard. There was no indication of [redacted] formation in the metabolism of palonoseron under the study conditions. The results are listed in the table below.

Table: [redacted] content in ^{14}C-Palonosetron standard and post incubation supernatants as determined by [redacted]

Sample	Relative Mole % Composition	
	Palonosetron	[redacted]
[^{14}C]-Palonosetron Standard	99.69	0.31
	99.72	0.28
Non-radiolabelled Palonosetron Microsomes, [^{14}C]-Palonosetron, 100 µM, 1 h Incubation + NADPH	99.89	0.11
	99.64	0.36
Hepatocytes, [^{14}C]-Palonosetron, 100 µM, 6 h Incubation	99.78	0.22
Male Liver Slices, [^{14}C]-Palonosetron, 100 µM, 6 h Incubation	99.80	0.20
Female Liver Slices, [^{14}C]-Palonosetron, 100 µM, 6 h Incubation	99.81	0.19

Sponsor's Conclusion:

^{14}C-palonosetron does not undergo conversion to [redacted] in human microsomes, hepatocytes or liver slices under the experimental condition used in this study.

Reviewer's Comments:

Based on the information provided, there was no indication of [redacted] formation under the study conditions. However, the chromatograms showed similar peak intensity for the control sample compared to the sample obtained following incubation with microsomes or hepatocytes. Upon request, the sponsor indicated that approximately 1% of palonosetron was metabolized under the experimental conditions. Because of this, the [redacted] method would not be sensitive enough to detect the formation of [redacted] unless it accounted for at least 60% of the metabolites.

The sponsor provided additional evidence on [redacted] analysis with microsomal system but the sensitivity of the study was unclear. In the studies using liver slices, there was more metabolism of polonosetron compared to microsomal or hepatocyte system and no [redacted] was detected. However, the sponsor did not indicate how much palonosetron was metabolized in these studies. Overall, it appears that [redacted] ; not a major metabolite of palonosetron. No further information was requested because the QT data and cardiac safety profiles reflected the overall effect following IV administration of palonosetron, including the effect of [redacted] if any was formed *in vivo* .

Study #PALO-98-02:
Characterization of human cytochrome P450 enzymes involved in the in vitro metabolism of palonosetron, the interaction of palonosetron and M9 with cytochrome P450, and possible induction of cytochrome P450 by palonosetron and M9

<u>Human cytochrome P450 enzymes in the metabolism of palonosetron</u>

Both cDNA-expressed enzymes (GENTEST microsomes) and human liver microsomes (a set of 14 samples) were used in this study. Enzyme kinetic parameters Km and Vmax were estimated. The rates of metabolism were correlated with the metabolism of enzyme-selective probe substrates by the same set of liver microsomes to estimate the relative contribution of the various human cytochrome P450 enzymes in the metabolism of palonosetron.

Incubations were performed — containing 0.1 M potassium phosphate buffer pH 7.4, 3 mM NADPH, ^{14}C-palonosetron, human liver microsomes (—) or GENTEST microsomes — . Controls were incubated without NADPH. The reactions were terminated by the addition of acetonitrile/acetic acid (50 : 2.7, v/v). After centrifugation, the supernatant was subject to — analysis.

Results

<u>GENTEST microsomes:</u>
Preliminary experiments were performed with CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4 to identify the cytochrome P450 enzymes involved in the *in vitro* metabolism of palonosetron. Incubations were performed in duplicate for 60 minutes using a microsomal protein concentration of 2 mg/mL and a ^{14}C-palonosetron concentration of 400 • M. The results indicated that CYP1A1 and CYP2D6 were the major enzymes involved in the metabolism of palonosetron, followed by CYP 1A2 and CYP3A4. CYP2C9 showed some formation of the more polar metabolites (see table below).

Three metabolites were observed in *in vitro* studies. Besides N-oxide metabolite (M9), the other two metabolites were more polar. No other in vitro metabolites were detected in the study.

Table: Formation of palonosetron metabolites following incubation of palonosetron (400 • M) with GENTIST microsomes for 60 minutes

P450 enzyme	Enzymatic activity (pmol/min/mg protein)	
	N-oxide metabolite of palonosetron (M9)	polar metabolites of palonosetron
CYP1A1	17.3	35.3
CYP1A2	3.3	10.0
CYP2A6	< 1.0	< 1.9
CYP2B6	< 1.0	< 1.9
CYP2C9	< 1.0	3.0
CYP2D6	34.1	59.1
CYP2E1	< 1.0	< 1.9
CYP3A4	8.5	13.5

Subsequently, incubations were performed for 60 minutes with CYP 1A1, CYP 1A2, CYP2D6 and CYP3A4 at ^{14}C-Palonosetron concentrations of 10, 20, 50, 80, 120, 200 and 400 • M. The rate of formation for M9 and the polar metabolites are presented in separate tables on the following page. For CYP 1A2, Km and Vmax were not estimated with respect to the formation of M9 because the rate of formation of M9 declined at concentrations higher than 120 • M. For CYP3A4, estimates of enzyme kinetic parameters might not be accurate because of the "delay" phenomenon. The Km values related to M9 formation were similar for CYP1A1 and CYP2D6.

Sponsor's conclusion:

- Based on the results generated from the GENTEST microsomes, CYP2D6 is the major enzyme for the metabolism of palonosetron followed by CYP1A1.

Reviewer's comments:

1. The Km values indicate that formation of M9 and the polar metabolites through 2D6 pathway will not be saturated at the therapeutic concentrations for extensive metabolizers.
2. Both the CYP3A4 and CYP1A2 studies appeared to show a "delay" phenomenon related to M9 formation (see the first table on the following page). The Km value provided by the sponsor for CYP3A4 does not seem reasonable. On the other hand, they do not follow the conventional Michaelis-Menten kinetics.

Table: Rate of M9 formation at various palonosetron concentrations and Km and Vmax values for CYP1A1, CYP1A2, CYP2D6 and CYP3A4

Palonosetron concentration (µM)	Enzymatic activity (pmol/min/mg protein)			
	CYP1A1	CYP1A2	CYP2D6	CYP3A4
10	< 0.4	< 0.4	5.4	< 0.4
20	3.2	< 0.4	8.8	< 0.4
50	6.3	< 0.4	16.8	< 0.4
80	8.3	2.4	25.7	< 0.4
120	9.8	5.6	30.0	3.5
200	9.3	4.7	28.0	4.6
400	10.1	3.2	27.5	4.2
Enzyme kinetic parmmeters				
K_m (µM)	39 ± 11	-	41 ± 15	39 ± 38
V_{max}	11.6 ± 0.8	-	34.0 ± 3.6	4.9 ± 0.8

- = enzyme kinetic parameters could not be calculated.

Table: Rate of formation for polar metabolites at various palonosetron concentrations and Km and Vmax values for CYP1A1, CYP1A2, CYP2D6 and CYP3A4

Palonosetron concentration (µM)	Enzymatic activity (pmol/min/mg protein)			
	CYP1A1	CYP1A2	CYP2D6	CYP3A4
10	2.2	< 0.4	8.5	< 0.4
20	4.0	3.5	15.6	< 0.4
50	7.7	3.8	26.4	2.3
80	12.8	4.8	37.4	2 0
120	11.5	5.6	42.7	3.0
200	13.6	6.5	45.4	4.5
400	19.6	9.9	52.1	6.4
Enzyme kinetic parameters				
K_m (µM)	93 ± 29	104 ± 48	55 ± 6	287 ± 111
V_{max}	22.7 ± 2.7	11.4 ± 2.1	59.7 ± 2.1	10.8 ± 2.3

Human liver microsomes:
Incubations with pooled human liver microsomes — were performed for 60 minutes at ^{14}C-Palonosetron concentrations of 10, 20, 50, 80, 120, 200 and 400 • M. The Km and Vmax values are 289±56 • M and 179±19 pmol/min/mg protein, respectively, for M9, and 201±42 • M and 244±25 pmol/min/mg protein, respectively, for the polar metabolites.

Incubations with individual human liver microsomes — were performed for 60 minutes at a ^{14}C-Palonosetron concentration of 200 • M. The rates of metabolism were correlated with the metabolism of enzyme-selective probe substrates by the same set of liver microsomes. The correlations for each cytochrome P450 enzyme is listed in the table below. The formation of both the N-oxide metabolite (M9) and the polar metabolites were significantly correlated with CYP2D6 activity (1'-hydroxylation of bufuralol). In addition, the formation of M9 was almost significantly correlated ($p = 0.0508$) with CYP3A activity (6β-hydroxylation of testosterone). The P-value for the correlation between the formation of the polar metabolites and CYP3A activity was 0.0861.

Table: Correlation coefficient (R) between the metabolism of cytochrome P450 probe substrates and the formation of in vitro metabolites of palonosetron (200 • M).

	CYP1A2	CYP2A6	CYP2B6	CYP2C9	CYP2D6	CYP2E1	CYP3A
N-oxide metabolite of palonosetron (M9)	0.2309	-0.3644	0.2487	-0.2739	0.5807*	-0.2365	0.5317
polar metabolites of palonosetron	0.2479	-0.3541	0.2491	-0.4103	0.7352**	-0.3539	0.4759

Student's *t*-test: * $p < 0.05$; ** $p < 0.01$

Conclusion:

- Among the cytochrome P450 enzymes investigated (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A), the correlation study suggested that CYP2D6 is the major enzyme for the metabolism of polonosetron followed by CYP3A.

Comment:

- The sponsor did not investigate the role of CYP2C19 in the metabolism of palonosetron and did not explain why.

Potential of palonosetron and M9 as inhibitor or inducer of cytochrome P450 enzymes

Evaluation of inhibition potential of palonosetron or M9:
In preliminary experiments, incubations with cytochrome P450 enzyme-selective probe substrates were performed in the absence and presence of six concentrations of palonosetron or M9: 1, 10 and 100 ng/mL, and 3, 30 and 300 • M. The latter three

concentrations were based on the obtained Km values. Incubations were performed in duplicate. In these preliminary experiments, incubations were performed with 0.4 • M 7-ethoxyresorufin (CYP 1A2), 10 • M coumarin (CYP2A6), 10 • M 7-ethoxy-4-trifluoromethylcoumarin (CYP2B6),20 • M diclofenac (CYP2C9),20 • M bufuralol (CYP2D6), 500 • M chlorzoxazone (CYP2E 1) and 100 • M testosterone (CYP3A). The results, expressed as % residual activity relative to the controls (controls = 100%), are presented in the following table.

Table: Percent of enzymatic activity in the metabolism of probe substrates in the presence of various concentrations of palonosetron or M9

Sample	Concentration	CYP1A2	CYP2A6	CYP2B6	CYP2C9	CYP2D6	CYP2E1	CYP3A
Control	-	100	100	100	100	100	100	100
palonosetron	1 ng/ml	99	100	101	101	96	87	97
	10 ng/ml	97	100	103	104	97	94	96
	100 ng/ml	99	95	100	103	93	83	89
	3 µM	99	97	102	98	94	83	92
	30 µM	95	96	98	103	88	80	83
	300 µM	69	94	88	98	60	97	68
M9	1 ng/ml	91	95	99	101	99	94	87
	10 ng/ml	103	100	101	93	98	98	77
	100 ng/ml	76	98	93	94	98	93	80
	3 µM	81	99	98	86	97	87	84
	30 µM	85	88	96	94	95	87	96
	300 µM	88	89	93	93	83	83	91

Based on these results, two concentrations of palonosetron were selected in order to establish the inhibition constants Ki: 300 and 500 • M for CYPI A2, and 300 and 600 • M for CYP2D6 and CYP3A, respectively. Seven probe substrate concentrations were used in the study. Palonosetron was found to be a competitive inhibitor of cytochrome P450 1A2, 2D6 and 3A. The inhibition constants Ki was 201±52 • M for CYP1A2, 118±13 • M for CYP2D6, and 423±119 • M for CYP3A.

Evaluation of cytochrome P450 induction by palonosetron or M9

Freshly isolated human hepatocytes were used to investigate *in vitro* the ability of palonosetron and M9 to induce enzyme activities catalyzed by CYP 1A2, CYP2D6 and

CYP3A. Cells were incubated for 72 hours with P450 probe substrates (phenacetin for CYP1A2, dextromethorphan for CYP2D6 and nifedipine for CYP3A4) in the absence and presence of 100 ng/mL palonosetron or M9. For CYP 1A2 and CYP3A, reference inducers (3MC at 2.5 • M and rifampicin at 50 • M) were incubated in parallell to validate the experiments.

Results

CYP1A2:

In the presence of the reference inducer, 3MC, phenacetin deethylase activity was significantly ($p<0.05$) increased by a factor of 24. This effect was expected and validated the experiment.

Neither palonosetron nor M9 did significantly modify phenacetin deethylase activity at 100 ng/mL over 72 hours of contact with this batch of hepatocytes.

Table: Phenacetin deethylase activity in human hepatocytes after a 72-hour incubation period in the presence of test compounds or reference inducer 3MC.

compound concentration	control	Palonosetron 100 ng/mL	M9 100 ng/mL	3MC 2.5 µM
phenacetin deethylase activity (nmol/h/mg protein)				
mean	1.11	0.95	1.01	26.47*
	+/-	+/-	+/-	+/-
std dev	0.1	0.12	0.05	4.24
% of control	*100*	*85*	*91*	*2378*

CYP2D6:

No reference inducer was available to validate a CYP2D6 induction experiment.

Neither palonosetron nor M9 did significantly modify dextromethorphan N-demethylase activity at 100 ng/mL over 72 hours of contact with this batch of hepatocytes.

Table: Dextromethorphan N-demethylation activity in human hepatocytes after a 72-hour incubation period in the presence of test compounds

compound concentration	control	Palonosetron 100 ng/mL	M9 100 ng/mL
dextromethorphan N-demethylase activity (nmol/h/mg protein)			
mean	0.56	0.59	0.57
	+/-	+/-	+/-
std dev	0.03	0.05	0.03
% of control	*100*	*104*	*102*

Dextromethorphan demethylase activity at T0: 1.24 ± 0.04 nmol/h/mg cellular protein.

CYP3A4:

In the presence of the reference inducer, rifampicin, nifedipine oxidase activity was significantly ($p<0.05$) increased by a factor of 5.4.

Neither palonosetron nor M9 did significantly modify nifedipine oxidase activity at 100 ng/mL over 72 hours of contact with this batch of hepatocytes.

Table: Nifedipine oxidase activity in human hepatocytes after a 72-hour incubation period in the presence of test compounds or reference inducer rifampicin

compound concentration	control	Palonosetron 100 ng/mL	M9 100 ng/mL	Rifampicin 50 µM
nifedipin oxidase activity (nmol/h/mg protein)				
mean	6.0	5.75	5.11	32.29*
	+/-	+/-	+/-	+/-
std dev	0.73	0.70	1.14	4.06
% of control	*100*	*95*	*85*	*535*

Conclusion:

- Inhibition of CYP1A2, CYP2D6 and CYP3A4 by palonosetron was observed at high palonosetron concentrations. At the therapeutic concentrations, there was no significant inhibition for all CYP enzymes studied.

- For M9, there was no inhibition at the therapeutic dose for all the CYP enzymes studied.
- The results obtained from the induction study indicate that at clinically relevant concentrations, palonosetron and M9 incubated with hepatocytes for 72 hours do not induce CYP1A2, 2D6 or CYP3A4.

PROTEIN BINDING

Binding of palonosetron to human plasma protein was investigated using ^{14}C-labeled compound and equilibrium dialysis technique (24 hrs at 37°C). Over the concentration range of 5-412 ng/mL, the percent bound was approximately constant and averaged 61.8%.

Table: Percent bound of palonosetron in human plasma at various palonosetron concentrations

Palonosetron Conc., ng/mL	5.15	10.3	25.8	51.5	103	206	412
%Bound	61.8±1.4	62.0±0.7	61.5±2.0	61.0±1.5	63.0±0.8	61.6±1.9	62.0±2.8

Study #: RGR/259 Study Date: Jun 1993

Type of Study: Mass balance Study

Study RGR/259 is entitled,

"PLASMA PHARMACOKINETICS, METABOLISM AND EXCRETION OF [^{14}C]-RS-25259-197 AFTER INTRAVENOUS INJECTION"

Objectives

- To determine the metabolic profile of palonosetron (referred to as RS-25259 throughout the study report) in plasma and urine following administration of a single I.V. injection of [^{14}C]-RS-25259 to human subjects.

Study Design

Open-label, single dose, disposition study in healthy male and female subjects

Subjects 6 healthy adult subjects (3 males/3 females)

Treatment Subjects received single I.V. doses of [^{14}C]-RS-25259 (10 µg/kg or 0.8 µCi/kg).

PK Sampling Samples were collected for determination of the metabolic profile of RS-25259 in plasma at -30 (pre-dose), 5, 15 and 30 min, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120 and 144 hrs post-dose.

Urine samples were also collected at 0 (pre-dose), (0-4), (4-8), (8-12), (12-24), (24-48), (72-96), (96-120), (120-144), (144-168), (168-192), (192-216) and (216-240) hrs post-dose.

Stool samples were collected at 24-hr intervals for 10 days, including a baseline 24 hr interval pre-dosing.

Analytical Assay

Total radioactivity in all biological samples was quantified using scintillation counting. The metabolic profiles were determined using

LOQ and LOD of the utilized analytical assays were not reported.

Pharmacokinetics

The following pharmacokinetic parameters were determined for total radioactivity and the free form of RS-25259 (RS-25259-007) after single dose administration of [^{14}C]-RS-25259: **T_{max}, C_{max}, $t_{1/2}$, AUC_{0-96}, $AUC_{0-\infty}$, CL* and V_d*.**

* PK parameter only calculated for RS-25259-007.

Results and Conclusions

- The free form of RS-25259 (RS-25259-007) accounts for 71.9% of total radioactivity in plasma over a 96-hr period following single dose administration. No other metabolites were detected in plasma over the same period.
- RS-25259 distributes extensively in the body as evidenced by a large Vd (8.34 L/kg).
- Systemic elimination of RS-25259 is slow after single I.V. dose administration with a mean apparent half-life of 37 hrs.
- *In vitro* binding data indicate that RS-25259 is 62% bound to plasma proteins.
- 79.5% of the administered dose is recovered in urine over a 144 hr period post-dose with 39.3% of the total recovered dose in urine being RS-25259. Overall, renal clearance amounts to 42% of the systemic clearance pointing to a major role for the kidneys in the clearance of RS-25259 in humans.
- About 50% of the administered dose of [^{14}C]-RS-25259 is metabolized in humans. The major metabolites detected in urine are the N-oxide-RS-25259 (M9; accounts for 12.5% of the administered dose) and an aryloxide-RS-25259 (M4; accounts for 10.9% of the administered dose).
- The disposition of RS-25259 is similar between males and females after I.V. administration.

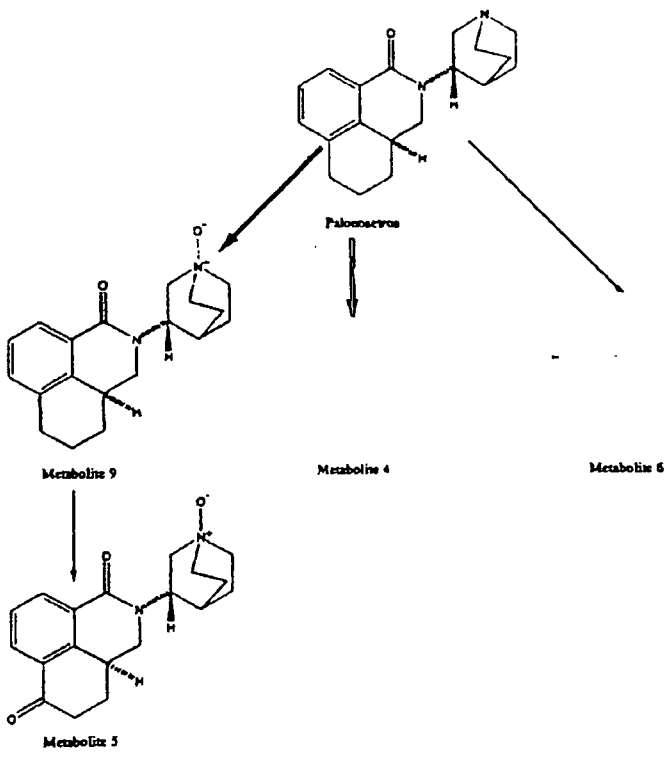
Table 1. Summary of the mean PK parameters for total radioactivity and the free form of RS-25259 (M9)

Parameter	Total Radioactivity	RS-25259-007
T_{max} (hr)	0.0833 (± 0)	0.0833 (± 0)
C_{max} (ng-Eq/mL)	3.93 (± 1.09)	3.13 (± 0.98)
$T_{1/2}$ (hr)	39.4 (± 7.9)	37.4 (± 14.2)
AUC 0–96 hr (ng-Eq·hr/mL)	76.4 (± 7.8)	55.2 (± 9.3)
% AUC 0–96 hr for Total Radioactivity	100	71.9 (± 5.7)
AUC 0–∞ (ng-Eq·hr/mL)	89.2 (± 9.8)	65.0 (± 13.8)
% AUC 0–∞ for Total Radioactivity	100	72.6 (± 11.3)
Systemic Clearance (mL·kg^{-1}·hr^{-1})	–[b]	160 (± 35)
Volume of Distribution (ß) (L·kg^{-1})	–[b]	8.34 (± 2.45)

[a]Mean (± SD), N = 6
[b]Not calculated

Biotransformation of palonosetron

The mass balance study did not confirm the position of hydroxylation of Metabolite M4. Further studies established M4 as the S form of C6-OH-palonosetron. Therefore, in man, palonosetron is metabolized by 2 principal biotransformation routes: oxidation at the nitrogen to form the N-oxide (M9) and hydroxylation to form 6-S-hydroxy-palonosetron (M4).



Bold arrows indicate major pathways

Study #RGR/25259S2092/USA:
A single ascending dose safety and pharmacokinetics study of IV RS-25259 in healthy volunteers

Objectives
(1) To monitor the safety and determine the maximum tolerated dose, and
(2) To study the pharmacokinetics of single IV doses of RS-25259-197.

Study Design:
This was a randomized, double-blind, placebo-controlled study of single ascending IV doses of RS-25259-197. Subjects were randomized in the ratio of 3:1 to receive either study drug or placebo.

- Subjects: 80 healthy men (age: 18-44 yrs; wt: 54-106 kg; ht: 160-193 cm; race: 72 Caucasians, 5 Blacks and 3 Asians)
- Treatments: IV infusion (over 5 min) of placebo and 9 dose levels of palonosetron (0.3, 1, 3, 10, 20, 30, 45, 60, and 90 • g/kg). Each dose cohort consisted of 8 subjects with 2 receiving placebo and 6 receiving the study drug. A second cohort of 8 subjects were randomized at the 10 • g/kg level during the trial because 2 subjects in the first 10 • g/kg cohort had elevated liver enzymes.

Sample Collection
Blood samples: predose, and at 5, 10, 15, 30 and 45 minutes and 1, 1.5, 2, 4, 6, 8, 12, 24, 36 and 48 hrs after completion of IV infusion. Subjects in the second 10 • g/kg cohort and those receiving doses higher than 10 • g/kg had a blood sample drawn at 72 hours and 1 week (168 hr) after dosing.
Urine samples: pre-dose, and 0-4, 4-8, and 8-24 hr postdose. (Samples were collected but no assay was reported.)

Assay:
Plasma samples were assayed for palonosetron and the N-oxide metabolite (M9) using a — RIA method. The quantitation limit is — ng/mL for palonosetron and — ng/L for M9.

Results

(A) Palonosetron (RS-25259):

Following the 5-minute IV infusion, a biphasic decline of plasma palonosetron concentration was observed with the mean terminal half-life ranging from 33.7 to 54.1 hrs for the various doses studied. The mean concentration-time profiles and mean pharmacokinetic parameters for the various doses of palonosetron are shown in the following figure and table, respectively.

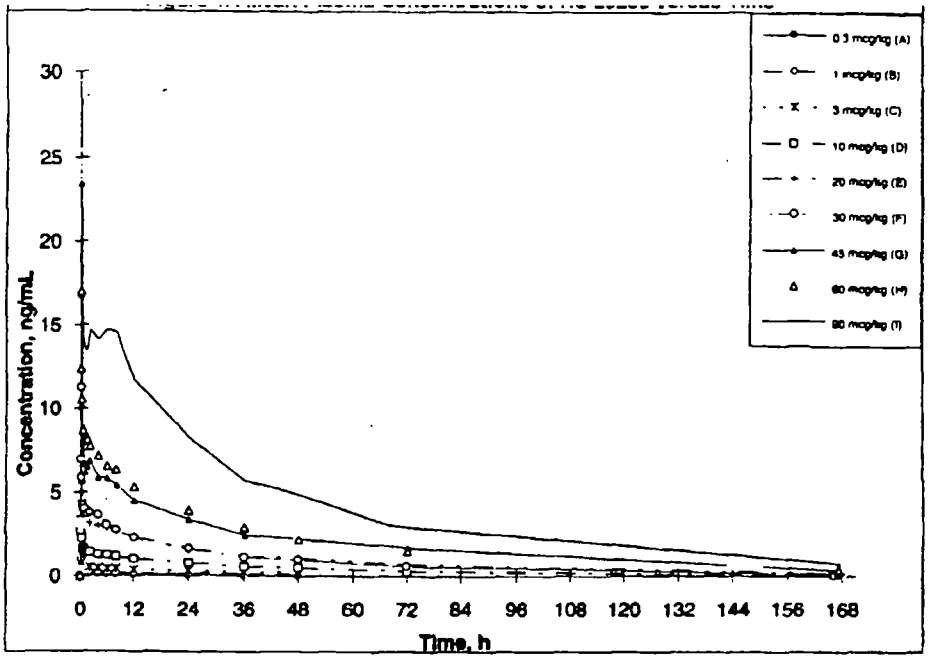


Figure: Mean plasma palonosetron concentration-time profiles following single IV infusion

Table: Mean pharmacokinetic parameters following single IV infusion of palonosetron

Dose (• g/kg)	Cmax (ng/mL)	Tmax (hr)	$AUC_{0-\infty}$ (ng.h/mL)	T1/2 (hr)	CL (mL/min/kg)	Vz (L/kg)
0.3	0.114 ± 0.063	0.74 ± 1.60	5.80 ± 3.46	54.1 ± 36.6	1.11 ±0.55	3.85 ± 0.65
1.0	0.35 ± 0.21	0.83 ± 1.56	9.35 ± 2.59	33.7 ± 16.8	1.89 ± 0.46	5.31 ± 2.35
3.0	0.92 ± 0.25	0.083 ± 0.0	29.8 ± 9.02	47.2 ± 14.7	1.81 ± 0.55	6.88 ± 0.87
10	3.53 ± 1.44	0.090 ± 0.024	65.7 ± 14.5	35.0 ± 8.8	2.66 ± 0.61	7.83 ± 1.81
20	5.71 ± 2.93	0.556 ± 0.732	153 ± 44.1	37.0 ± 6.2	2.36 ± 0.77	7.27 ± 1.19
30	11.5 ± 8.71	0.403 ± 0.782	150 ± 56.1	37.8 ± 6.6	3.90 ± 0.181	12.6 ± 5.52
45	26.0 ± 23.7	0.333 ± 0.573	348 ± 137	41.2 ± 7.3	2.39 ± 0.72	8.23 ± 1.90
60	17.1 ± 4.37	0.083 ± 0.0	370 ± 70.1	41.8 ± 9.6	2.78 ± 0.49	9.78 ± 1.17
90	23.9 ± 3.87	1.40 ± 3.23	750 ± 271	40.2 ± 6.6	2.17 ± 0.58	7.50 ± 2.25
Mean ± SE	-	0.083	-	37.4 ± 14.2	160 ± 35 mL/h/kg	8.34 ± 2.45

Dose Proportionality:
Both AUC and Cmax from the above table were dose normalized to check for dose proportionality. The sponsor performed a statistical analysis and concluded that dose proportionality was not demonstrated.

(2) N-Oxide Metabolite (RS-17825 or M9)

Plasma concentrations of M9 were below the quantification limit (BQL) at dose levels of — • g/kg and below. Plasma concentrations were mostly BQL at the — g/kg dose level

but were quantifiable above this dose level. Maximal plasma concentrations occurred at a mean Tmax of 3.42-6.00 hrs over the 10- to 90-• g/kg dose range. The mean concentration-time profiles for M9 are illustrated in the figure below.

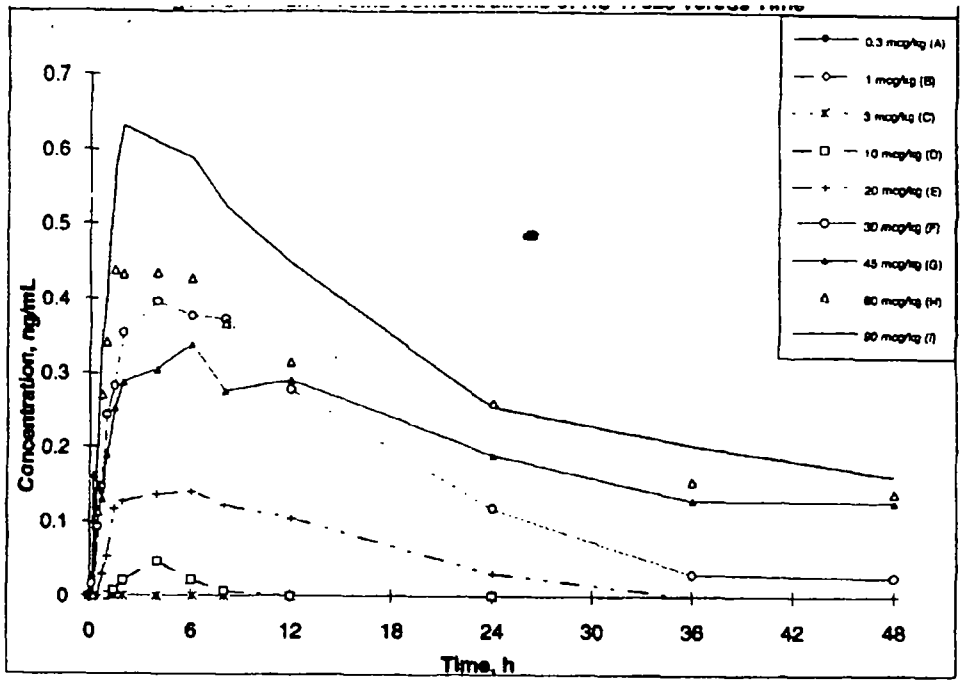


Figure: Mean concentration-time profiles for the metabolite M9 following single IV infusion of palonosetron

Mean pharmacokinetic parameters for the metabolite M9 is listed in the table below. AUC for M9 was 5.6±2.4% that of the parent compound.

Table: Mean PK parameters for M9 following single IV infusion of palonosetron

	Dose of RS-25259								
RS-17825 Parameter	0.3 µg/kg	1.0 µg/kg	3.0 µg/kg	10 µg/kg	20 µg/kg	30 µg/kg	45 µg/kg	60 µg/kg	90 µg/kg
C_{max} (ng/mL)	NC	NC	NC	0.102	0.156	0.443	0.469	0.525	0.703
T_{max} (hr)	NC	NC	NC	3.67	6.00	5.33	5.71	3.42	4.67
Half-life (hr)	NC	NC	NC	NC	19.6	19.3	54.3	39.6	33.3
Total AUC (ng.hr/mL)	NC	NC	NC	NC	5.51	10.3	23.8	20.4	25.0
AUC Ratio (RS-17825/ RS-25259)	NC	NC	NC	NC	0.0332	0.0927	0.0628	0.0581	0.0350

NC = not calculable because of BQL values.

Reviewer's Comment:

Dose Proportionality:
Both AUC and Cmax of palonosetron were dose normalized to check for dose proportionality. The sponsor performed a statistical analysis and concluded that dose proportionality was not demonstrated. This reviewer plotted dose normalized parameters versus dose (see figure below) and consider both AUC and Cmax were roughly dose proportional but with outliers.

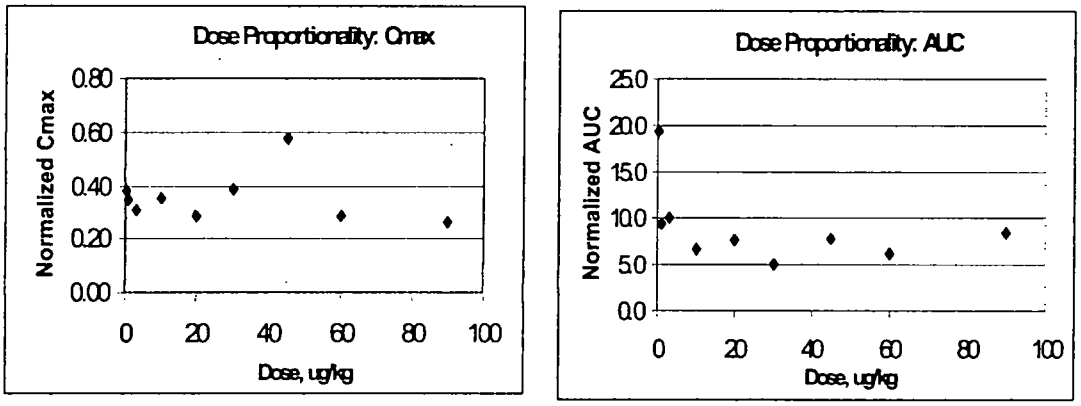


Figure : Dose Normalized Cmax (left panel) and AUC (right panel) vs. Dose

PALO-99-39:
The pharmacokinetics and metabolic disposition of 0.75 mg palonosetron IV in extensive and poor metabolizers of dextromethorphan, a CYP2D6 substrate (v.1.86, Jan-Mar 2000)

Background:
This study was conducted because of the following reasons:
(1) Palonosetron is metabolized by cytochrome P450 enzymes including CYP2D6, which shows polymorphism in the general population with 7-15% of Caucasians being poor metabolizers. In Phase 2 studies, some subjects had longer half-lives of palonosetron, suggesting the possibility of a polymorphic metabolism.
(2) [redacted] in the synthesis of palonosetron and, therefore, it is a specified related substance of palonosetron. It is also a compound with 5-HT_3 receptor antagonistic activity. Development of [redacted] was discontinued as it was suspected of causing cardiac arrhythmia in one subject. [redacted] is primarily metabolized in humans to [redacted] There was question as to whether palonosetron would be metabolized to [redacted] *in vivo*.

Objectives:
(1) To evaluate the pharmacokinetics of palonosetron and its main metabolite M9 in extensive and poor metabolizers of CYP2D6 following the administration of 0.75 mg palonosetron IV;
(2) To assess the presence of [redacted] and its [redacted] in plasma and urine; and
(3) to assess the safety and tolerability of a single IV dose of 0.75 mg palonosetron in poor and extensive metabolizers of CYP2D6 substrates.

Study design:
This was a single-dose study in healthy volunteers.

Subjects: 3 poor metabolizers and 3 extensive metabolizers of CYP2D6 substrate as phenotyped using dextromethorphan metabolism. Both groups had 2 males and 1 female (poor metabolizers - age: 39±20.5 yrs; ht: 175±8.1 cm; wt: 78.6±8.8 kg; extensive metabolizers – age 46±14.2 yrs; ht: 174±9.2 cm; wt: 72.4±16.0 kg).
- Definition of CYP2D6 poor metabolizers: >12.6 for the ratio of dextromethorphan: dextrorphan as measured in the 2-hour plasma sample following an oral dose of 30 mg dextromethorphan HBr.

Treatment: a single IV dose of palonosetron 0.75 mg, infused over 30 sec.

Sample collections:
Blood samples: pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 30, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hrs postdose.
Urine samples: pre-dose, 0-24, 24-48, 48-72,

Assay:

[redacted] method. Assay qualification results based on the quality control samples are shown below.

	Palonosetron	M9	[redacted]	
Plasma Samples				
Detection Limit, ng/L	-	-	~10	~500
Linearity, ng/L	[redacted]		-	-
Precision (%CV)	≤12.8	≤14.2	-	-
Accuracy (%bias)	≤ 9.16	≤9.56	-	-
Urine Samples				
Detection Limit, ng/L	-	-	100	~2000
Linearity, ng/L	[redacted]		-	-
Precision (%CV)	≤12.1	≤11.6	-	-
Accuracy (%bias)	≤17.5%	≤16.4%	-	-

Results

Palonosetron in Plasma

Mean palonosetron concentrations were slightly higher in poor metabolizers compared to extensive metabolizers. After an initial decline of the plasma concentrations, increases were seen in five of the six subjects at 2 to 4 hrs postdose. The secondary peak may be related to enterohepatic recirculation of palonosetron.

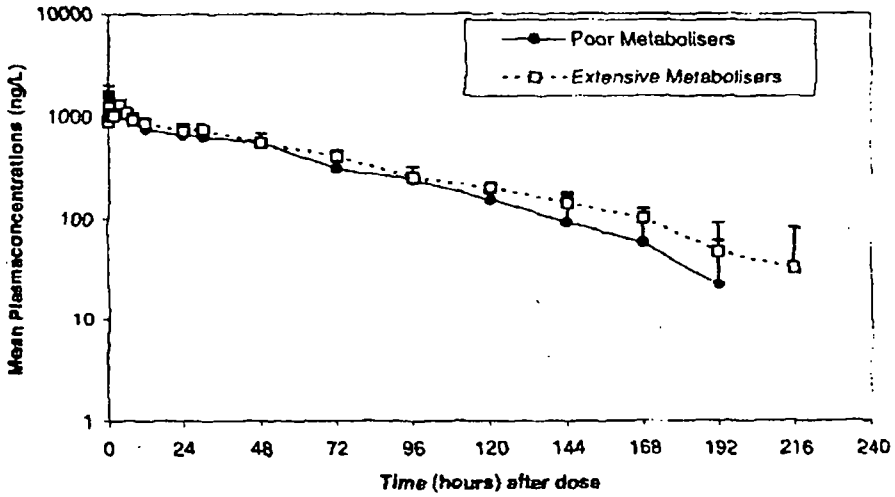


Figure: Mean palonosetron plasma concentrations following single IV administration of palonostron HCl 0.75 mg in extensive and poor metabolizers of CYP2D6

Mean palonosetron pharmacokinetic parameters following single IV administration of palonosetron 0.75 mg are presented in the table below. Cmax values were similar between the extensive and poor metabolizers. The AUC values appear to be somewhat lower in the group of poor metabolizers. There is no evidence of slower palonosetron metabolism in CYP2D6 poor metabolizers.

Table: Mean palonosetron PK parameters in extensive and poor metabolizers of CYP2D6 substrates

Parameters	C_{max}	t_{max}	AUC_{0-last}	$AUC_{0-\infty}$	λ_z	$t_{1/2}$	CL_{tb}	CL_r	V_z
Unit	(ng/L)	(h)	(µg*h /L)	(µg*h /L)	(1/h)	(h)	(mL/min)	(mL/min)	L
Extensive metabolisers (n=3)									
Subject 001									
Subject 002									
Subject 003									
Mean[1]	1600	1.50	72.3	78.1	0.0140	49.5	161	54	686
SD[2]	19.2	2.17	9.03	8.76	0.00069	2.44	14.5	5.7	31.0
Poor metabolisers (n=3)									
Subject 004									
Subject 005									
Subject 006									
Mean[1]	1571	0.83	61.1	66.0	0.0164	44.1	192	58	723
SD[2]	26.6	1.01	23.5	21.6	0.00403	10.68	39.8	23.5	182.0

[1]Geometric mean for Cmax and AUC; arithmetic mean for other parameters
[2] It is %CV for Cmax and AUC, SD for other parameters.
[3]The value is an underestimation because sampling time was delayed.

M9 in Plasma

Mean plasma M9 concentrations appears to be somewhat higher in extensive metabolizers than in poor metabolizers (See figure below). Reviewer's note: There was high variability in extensive metabolizers. An examination of the individual data did not reveal obvious differences between the two groups (See table below).

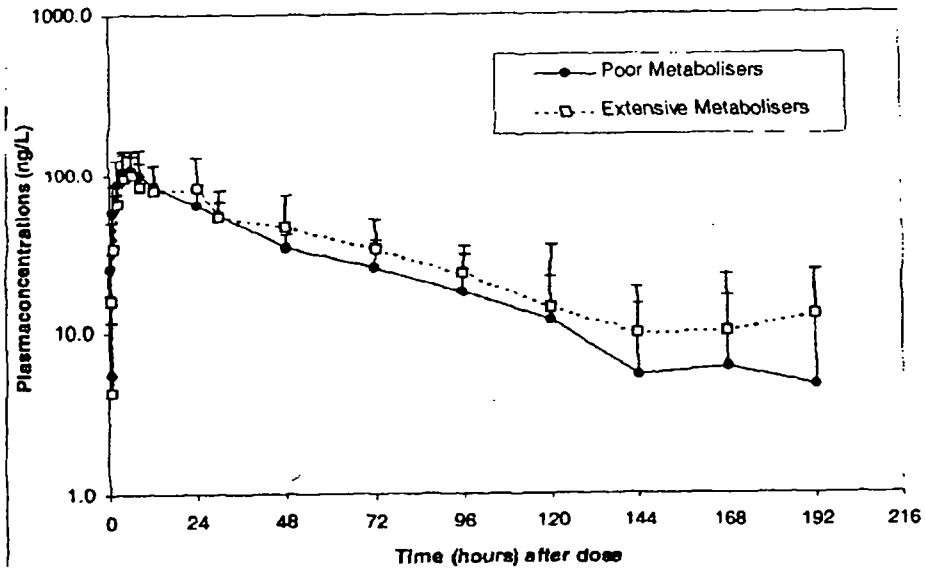


Figure: Mean Plasma M9 concentrations following single IV injection of 0.75 mg palonosetron HCl in extensive and poor metabolizers of CYP2D6 substrates

Table: M9 pharmacokinetic parameters in extensive and poor metabolizers

Parameters	C_{max}	t_{max}	$AUC_{0-tlast}$	$AUC_{0-\infty}$	λ_z	$t_{1/2}$	CL_{tb}/F	CL_r/F	V_z/F
Unit	(ng/L)	(h)	(µg*h /L)	(µg*h /L)	(1/h)	(h)	(mL/min)	(mL/min)	L
Extensive metabolisers (n=3)									
Subject 001									
Subject 002									
Subject 003									
Mean[1]	95	5.33	5.29	7.58	0.0082	87.7	1897	342	13356
SD[2]	43.1	1.16	62.9	57.2	0.00183	20.81	874.4	148.2	3757.9
Poor metabolisers (n=3)									
Subject 004									
Subject 005									
Subject 006									
Mean[1]	114	6.00	4.85	6.00	0.0157	64.74	2362	265	10769
SD[2]	28.0	2.00	33.1	38.6	0.01188	44.363	1162.6	51.2	4364.7

*Clearance of M9 was calculated assuming an equimolar dose of M9.

Urinary Excretion of palonosetron and M9:

Excretion of palonosetron in extensive and poor metabolizers were similar (see table below).

Table: Mean (range) accumulative renal excretion of palonosetron and M9 in extensive and poor metabolizers 240 hrs following single IV dose of palonosetron HCl 0.75 mg

Group	Palonosetron (% of dose)	M9 (% of dose)	Palonosetron + M9 (% of dose)
Extensive Metabolizers	33.1	14.4	47.5
Poor Metabolizers	31.3	11.8	43.2

and

These two compounds were not detected in plasma or urine samples.

Conclusion:

- The results of this study give no indication that poor metabolizers of CYP2D6 substrates is associated with prolonged elimination half-lives of palonosetron or with any other differences between the PK parameters obtained in plasma and urine for palonosetron and the metabolite M9.
- The sum of the renal excretion of palonosetron and metabolite M9 in the period up to 240 h after dosing accounted for approximately 34-55% of the dose. Excretion was not complete at 240 h postdose for either parent compound or metabolite.
- There is no indication that palonosetron is metabolized to in man.

Study #: PALO-99-35 Study Date: Sep 2000-Sep 2001

Type of Study: Renal Impairment Study

Study PALO-99-35 is entitled,

"AN EVALUATION OF THE PHARMACOKINETICS OF A SINGLE INTRAVENOUS DOSE OF 0.75 mg PALONOSETRON IN PATIENTS WITH VARYING DEGRESS OF RENAL IMPAIRMENT COMPARED TO HEALTHY VOLUNTEERS"

Objectives

- To evaluate the effect of varying grades of renal impairment on the PK of palonosetron.

Study Design

Open-label, single-center PK study

Subjects 9 healthy subjects and 16 patients with mild to severe renal impairment (9 patients with mild to moderate renal impairment and 7 patients with severe renal impairment).

Treatment Subjects received single I.V. doses of 0.75 mg palonosetron.

PK Sampling Samples were collected for determination of palonosetron and its major metabolite (M9) in plasma at 0 (pre-dose), 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216 and 240 hrs post-dose.

Total urine output was additionally collected at 12 hr intervals on the day of dosing and daily thereafter for 10 days.

Pharmacokinetics

The following pharmacokinetic parameters were determined for palonosetron and its M9 metabolite: T_{max}, C_{max}, $t_{1/2}$, CL_R, AUC_{0-t} and $AUC_{0-\infty}$.

Analytical assay

Plasma and urine concentrations of palonosetron and M9 were determined by a validated — analytical assay. The plasma assay had a quantification range of — — ng/ml for palonosetron and — ng/ml for M9. The urine assay has a quantification range of . — ng/ml for palonosetron and — ng/ml for M9.

Results and Conclusions

Table. Summary of the mean PK parameters for **palonosetron** in varying grades of renal impairment

Group A Healthy subjects	C_{max} (ng/L)	t_{max}[3] (h)	$AUC_{0-tlast}$ (h*µg/L)	$AUC_{0-\infty}$ (h*µg/L)	$t_{1/2}$ (h)	N in regression	CL_{tb} (mL/min)	CL_{ren} (mL/min)	V_z (L)
N	9	9	9	9	9	9	9	9	9
Mean[1]	2549	3.31	73.3	78.0	39.3	4.4	173	52.5	617
SD/CV[2] (%)	34.7%	7.86	38.3%	35.6%	9.84	1.1	73.1	28.6	396
Min									
Median	2497	0.25	91.7	95.2	37.6	4	131	41.5	432
Max									
Group B: Mild/Mod Renal Impairment	**C_{max} (ng/L)**	**t_{max} (h)**	**$AUC_{0-tlast}$ (h*µg/L)**	**$AUC_{0-\infty}$ (h*µg/L)**	**$t_{1/2}$ (h)**	**N in regression**	**CL_{tb} (mL/min)**	**CL_{ren} (mL/min)**	**V_z (L)**
N	9	9	9	8	8	8	8	9	8
Mean[1]	2574	0.25	78.2	83.5	47.3	4.5	154	62.1	607
SD/CV[2] (%)	40.1%	0.00	23.6%	24.5%	13.8	1.7	38.8	15.9	142
Min									
Median	2413	0.25	82.2	87.7	44.6	4	143	65.8	625
Max									
Group C: Severe Renal Impairment	**C_{max} (ng/L)**	**t_{max} (h)**	**$AUC_{0-tlast}$ (h*µg/L)**	**$AUC_{0-\infty}$ (h*µg/L)**	**$t_{1/2}$ (h)**	**N in regression**	**CL_{tb} (mL/min)**	**CL_{ren} (mL/min)**	**V_z (L)**
N	7	7	7	4	4	4	4	7	4
Mean[1]	2600	0.40	106	100	61.5	4.3	149	23.3	668
SD/CV[2] (%)	47.1%	0.28	44.0%	59.0%	18.4	1.3	107	18.5	226
Min									
Median	2696	0.25	116	110	70.2	4	116	13.0	701
Max									

Source: Table 8, Appendix B

[1] Geometric mean for C_{max}, $AUC_{0-tlast}$ and $AUC_{0-\infty}$, arithmetic mean for the other parameters

[2] For C_{max}, $AUC_{0-tlast}$ and $AUC_{0-\infty}$ this is the %CV, SD for other parameters

[3] The value of 24 h for Subject 906 (value of doubtful validity) considerably influenced the mean t_{max}; the median value was 0.25 h.

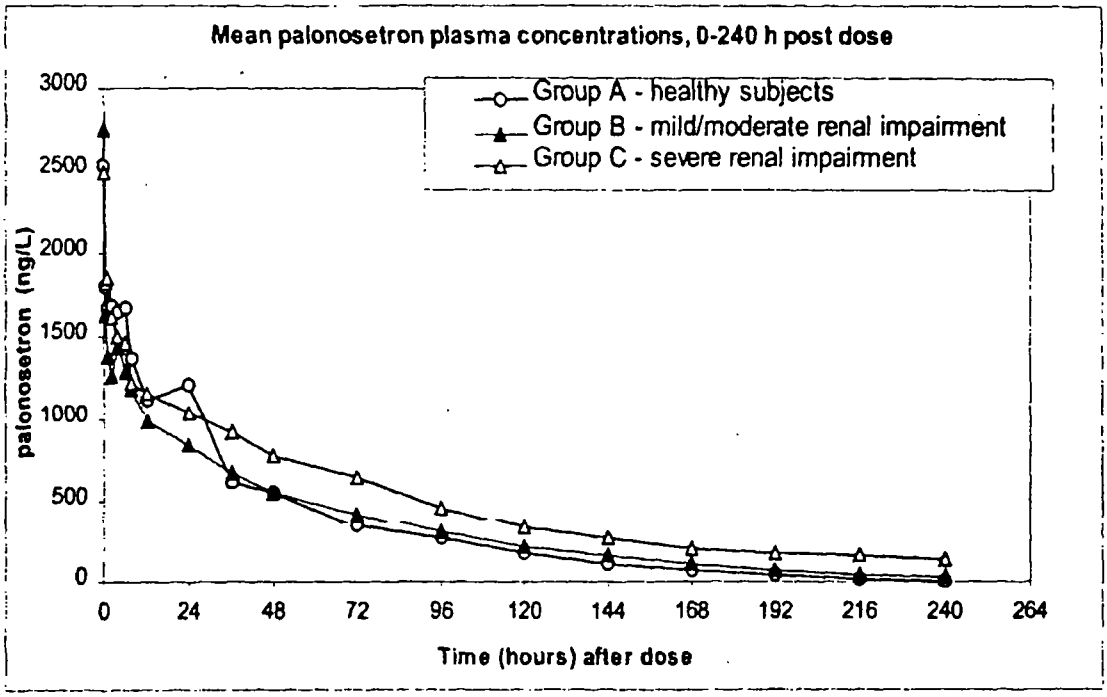


Figure: Mean **palonosetron** plasma conc.-time profile in subjects with varying grades of renal impairment.

Table. Statistical analysis of log-transformed C_{max} and $AUC_{0-\infty}$ values

Parameter	Estimate of the ratio	P-value	90% Confidence interval	
			Lower limit	Upper limit
Palonosetron $AUC_{0-\infty}$				
Severe RI (n=4) vs. Healthy Subjects (n=9)	1.285	0.3273	0.834	1.979
Mild/Moderate RI (n=7) vs. Healthy Subjects (n=9)	1.070	0.7393	0.755	1.518
Palonosetron C_{max}				
Severe RI (n=7) vs. Healthy Subjects (n=9)	1.020	0.9244	0.720	1.445
Mild/Moderate RI (n=9) vs. Healthy Subjects (n=9)	1.010	0.9600	0.729	1.399

Source: Table 17, Appendix B

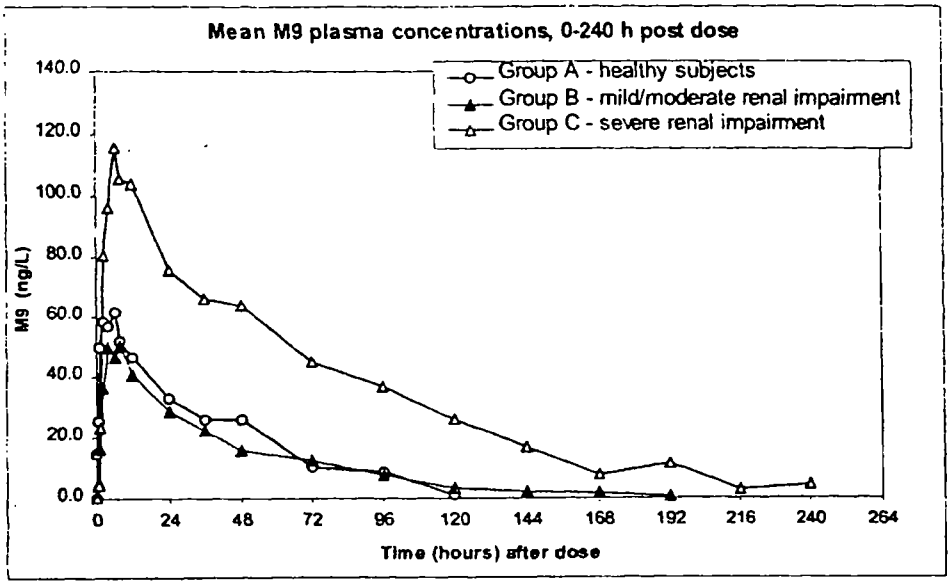


Figure: Mean **M9** plasma conc-time profile in subjects with varying grades of renal impairment.

Table 4. Summary of the mean PK parameters for **M9** in varying grades of renal impairment

Group A: Healthy Subjects	C_{max} (ng/L)	t_{max} (h)	$t_{last\text{-}plasma}$ (h)	$AUC_{0\text{-}tlast}$ (h*ug/L)	Ratio AUC M9/Palonosetron	CL_{ren}[3] (mL/min)
N	9	9	9	9	9	9
Mean[1]	64.2	4.3	58.7	1.59	0.031	1440
SD/CV[2] (%)	47.8%	3.5	24.3	61.8%	0.028	1507
Min						
Median	76.9	4.0	48.0	2.35	0.024	804
Max						
Group B: Mild/Mod Renal Impairment	**C_{max} (ng/L)**	**t_{max} (h)**	**$t_{last\text{-}plasma}$ (h)**	**$AUC_{0\text{-}tlast}$ (h*ug/L)**	**Ratio AUC M9/Palonosetron**	**CL_{ren}[3] (mL/min)**
N	9	9	9	9	9	9
Mean[1]	54.0	13.3	81.3	1.57	0.027	545
SD/CV[2] (%)	35.8%	22.2	51.2	54.1%	0.016	267
Min						
Median	58.9	4.0	72.0	1.94	0.025	451
Max						
Group C: Severe Renal Impairment	**C_{max} (ng/L)**	**t_{max} (h)**	**$t_{last\text{-}plasma}$ (h)**	**$AUC_{0\text{-}tlast}$ (h*ug/L)**	**Ratio AUC M9/Palonosetron**	**CL_{ren}[3] (mL/min)**
N[4]	6	6	6	6	6	6
Mean[1]	99.2	10.7	156	4.91	0.059	179
SD/CV[2] (%)	65.9%	12.6	75.5	75.8%	0.033	180
Min						
Median	121	6.0	180	8.59	0.063	127
Max						

Source: Table 9 and 15, Appendix B

[1] Geometric mean for C_{max} and $AUC_{0\text{-}tlast}$, arithmetic mean t_{max};

[2] For C_{max} and $AUC_{0\text{-}tlast}$ this is the %CV, SD for t_{max};

[3] Calculated as: Amount excreted to time of t_{last} in plasma, divided by $AUC_{0\text{-}tlast}$;

[4] There were no valid plasma concentrations for Patient 006.

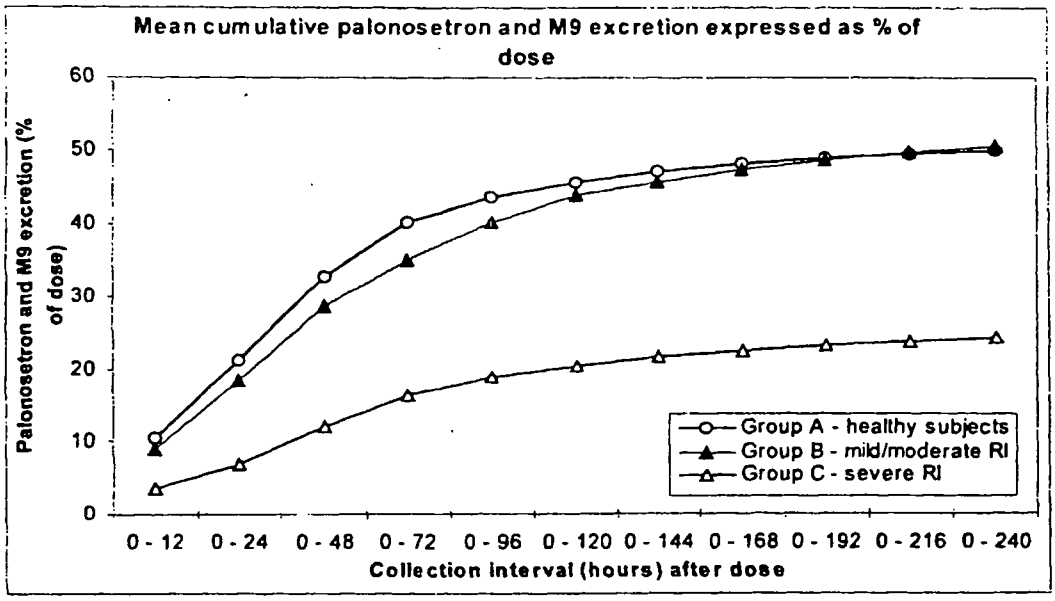


Figure: Mean Cumulative urinary palonosetron and M9 excretion expressed as % of administered dose

- Mean values of the primary PK parameters for palonosetron in patients with mild to moderate renal impairment were similar to those of healthy subjects. In patients with severe renal impairment, the mean $AUC_{0-\infty}$ increased by around 30% compared to healthy subjects. The cumulative palonosetron excretion in patients with severe renal impairment over a 240-hr period following dose administration was 50% of that observed in healthy subjects and patients with mild to moderate renal impairment. In addition, C_{max} and $AUC_{0-\infty}$ of M9 increased by 1.5 to 2-fold and 3-4 –fold, respectively, in severe renal impairment. Altogether, this points to reduced clearance as well as prolonged $t_{1/2}$ of palonosetron in severe renal impairment relative to healthy subjects.
- The sponsor combined patients with mild and moderate renal impairment into one group, which obscured the interpretation of the impact of each of the two individual categories of renal impairment on the PK of palonosetron. However, this may not be of great importance given that only a small effect on the PK of palonosetron is observed in patients with severe renal impairment (i.e., worst case scenario).
- It is not clear why the sponsor has only quantified the M9 metabolite but not other relevant metabolites such as the M4 metabolite.

Study #: PALO-99-51 **Study Date: Sep 2000-Oct 2001**

Type of Study: Hepatic Impairment Study

Study PALO-99-51 is entitled,

"AN EVALUATION OF THE PHARMACOKINETICS OF A SINGLE INTRAVENOUS DOSE OF 0.75 mg PALONOSETRON IN PATIENTS WITH VARYING DEGRESS OF HEPATIC IMPAIRMENT IN COMPARISON TO HEALTHY VOLUNTEERS"

Objectives

- To evaluate the effect of varying grades of hepatic impairment on the PK of palonosetron.

Study Design

Open-label, single-center PK study

Subjects	24 patients (8 patients/group) with mild to severe hepatic impairment (based on the Child-Pugh classification)
Treatment	Subjects received single I.V. doses of 0.75 mg palonosetron.
PK Sampling	Samples were collected for determination of palonosetron and its major metabolite (M9) in plasma at 0 (pre-dose), 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216 and 240 hrs post-dose. Total urine output was additionally collected at 12 hr intervals on the day of dosing and daily thereafter for 10 days.

Pharmacokinetics

The following pharmacokinetic parameters were determined for palonosetron and its M9 metabolite: T_{max}, C_{max}, $t_{1/2}$, CL_R, AUC_{0-t} and $AUC_{0-\infty}$. PK data from 9 healthy subjects who had received a single 0.75 mg I.V. dose of palonosetron in study PALO-99-35 were used as control.

Analytical Assay

Plasma and urine concentrations of palonosetron and M9 were determined by a validated —— analytical assay. The plasma assay had a quantification range of —— —— ng/L for palonosetron and —— ng/L for M9. The urine assay has a quantification range of: —— ng/L for palonosetron and —— ng/L for M9.

Results and Conclusions

Table 1. Summary of the mean PK parameters for **palonosetron** in varying grades of hepatic impairment

Parameters	C_{max}	t_{max}	$AUC_{0\text{-}tlast}$	$AUC_{0\text{-}\infty}$	$t_{½}$	N in	CL_{tb}	CL_r	V_z
Unit	(ng/L)	(h)	(µg*h /L)	(µg*h /L)	(h)	regression	(mL/min)	(mL/min)	L
Group A, mild hepatic impairment									
n	8	8	8	8	7	7	7	7	7
Mean[1]	1779	1.63	53.9	57.2	30.7	4	214	66	564
SD/CV[2]	46	2.65	34.6	32.7	5.6	1	64	41	176
Group B, moderate hepatic impairment									
n	8	8	8	7	8	8	7	7	7
Mean[1]	1799	0.34	64.3	82.5	56.3	4	160	62	636
SD/CV[2]	31	0.27	46.9	33.6	28.4	1	60	39	230
Group C, severe hepatic impairment									
n	8	8	8	7	8	8	7	7	7
Mean[1]	994	1.94	58.0	60.6	59.9	5	248	87	913
SD/CV[2]	36	2.58	48.9	53.4	26.1	2	183	77	252
Group D, healthy subjects									
n	9	9	9	9	9	9	9	9	9
Mean[1]	2549	3.31[3]	73.3	78.0	39.3	4	173	52	617
SD/CV[2]	35	7.86	38.3	35.6	9.8	1	73	29	396

Source: Appendix B2, Table 5

[1] Geometric mean for C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$, arithmetic mean for the other parameters

[2] For C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$ this is the %CV, SD for other parameters

[3] The value of 24 h for Subject 906 (value of doubtful validity) considerably influenced the mean t_{max}; the median value was 0.25 h.

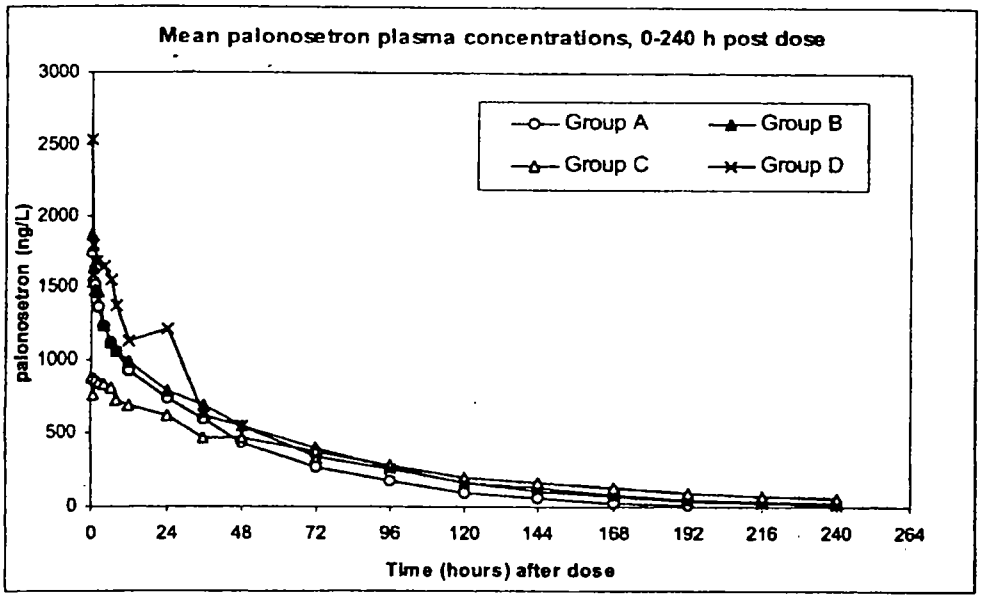


Fig.1. Mean **palonosetron** plasma conc.-time profile in subjects with varying grades of hepatic impairment.

Table 2. Statistical analysis of log-transformed C_{max} and $AUC_{0-\infty}$

Parameter			Estimate of the ratio	P-value	90% Confidence interval	
					Lower limit	Upper limit
Palonosetron $AUC_{0-\infty}$						
Mild H.I.	vs.	Healthy subjects	0.734	0.1556	0.511	1.053
Moderate H.I.	vs.	Healthy subjects	1.058	0.8002	0.727	1.538
Severe H.I.	vs.	Healthy subjects	0.777	0.2607	0.534	1.130
Palonosetron C_{max}						
Mild H.I.	vs.	Healthy subjects	0.698	0.0514	0.517	0.943
Moderate H.I.	vs.	Healthy subjects	0.761	0.1468	0.557	1.039
Severe H.I.	vs.	Healthy subjects	0.413	0.0001	0.303	0.565

Source: Appendix B2, Table 7
H.I.: Hepatic impairment

Table 3. Summary of the mean PK parameters for **M9** in varying grades of hepatic impairment

Parameters Unit	C_{max} (ng/L)	t_{max} (h)	$AUC_{0\text{-}tlast}$ (µg*h /L)
Group A, mild hepatic impairment			
n	8	8	8
Mean[1]	72	5.0	2.55
SD/CV[2]	41	2.4	44
Group B, moderate hepatic impairment			
n	8	8	8
Mean[1]	31	21.8	0.60
SD/CV[2]	35	24.7	81
Group C, severe hepatic impairment			
n	7	7	7
Mean[1]	24	37.6	0.36
SD/CV[2]	48	59.7	158
Group D, healthy subjects			
n	9	9	9
Mean[1]	64	4.3	1.59
SD/CV[2]	48	3.5	62

Source: Appendix B2, Table 6

[1] Geometric mean for C_{max}, $AUC_{0\text{-}tlast}$ arithmetic mean t_{max}

[2] For C_{max} and $AUC_{0\text{-}tlast}$ this is the %CV, SD for t_{max}

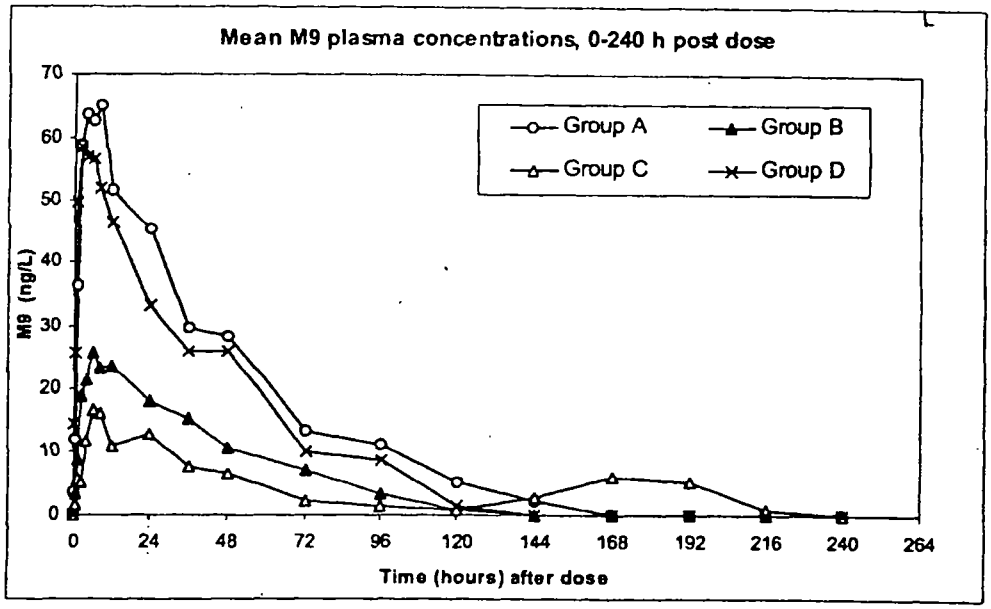


Fig.2. Mean **M9** plasma conc.-time profile in subjects with varying grades of hepatic impairment.

Table 4. Mean cumulative urinary palonosetron and M9 excretion expressed as % of administered dose.

Collection	Group A		Group B		Group C		Group D	
period (h)	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cumulative recovery of palonosetron and M9 (% of dose)								
0 - 24	16.4	6.5	18.1	10.6	15.1	17.5	21.3	5.9
0 - 72	28.6	10.1	32.9	18.0	30.7	22.5	40.3	8.3
0 - 120	33.1	10.8	40.4	21.2	38.0	22.8	45.7	7.8
0 - 168	35.4	10.6	45.5	24.7	42.6	22.7	48.2	7.5
0 - 240	37.3	10.6	49.3	26.1	47.0	22.7	49.9	7.2
Cumulative recovery of palonosetron (% of dose)								
0 – 24	13.2	5.1	15.5	10.2	10.4	11.7	13.1	5.2
0 – 72	22.9	8.3	27.6	16.4	20.2	16.1	24.6	8.8
0 – 120	26.4	8.9	33.3	18.5	25.8	16.8	27.9	9.5
0 – 168	28.1	8.8	37.8	21.9	29.5	17.3	29.6	9.8
0 – 240	29.9	8.8	41.0	23.1	33.3	18.1	30.7	10.1
Cumulative recovery of M9 (% of dose)								
0 - 24	3.2	1.6	2.6	1.4	4.7	6.3	8.2	4.9
0 - 72	5.7	2.2	5.4	2.4	10.5	12.3	15.7	8.9
0 - 120	6.7	2.5	7.1	3.7	12.2	13.0	17.8	9.7
0 - 168	7.2	2.5	7.8	4.0	13.1	12.8	18.6	10.2
0 - 240	7.5	2.5	8.3	4.4	13.8	12.6	19.2	10.5

Source: Appendix B2, Table 10

- The mean values of the primary PK parameters (C_{max} and AUC) for palonosetron in patients with mild to severe hepatic impairment were significantly reduced relative to those of healthy subjects. The mean values of the primary PK parameters (C_{max} and AUC) for M9 metabolite were significantly reduced in patients with moderate to severe hepatic impairment relative to those of healthy subjects. This has been attributed to the combination of a reduction in the metabolic pathway in hepatic impairment with an increase in the volume of distribution caused by reduced protein binding, altogether resulting in a net reduction in palonosetron and M9 plasma concentrations. In addition, the apparent half-life of palonosetron was significantly prolonged in patients with moderate to severe hepatic impairment compared to that of healthy subjects (Table 1).
  The cumulative palonosetron excretion in patients with severe hepatic impairment over a 240-hr period following dose administration was similar to those observed in healthy subjects and patients with mild to moderate hepatic impairment.
- It is not clear why the sponsor has only quantified the M9 metabolite but not other relevant metabolites such as the M4 metabolite (

Study #: PALO-99-34 Study Date: Dec 2000-Apr 2001

Type of Study: Drug-Drug Interaction Study

Study PALO-99-34 is entitled,

"AN EVALUATION OF PHARMACOKINETIC INTERACTION BETWEEN PALONOSETRON (0.75 mg IV) AND METOCLOPRAMIDE (10 mg PO EVERY 6 HOURS): A RANDOMIZED THREE-WAY CROSSOVER STUDY IN HEALTHY MALES AND FEMALES"

Objectives

- To evaluate the pharmacokinetic drug-drug interaction between palonosetron and metoclopramide in healthy subjects.

Study Design

Randomized, open-label, three-way, crossover PK study

Subjects 12 healthy subjects (6 males and 6 females)

Treatment Subjects were randomized to receive the following three treatments in successive manner:

- **A single I.V. dose of 0.75 mg palonosetron**
- **Six P.O. metoclopramide doses (10 mg Q 6 hrs)**
- **Six P.O. metoclopramide doses (10 mg Q 6 hrs) and a single I.V. dose of 0.75 mg palonosetron administered concurrently with the last metoclopramide dose**

A washout period of 21 days separated successive treatment periods.

PK Sampling Samples were collected for determination of palonosetron and its major metabolite (M9) in plasma at 0 (pre-dose), 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216 and 240 hrs post-dose.

Samples were collected for determination of metoclopramide in plasma at 0 (pre-dose), 0.5, 1, 2, 4, 6, 8, 12, 16 and 24 hrs following the last metoclopramide dose

Pharmacokinetics

The following pharmacokinetic parameters were determined for palonosetron, the M9 metabolite and metoclopramide: T_{max}, C_{max}, $t_{1/2}$, CL_R, AUC_{0-t} and $AUC_{0-\infty}$.

Analytical Assay

Plasma concentrations of palonosetron and its M9 metabolite as well as metoclopramide were determined by a validated [redacted] analytical assay. The plasma assay had quantification ranges of [redacted] ng/ml for palonosetron, [redacted] ng/ml for M9 and [redacted] µg/ml for metoclopramide.

Results and Conclusions

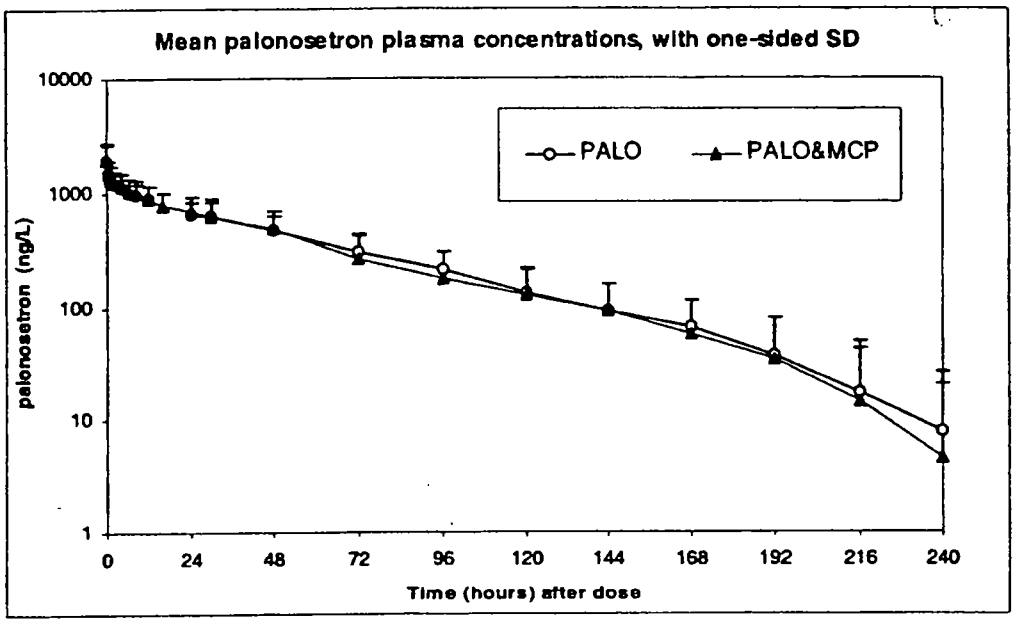


Fig.1. Mean **palonosetron** plasma conc.-time profile after administration of a single I.V. palonosetron dose either alone or concurrently with metoclopramide dosed to steady state.

Table 1. Summary of the mean PK parameters for **palonosetron** after administration of a single I.V. palonosetron dose either alone or concurrently with metoclopramide dosed to steady state.

PALO (N = 11)									
palonosetron parameters	C_{max} (ng/L)	t_{max} (h)	$AUC_{0-\infty}$ (µg.h/L)	$AUC_{0-tlast}$ (µg.h/L)	AUC; % extrap.[3]	$t_{½}$ (h)	λ (1/h)	Corr.[4] coeff.	n in regression
Mean[1]	1726	1.48	60.1	56.2	6.42	41.5	0.0180	0.990	5
CV/SD[2]	38	2.77	37	38	2.05	10.9	0.0054	0.007	2
Median	1610	0.25	58.9	55.5	5.80	44.5	0.0156	0.991	5
Minimum									
Maximum									
PALO & MCP (N = 9)									
palonosetron parameters	C_{max} (ng/L)	t_{max} (h)	$AUC_{0-\infty}$ (µg.h/L)	$AUC_{0-tlast}$ (µg.h/L)	AUC; % extrap.	$t_{½}$ (h)	λ (1/h)	Corr.[3] coeff.	n in regression
Mean[1]	1878	0.76	63.9	59.7	6.61	39.1	0.0184	0.994	5
CV/SD[2]	37	1.25	41	44	2.62	7.7	0.0041	0.006	1
Median	1645	0.25	62.6	57.2	6.77	38.2	0.0181	0.997	4
Minimum									
Maximum									

Source: Table 15.2.1, part 1

[1] Geometric mean for C_{max}, $AUC_{0-tlast}$ and $AUC_{0-\infty}$, arithmetic mean for the other parameters

[2] For C_{max}, $AUC_{0-tlast}$ and $AUC_{0-\infty}$ this is the %CV, SD for other parameters

[3] extrap. : extrapolation; [4]Corr. coeff. : Correlation coefficient

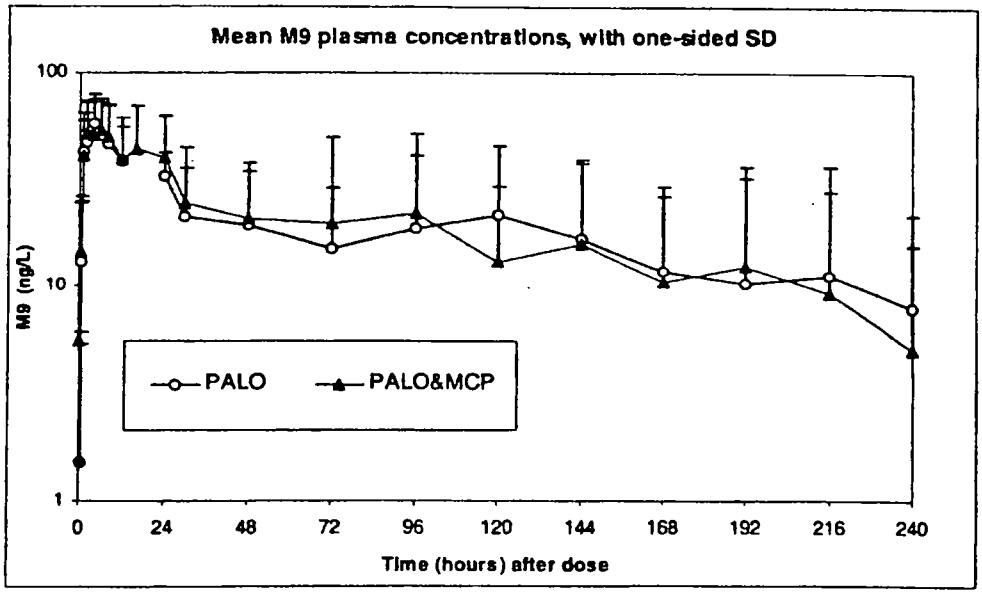


Fig.2. Mean **M9** plasma conc.-time profile after administration of a single I.V. palonosetron dose either alone or concurrently with metoclopramide dosed to steady state.

Table 2. Summary of the mean PK parameters for **M9** after administration of a single I.V. palonosetron dose either alone or concurrently with metoclopramide dosed to steady state.

M9 parameters	PALO (N=12)			PALO & MCP (N=12)		
	C_{max} (ng/L)	t_{max} (h)	$AUC_{0\text{-tlast}}$ (ng.h/L)	C_{max} (ng/L)	t_{max} (h)	$AUC_{0\text{-tlast}}$ (ng.h/L)
Mean[1]	62.3	15.3	2849	64.9	17.8	2667
CV/SD[2]	36	40.6	84	33	31.4	92
Median	71.4	4	2986	74.2	5	2849
Minimum						
Maximum						

Source: Table 15.2.1, part 1

[1]Geometric mean for C_{max} and $AUC_{0\text{-tlast}}$, arithmetic mean for t_{max}

[2] For C_{max} and $AUC_{0\text{-tlast}}$ this is the %CV, SD for t_{max}

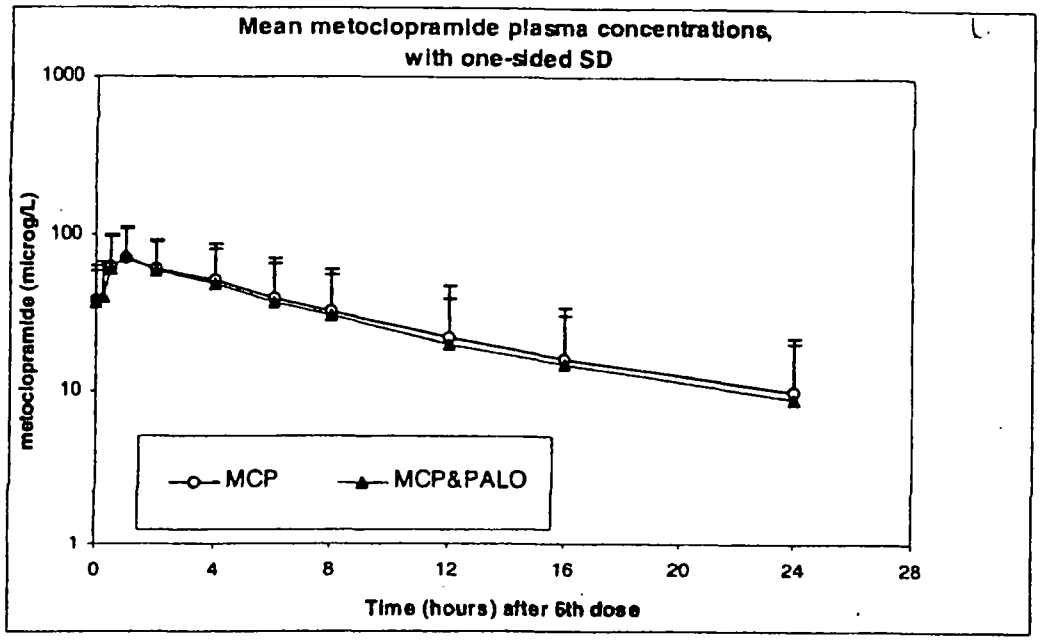


Fig.3. Mean **metoclopramide** plasma conc.-time profile after administration of to steady state either alone or concurrently with a single I.V. dose of 0.75 mg palonosetron.

Table 3. Summary of the mean PK parameters for **metoclopramide** after administration to steady state either alone or concurrently with a single I.V. dose of 0.75 mg palonosetron.

MCP (N = 11)									
metoclopramide parameters	C_{max} (µg/L)	t_{max} (h)	$AUC_{0-\infty}$ (µg.h/L)	$AUC_{0-tlast}$ (µg.h/L)	AUC; % extrap.	$t_{½}$ (h)	λ (1/h)	Corr.[3] coeff.	n in regression
Mean[1]	59.0	1.00	551	482	12.4	7.8	0.0947	0.988	3
CV/SD[2]	29	0.55	40	38	3.6	2.0	0.0281	0.026	1
Median	61.8	1.00	622	519	11.6	8.1	0.0855	0.997	3
Minimum									
Maximum									
MCP & PALO (N = 9)									
metoclopramide parameters	C_{max} (µg/L)	t_{max} (h)	$AUC_{0-\infty}$ (µg.h/L)	$AUC_{0-tlast}$ (µg.h/L)	AUC; % extrap.[3]	$t_{½}$ (h)	λ (1/h)	Corr.[4] coeff.	n in regression
Mean[1]	63.8	0.95	578	506	12.3	8.2	0.0894	0.983	3
CV/SD[2]	22	0.17	26	24	3.8	1.8	0.0237	0.011	1
Median	67.2	1.00	619	527	12.3	8.5	0.0811	0.980	3
Minimum									
Maximum									

Source: Table 15.2.1, part 2

[1] Geometric mean for C_{max}, $AUC_{0-tlast}$ and $AUC_{0-\infty}$, arithmetic mean for the other parameters

[2] For C_{max}, $AUC_{0-tlast}$ and $AUC_{0-\infty}$ this is the %CV, SD for other parameters

[3] extrap. : extrapolation; [4] Corr. coeff. : Correlation coefficient

- Administration of a single I.V. dose of 0.75 mg palonosetron does not have a significant effect on the steady state pharmacokinetics of metoclopramide (10 mg Q 6 hrs). Also, metoclopramide dosed to steady state does not have a relevant effect on the pharmacokinetics of a single I.V. dose of 0.75 mg palonosetron.

Study #25259S2330:

A Dose-Ranging efficacy, Safety, and Pharmacokinetic Study of Single Intravenous Doses of RS-25259 for Prevention of Nausea and Vomiting in Chemotherapy-Naive Cancer Patients Receiving Highly Emetogenic Chemotherapy

Study Period: April 1994—April 1995; V1.104 and 115

Objectives:

(1) To determine the dose-response relationship among single IV doses of RS-25259 over the dose range 1-90 • g/kg; the primary endpoint was the proportion of patients with a complete antiemetic response (no vomiting or retching) for 24 hours after highly emetogenic chemotherapy in chemotherapy-naive cancer patients; the efficacy of each dose was compared with the efficacy of the lowest dose;

(2) To assess the safety of single IV doses of RS-25259 administered over the range of doses tested in this patient population; and

(3) To assess the pharmacokinetics of single IV doses of RS-26259 over the range of doses tested in this patient population.

Study Design:

This was a randomized, double-blind, multicenter, dose-ranging efficacy, safety, and pharmacokinetic study. Patients were randomized to receive one of five doses of study drug and were observed as inpatients and/or outpatients. Safety and efficacy evaluations were recorded periodically during the first 24 hours and then daily for the next 6 days following administration of study medication. Additionally, each patient was contacted 14 days postdose to obtain further safety information.

Subjects:

One hundred sixty-one patients (129 males, 32 females), 23-79 years of age were enrolled in this study. All patients are included in the safety evaluations. However, 13 patients were excluded from all efficacy analysis. Reasons for exclusion included various protocol violations (8 patients). Subsequently to establishing evaluability, 5 additional patients, all of whom received cyclophosphamide (>1100 mg/m^2), were also excluded. Thus, efficacy analyses focused on only patients who received cisplatin-based (≥70 mg/m^2) chemotherapy. The distribution of evaluable patients by dose group is as follows: 0.3-1 • g/kg, 29 patients; 3 • g/kg, 24 patients; 10 • g/kg, 25 patients; 30 • g/kg, 24 patients; and 90 • g/kg, 46 patients.

Sample collection:

Blood samples for pharmacokinetic analysis were collected from patients at selected investigational sites. Samples were drawn pre-dose and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 12, 24, 48, 72, 120 and 168 hrs postdose. Plasma samples were assayed for palonosetron and the N-oxide metabolite concentrations using a [redacted] method. The quantitation limit was [redacted] ng/L for palonosetron and [redacted] ng/L for M9.

Test Product: Formulation #F25259-006

RS-25259 was supplied in 5-mL glass vials at a concentration of 0.5 mg/mL. Patients were randomly assigned to one of five dose levels. Prior to Amendments III and IV of the

protocol, the treatments were 0.3, 1, 3, 10, or 30 • g/kg; following those amendments, they were 1, 3, 10, 30, or 90 • g/kg. Normal saline was used to dilute RS-25259 to a total injection volume of 25 mL. Study drug was administered 30 minutes before start of chemotherapy and given as a single bolus IV dose over 30 seconds.

Evaluation criteria:

The primary endpoint was the proportion of patients with a complete antiemetic response (no vomiting, retching or rescue medication) for 24 hours after highly emetogenic chemotherapy in chemotherapy-naive cancer patients; the efficacy of each dose was compared with the efficacy of the lowest dose.

Secondary efficacy variables:

- Time to the first emetic episode
- Time to administration of rescue therapy
- Area under the nausea-intensity-by-time (NIT) curve based on categorical scale
- Time to treatment failure (either emesis or need for rescue medication, whichever occurred first)
- Proportion of patients with complete control of emesis (no vomiting and only mild nausea or no nausea), and
- Global rating of satisfaction with the control of nausea and vomiting based on a visual analog scale.

These variables were supplemented by physical examination and vital signs data, laboratory findings, and adverse event data, and pharmacokinetic data.

Results

(A) Pharmacokinetics:

Palonosetron

A total of 37 patients particiapted in the PK portion of the study. There were 6, 6, 5, 8 and 12 patients for the 1, 3, 10, 30 and 90 • g/kg dose levels, respectively. Mean plasma palonosetron concentration-time profiles for the various dose levels and mean PK parameters are shown below.

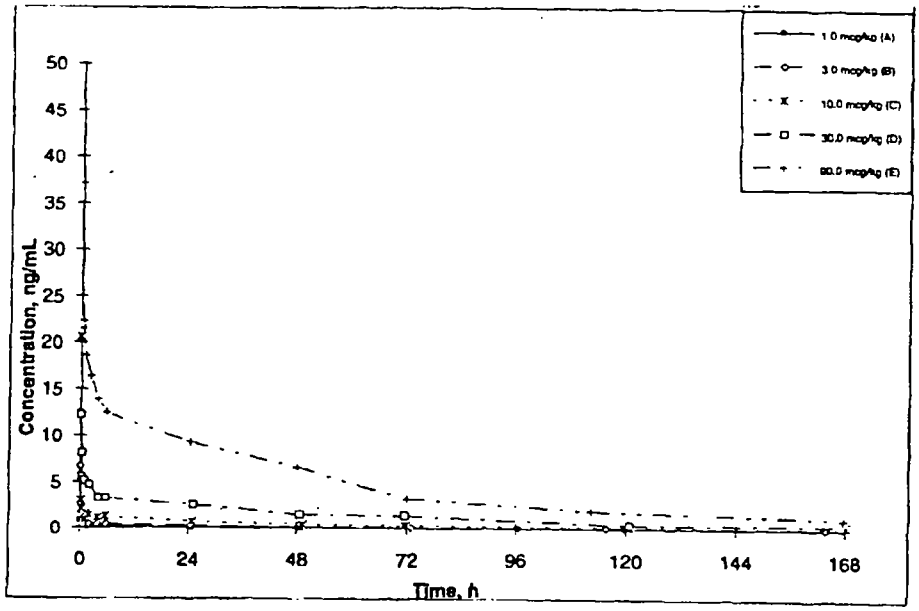


Figure: Mean plasma concentrations of palonosetron following a single IV administration.

Table: Mean palonosetron PK parameters following single IV administration.

RS-25259 Parameter	Mean (± SD)				
	1 µg/kg (n = 6)	3 µg/kg (n = 6)	10 µg/kg (n = 5)	30 µg/kg (n = 8)	90 µg/kg (n = 12)
C_{max} (ng/mL)	0.888 (0.917)	5.63 (5.48)	13.0 (20.1)	35.7 (37.0)	336 (940)
T_{MAX} (hr)	0.150 (0.180)	0.144 (0.196)	0.827 (1.51)	0.360 (0.684)	0.564 (0.744)
Half-life (hr)	128 (93.8)	56.4 (5.81)	49.8 (14.4)	86.4 (121)	43.7 (12.2)
AUC_{0-24} (ng•hr/mL)	4.17 (4.97)	8.57 (4.22)	26.6 (5.99)	82.6 (25.5)	310 (155)
Total AUC (ng•hr/mL)	13.8 (7.58)	35.8 (20.9)	81.8 (23.9)	348 (295)	957 (450)
Clearance (mL/min/kg)	1.51 (0.703)	1.66 (0.594)	2.23 (0.834)	2.13 (1.21)	1.90 (0.822)
Volume (L/kg)	12.5 (4.19)	7.91 (2.53)	9.56 (4.21)	9.18 (4.61)	6.83 (2.67)

*The individual data listed showed that blood samples were also taken at 1 and 5 minutes after dosing.

Metabolite M9

The pharmacokinetics of metabolite M9 was not well characterized at low dose levels of palonosetron because of analytical limitations. PK parameters were obtained mostly from the highest two dose levels (30 and 90 • g/kg). The AUC ratio of M9 to parent compound was 0.118 and 0.079 at the dose levels of 30 and 90 • g/kg, respectively.

RS-17825 Parameter	Mean (± SD)				
	1 µg/kg (n = 6)*	3 µg/kg (n = 6)*	10 µg/kg (n = 5)	30 µg/kg (n = 8)	90 µg/kg (n = 12)
C_{max} (ng/mL)	0.0549 (0.0052)	0.489 (0.297)	0.141 (0.104)	0.481 (0.262)	0.855 (0.679)
T_{max} (hr)	0.208 (0.0589)	112 (84.3)	45.1 (62.3)	52.3 (73.2)	2.87 (1.59)
Half-life (hr)	NC	NC	NC	59.1 (43.6)	110 (115)
AUC_{0-24} (ng•hr/mL)	0.0041 (0.0003)	0.172 (0.243)	1.60 (0.664)	6.11 (1.82)	10.5 (6.74)
Total AUC (ng•hr/mL)	NC	NC	NC	25.1 (11.3)	72.7 (45.5)
Total AUC Ratio RS-17825/ RS-25259	NC	NC	NC	0.1178 (0.0586)	0.0789 (0.0466)

* Most pharmacokinetic parameters were calculable for only 2 subjects at this dose level, even though 6 were dosed.
NC = not calculable due to missing or BQL plasma concentrations

(B) Dose-Response:

The following table summarizes key efficacy parameters. At the dose levels of 3, 10, 30 and 90 • g/kg, administered 30 minutes prior to high-dose cisplatin chemotherapy, were approximately equally effective as compared with the combined results from a cohort of 0.3 and 1 • g/kg in suppressing chemotherapy-induced emesis for 24 hours.

Parameters	RS-25259 Dose (µg/kg)				
	0.3–1	3	10	30	90
% Complete Control (24 hours)	24	46	40	50*	46
% Complete Response (24 hours)	24	39	40	48	46
Median Time (hours) to Failure (first emetic episode or rescue R_x)	5.6	22.7*	19.0	> 24*	21.8*

*Statistically significant differences ($p < 0.05$) vs. lowest dose group
*Complete control: free from emetic episodes and requiring no rescue medication
***Complete response: free from emetic episodes and rescue medication who experineced only mild or no nausea.

Conclusion:

- Based on the results of this study, a dose of 3 • g/kg or 10 • g/kg RS-25259 might be appropriate for further development.
- In the target patient population, exposure to the N-oxide metabolite (RS-17825) in the plasma was minor relative to the parent compound.

Reviewer's comment:
In view of intersubject variabilities, sampling time might not be long enough for accurate estimate of palonosetron half-life.

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ON ORIGINAL

PALO 99-33:
Population Pharmacokinetic and Pharmacodynamic Modeling of Palonosetron

Table: Summary of data source for population PK and PD analysis

Objective	To develop a population pharmacokinetic-pharmacodynamic (PK-PD) model for palonosetron using data obtained during phase III trials and to determine the influence of demographic variables, underlying disease and concomitant medications on the PK of palonosetron in patients receiving chemotherapy. PD measure of interest here is QTc.
Clinical Trials	Single-dose Phase 3 trials in patients undergoing chemotherapy: PALO-99-03, PALO-99-04, PALO-99-05: double-blind PALO-99-06: open-label; for returning patients from the above 3 trials Various demographic subpopulations in the clinical trials: elderly patients (age > 65 y): 19% of the studied population female: 67% Caucasian and Hispanic: 65% and 31%, respectively
Dose	Palonosetron: 0.25 mg or 0.75 mg IV, 30 min before chemotherapy
PK Sampling	Day 1: 3-6 h postdose (one sample; all Holtered and 50% of non-Holtered patients) Day 2: 24 h post-dose (for patients with non-Holter monitoring only) Day 6-8: one sample (all Holtered and 50% of non-Holtered patients) Day 15-28: one pre-dose sample (for non-Holtered patients in PALO-99-06)
Assay	LLOQ: [redacted] ng/L; Linearity: [redacted] Precision (%CV): <20% ; Bias: <±20%
PD Sampling	12-lead ECG read by a central cardiologist Patients with non-Holter monitoring: Baseline, 24 h, Day 6-8 (one measurement) Patients with Holter monitoring: Baseline, 15 min, 24 h, Day 8
Data	PK: 688 patients (218, 209 and 261 patients with a total of 607, 570 and 664 concentration measurements from the 3 trials, respectively) PD: 678 patients; QT data were collected with 12-lead ECG and were corrected using both Fredericia and Bazett formulae.
PK modeling	NONMEM software Internal validation: 70% of PK data were used as the index dataset and 30% as the validation dataset Final model: all data included Two-compartment model with 1st order elimination Covariates evaluated: Demographic (age, sex, body weight, and race), lab markers of hepatic and renal function, underlying disease concomitant medications (chemotherapeutic agent etc.)
PD modeling	Linear and Emax models to relate palonosetron concentrations to QTc or heart rate. Linear model to correlate AUC with QTc or heart rate.

Demographics

Table: Summary of demographic characteristics by study and for combined data

Covariate	PALO-99-03 N = 218	PALO-99-04 N = 209	PALO-99-05 N = 261	OVERALL N = 688
Body weight (kg)				
Median	69	69	67	68
Range	40 – 120	33 – 151	37 – 150	33 – 151
Age (y)				
Median	56	55	53	54
Range	27 – 82	18 – 91	18 – 79	18 – 91
Sex				
Female	160 (73%)	175 (84%)	129 (49%)	464 (67%)
Male	58 (27%)	34 (16%)	132 (51%)	224 (33%)
Race				
Caucasian	216 (99%)	67 (32%)	161 (62%)	444 (65%)
African origin	0	11 (5%)	7 (3%)	18 (3%)
Hispanic	1 (0.5%)	125 (60%)	90 (34%)	216 (31%)
Asian	1 (0.5%)	5 (2%)	2 (1%)	8 (1%)
Other		1 (0.5%)	1 (0.4%)	2 (0.3%)

Results

PK Analysis:

The population mean palonosetron clearance was 3.25 L/h (95% confidence interval: 2.21- 4.29 L/h). The results showed a large interindividual variability (88.8%). However, none of the tested covariates were identified as significant sources of variability. Covariates for central compartment volume (Vc) were body weight, serum albumin, study, Karnofsky score and race (see table below).

Parameter	Mean Estimate (%RSE)	Intersubject variability (%RSE)	Remark
CL (L/h)	3.25 (16.3%)	88.8% (32.6%)	Run #400
Vc (L)	632 (3.9%)	35.8% (13.7%)	For subject with median body wt (68.5 kg) and median serum albumin (40 g/L)
Covariates[a] for Vc Wt Serum albumin Study 05 Karnofski score ≤80 Race (non-Caucasian)	 4.4 (20.1%) 13.9 (19.0%) 0.8 (4.9%) 0.8 (5.8%) 0.8 (5.7%)	-	Continuous covariates were modeled with linear relationship; categorical covariates were modeled for the non-primary category as fraction of the primary category.
Q (L/h)	4.9 (15.3%)	88.8% (32.6%)	-
Vp (L)	1740 (36.3%)	35.8% (13.7%)	For subject with median serum creatinine (71 • mol/L)
Covariate[a] for Vp Serum Creatinine	 -7.0 (40.2%)	-	modeled with linear relationship.
Covariance (CL and Vc; Q and Vp)	-	0.39 (42.9%)	-
Residual error Proportional: σ^2 Additive: σ^2	 0.04 (27.2%) 11300 (43.3%)	 %CV: 18.8 SD = 106 ng/L	-

[a]Continuous covariates were modeled with linear relationship; categorical covariates were modeled for the non-primary category as fraction of the primary category.

PD Analysis:

The sponsor stated that pharmacodynamic analysis of palonosetron concentrations and markers of cardiac function, including heart rate and QTc interval after Bazett's and Fridericia's correction, did not reveal any significant concentration response relationships. The relationship between palonosetron AUC and median QTc or heart rate was also explored and no relationship was found (see figures below).

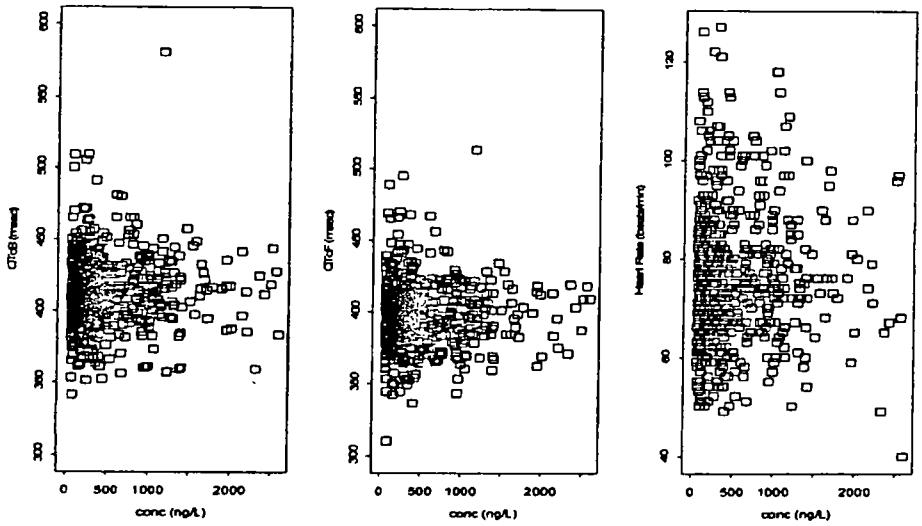

Figure : QTc (left panel: corrected using Bazzette's formula; middle panel: corrected using Fredericia's formula) and hear rate (right panel) vs. palonosetron concentration

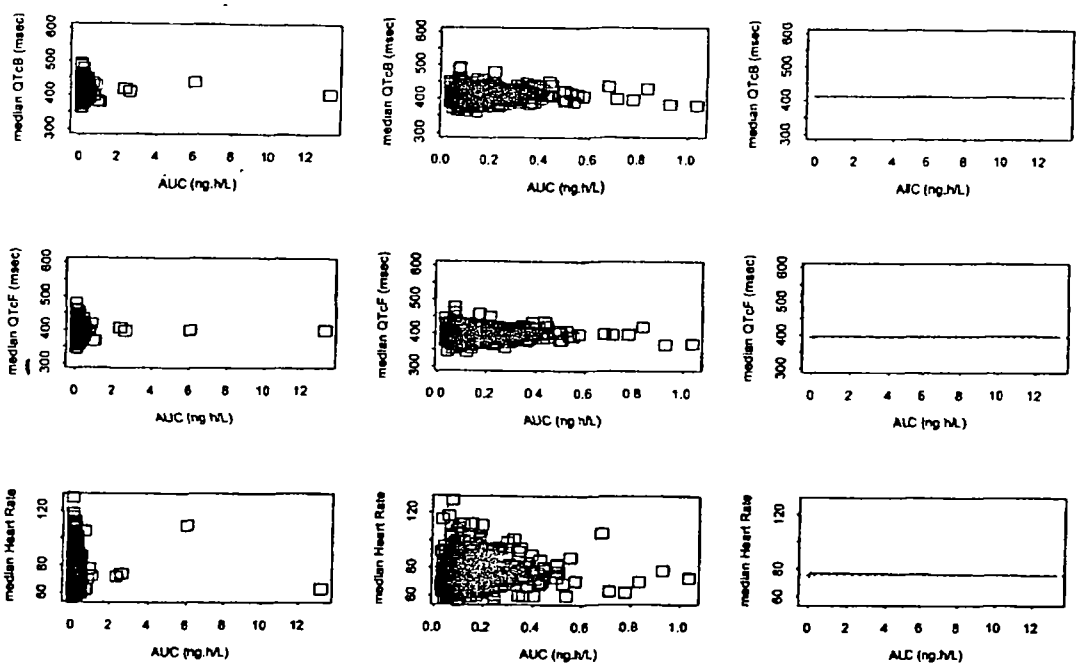

Figure : Squares represent individual data points for 630 subjects (left panel) and for 626 subjects, excluding exposures > 2 ng.h/L (middle panel). In the right panel, solid line is a smooth (using the supsmu function in SPlus) showing trend between exposure and response and dotted line represents the median response.

Reviewer's Comments:

1. Regarding population PK analysis:
   a. In this analysis, 65% of the population was Caucasian and 31% was Hispanic. Blacks were poorly represented.
   b. Concomitant drugs were lumped as one factor. This reduced the sensitivity to detect the factor unless there were reasons to think that they all interacted with palonosetron to the same degree.
   c. None of the covariates investigated was found to be a significant factor for palonosetron clearance. However, the power for detecting a specified difference was not indicated, which is particularly crucial in view of the high intersubject variability (88.8% for CL estimate).
   d. The population mean CL was estimated to be 3.25 L/h, which is lower than the values seen in a Phase 1 dose escalation study (160±35 mL/h/kg or 11.2±2.5 L/h/70 kg).
2. Regarding PD analysis:
   a. The information that can be derived from this study is limited because QT measurements were not performed frequently following the IV administration of palonosetron. Most patients had ECG measurements at pre-dose, 24 hr postdose and on Day 6-8. Although some patients did have a measurement at 15 minutes postdose, it is not sufficient to capture the maximum QTc change since C_{max} and E_{max} do not necessarily coincide.
   b. No relationship between palonosetron exposure and QTc or heart rate was found in this analysis. However, the changes in heart rate or QTc, and not heart rate or QTc itself, in relation to palonosetron exposure should have been examined.

ANALYTICAL METHODS

A. Plasma samples

Three analytical methods have been utilized to measure palonosetron and M9 in plasma samples during the development of palonosetron. The methods are described below.

(2) RIA Method for Determination of Palonosetron and M9 (JAR B-1009)
This method was used to measure palonosetron in plasma in Studies 2092.

Method: Plasma samples were eluted through a column. Small amounts of tritiated RS-25259 or RS-17825 was added to each plasma sample before extraction to provide a determination of procedural recovery of each analyte. The extract was subject to analysis. A portion of each that contained a purified analyte was then analyzed by scintillation counting to determine the procedural recovery, and another portion was analyzed by radioimmunoassay (RIA). The concentration determined by RIA was corrected for the procedural recovery, and the concentration of the analyte in the original plasma sample was calculated. The validation results are given below.

Parameter	Palonosetron	M9
Linearity		
Precision (%CV)	< 15%	≤ 15.7%
Accuracy (% bias)	< 20%	< 20%
Stability (-20°C for > 6 wks)		
Selectivity		

(2) Method for Assay of Palonosetron (RS-25259) and M9 (RS-17825) (IAR-B-1058)

An method for simultaneous determination of palonosetron and M9 in plasma was developed by Syntex Laboratories, and used to evaluate samples from studies 0100 and 2330.

Method: An aliquot of internal standard was added to plasma samples. The analytes were extracted from plasma and concentrated using column prior to injection onto an ystem. The separation of the metabolite from the parent was accomplished with a column and an appropriate mobile phase. Detection of the analytes was by Limits of quantification in plasma were pg/mL and pg/mL for paionosetron and M9, respectively.

Parameter	Palonosetron	M9
Linearity		

Precision (%CV)	≤ 19.3%	≤ 25%
Accuracy	≤ 20%	≤ 15%
Stability (24h at RT)		
Selectivity	Information not provided.	

(3). Method for Determination of Palonosetron and M9 (PALO-99-09; July 2001)

The method was developed and validated by . The assay was used to quantitate plasma palonosetron and M9 concentrations in studies PALO-99-03, PALO-99-04, and PALO-99-05 for the population PK analysis. Originally, the assay was validated with a 5-fold higher limit of quantitation (LOQ) for M9. Since concentrations of M9 were very low, additional work to improve the LOQ was undertaken.

Method: Plasma samples were spiked with internal standard . Palonosetron, M9 and the internal standard were isolated from plasma by . An aliquot of the extract was and analyzed .

Note: The validated assay can be used to detect . and in human plasma. No interference was observed for . There are interference peaks mimicing a . concentration of about 500-1000 ng/L.

Validation: Satisfactory

Parameter	Palonosetron	M9
Detection Limit	~ 5 ng/L	~ 5 ng/L
Linearity		
Precision (%CV)	≤ 18.75%	≤18.40 %
Accuracy (%bias)	≤11.51%	≤9.75%
Stability (freeze/thaw, 24h at RT,)	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.

B. Urine samples

The method of analysis for urine samples developed by Syntex and were similar to the methods for plasma samples described above with some modifications. Studies 0101 and 0100 utilized the method and reported lowest levels of quantitation of ng/L for both parent drug and M9. The assay was employed in the Helsinn-sponsored trials PALO-99-33, PALO-99-34, PALO-99-35 and PALO-99-51.

Validation: The results are listed in the table below.

Table: Validation results for the [redacted] Method for assay of urine samples

Parameter	Palonosetron	M9
Linearity	[redacted]	
Precision (%CV)	< 5%	< 10.3%
Accuracy (%bias)	< 21%	< 11%
Stability (-20°C for > 55 days;	[redacted]	
Selectivity	No interference observed in blank plasma samples	No interference found in blank plasma samples

Table: Validation results for the [redacted] Method* for assay of urine samples

Parameter	Palonosetron	M9
Detection Limit	~ 50 ng/L	~ 200 ng/L
Linearity	[redacted]	
Precision (%CV)	≤ 12.6%	≤16.47%
Accuracy (%bias)	≤11.3%	≤8.97%
Stability (freeze/thaw, 24h at RT,	Mean: 92.55-105.18%	Mean: 74.07**-100.43%
Selectivity	No interference observed in blank plasma samples	No interference found in blank plasma samples

*The method could be used to detect [redacted] and [redacted] in human urine.

**Low assay was found for samples with low M9 concentrations [redacted] ng/L, respectively). For samples containing higher M9 concentrations, the decrease in M9 concentration in the stability testing was ≤11.04%.

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ON ORIGINAL

The analytical methods used in various studies are listed in the table below.

Study Number	Report Date	Type of Biological Fluid	Method	Sensitivity of Method	Specificity (parent/metabolites)
IV Studies					
2216	Sept 1994	Plasma Urine			Specific
PALO-99-39	19 Dec 2001	Plasma Urine			Specific
2092	Dec 1994	Plasma			Specific
0100	Feb 1996	Plasma Urine			Specific
PALO-99-34	30 Jan 2002	Plasma			Specific
PALO-99-35	24 Jul 2002	Plasma Urine			Specific
PALO-99-51	26 Apr 2002	Plasma Urine			Specific
2330	July 1995	Plasma			Specific
2500	May 1995	Plasma			Specific
PALO-99-33	8 Aug 2002	Plasma			Specific

...ition report is IAR-B-1009
...validation reports are IAR-B-1058 and IAR-B-1050
assay validation reports are PALO-99-09

6.2 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	21-372	Brand Name	Aloxi
OCPB Division (I, II, III)	II	Generic Name	Palonosetron
Medical Division	Division of Gastroenterology & Coagulation Drug Products (HFD-180)	Drug Class	5-HT_3 Receptor Antagonist
OCPB Reviewers	Sue-Chih Lee Suliman Al-Fayoumi	Indication(s)	Prevention of nausea and vomiting associated with emetogenic chemotherapy
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	IV Injection
Date of Submission	9/27/2002	Dosing Regimen	0.25 mg, administered 30 min before chemotherapy
Estimated Due Date of OCPB Review	June 20, 2003	Route of Administration	IV bolus
Medical Division Due Date	June 27, 2003	Sponsor	Helsinn Healthcare
PDUFA Due Date	July 27, 2003	Priority Classification	Standard

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	x	1	1	
Isozyme characterization:	x	2	2	
Blood/plasma ratio:				
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:				
Patients-				
single dose:	X	1	1	
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1	1	
hepatic impairment:	X	1	1	
PD:				
Phase 2:	X	1	1	

Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1	1	
Phase 3 clinical trial:	X	1	1	
Population Analyses -				
Data rich:	x			
Data sparse:	x	1	1	
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	X	1	1	
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]12	12	12	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	x	Comments have been sent to firm (or attachment included). FDA letter date if applicable. Request for information related to ——
QBR questions (key issues to be considered)	**Does the information submitted in the application support safety related to the QT effect of palonosetron? Does the in vitro data on drug metabolism/drug interaction sufficient for the application?**	
Other comments or information not included above	**Oral formulation is not the subject of this NDA; All studies with oral formulations were not reviewed.**	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-372, HFD-870 (Electronic Entry or Lee), HFD-180 (Strongin), HFD-870 (Doddapaneni, Hunt, Malinowski), CDR (B. Murphy)

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

/s/

Sue Chih Lee
6/24/03 12:41:18 PM
BIOPHARMACEUTICS

Suliman Alfayoumi
6/24/03 01:13:53 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
6/24/03 01:18:32 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-372	Brand Name	Not Yet determined
OCPB Division (I, II, III)	II	Generic Name	Palanosetron
Medical Division	GI	Drug Class	Antiemetic
OCPB Reviewer	Sam Haidar	Indication(s)	Prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Parenteral solution
		Dosing Regimen	0.25 mg intravenoulsy
Date of Submission	9/30/02	Route of Administration	Intravenous
Estimated Due Date of OCPB Review	6/14/02	Sponsor	Helsinn Healthcare SA
PDUFA Due Date	7/30/02	Priority Classification	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:	Study 2216	1		
Isozyme characterization:	PALO-98-02	1		
Blood/plasma ratio:				
Plasma protein binding:	Report CL 6204	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	Studies 0100 & 2092	2		
multiple dose:				
Patients-				
single dose:	Studies 2330 & 2120	2		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	Studies 0100 & 2092			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				POP PK
In-vivo effects on primary drug:	Study PALO-99-34	1		
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

ethnicity:				POP PK
gender:				POP PK
pediatrics:				
geriatrics:				POP PK
renal impairment:	Study PALO-99-35	1		
hepatic impairment:	Study PALO-99-51	1		
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	Study PALO-99-33	1		
II. Biopharmaceutics				
Absolute bioavailability:				Intravenous-not needed
Relative bioavailability -				Intravenous-not needed
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				No formulation changes
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				Intravenous-not needed
Dissolution:				Intravenous-not needed
(IVIVC):				Intravenous-not needed
Bio-wavier request based on BCS				Intravenous-not needed
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	Study PALO-99-39	1		
Chronopharmacokinetics				
Pediatric development plan				Deferral
Literature References				
Total Number of Studies		12		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**(1) Is there exposure response for efficacy and safety?** **(2) Is the metabolism adequately described?** **(3) Is there adequate information describing the pharmacokinetics in special populations?**	

Other comments or information not included above	
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

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

/s/

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11/8/02 06:37:07 AM
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