CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-233

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

REVIEW OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NDA	**22-233**	*Submission Date(s)*	**October 22, 2007** **December 17, 2007**
Brand Name		**Aloxi® capsules for oral administration**	
Generic Name		**Palonosetron hydrochloride**	
Reviewer		**Insook Kim, Ph.D.**	
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OCP Division		**Division of Clinical Pharmacology 3**	
OND Division		**Division of Gastroenterology Products and In-Born Errors of Metabolism**	
Sponsor		**Helsinn Healthcare SA**	
Relevant IND and NDA		**IND 42,886** **NDA 21-372 Palonosetron for intravenous injection**	
Submission Type; Code		**Original**	**505 (b)(1)**
Formulation; Strengths; Regimen		**0.5 mg liquid-filled soft gelatin capsule** **One 0.5 mg capsule administered approximately one hour prior to the start of chemotherapy**	
Proposed Indication		**Prevention of acute (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy**	

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1 Executive Summary

The sponsor is seeking an approval of single oral dose of palonosetron hydrochloride 0.5 mg for the prevention of acute (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer therapy (MEC). Palonosetron is a 5-HT_3 receptor antagonist and a single dose of 0.25 mg palonosetron for intravenous injection was approved in 2003 (b) (4) in addition to the prevention of acute nausea and vomiting associated with highly emetogenic cancer therapy. The sponsor proposed to support the oral product by a single pivotal phase 3 trial based on the similar dose-response relationship between oral administration and intravenous administration observed in phase 2 and 3 trials. In the single pivotal phase 3 trial, the non-inferiority of oral administration of 0.25 mg, 0.5 mg and 0.75 mg compared to 0.25 mg IV administration

was demonstrated for the prevention of acute nausea and vomiting associated with initial course of MEC. (b) (4)

1.1 Recommendations

The clinical pharmacology and biopharmaceutics information was reviewed by the division of clinical pharmacology III and found acceptable provided 1) the DSI inspection currently scheduled in the week of 11th of August finds the BE study acceptable and 2) a mutual agreement regarding the label language can be reached between the sponsor and the Agency.

Should the proposed product of palonosetron be approved for the prevention of acute CINV, we recommend that the dose be reduced to 0.25 mg from the proposed 0.5 mg. The dose of 0.25 mg was found to be effective and no dose-response relationship was demonstrated among the three dose levels of 0.25 mg, 0.5 mg and 0.75 mg. This recommendation is consistent with the finding that the absolute bioavailability of oral capsules was 97% and the approved dose for IV administration for the prevention of both acute and delayed CINV is 0.25 mg.

If the clinical division determined that there was clinically meaningful efficacy for oral palonosetron in the prevention of delayed CINV based on the endpoint of Complete Response from 24hr to 120hr following chemotherapy (CR 24-120), we also recommend that the dose be reduced to 0.25 mg because no dose-response relationship was evident among the three dose levels of 0.25 mg, 0.5 mg and 0.75 mg for CR 24-120.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

In support of the new oral formulation of palonosetron HCl, included were the final study reports of nine phase 1 and 2 studies: oral ADME, dose-proportionality, single dose pharmacokinetics, bioavailability and bioequivalence studies, food effect and drug interaction studies, pharmacokinetics in CINV and PONV patients and in the healthy elderly subjects. (b) (4) The single pivotal phase 3 study and an open-label phase 3 safety study were submitted to support the efficacy and the safety of oral capsules of palonosetron.

For some early phase 1 and 2 studies, the IV formulation was used as a drinkable oral solution for the body-weight based doses while oral capsule formulation was used for later studies including phase 3 trials conducted for the fixed doses.

PK characteristics

After oral administration, palonosetron is well-absorbed with an absolute bioavailability of 97-100%. The peak plasma concentrations are generally achieved within 4-6 hours and the Cmax and AUC after oral solution administration are generally dose-proportional over 1 to 80 μg/kg dose range in healthy subjects. Mean plasma half-life after oral dosing is approximately 40 hours in healthy subjects and 40-60 hours in CINV patients. The systemic exposure to palonosetron was higher in cancer patients by about 26-86% in terms of AUC than in healthy subjects (Table 1). (It should be noted that the data in Table 1 were gathered from three separate studies.)

Approximately 40% of orally administered palonosetron was cleared renally as unchanged drug and approximately 50% of palonosetron is metabolized. Two primary metabolites M9 and M4 were excreted in the urine amounting to about 12.1% and 17.2% of the administered dose, respectively. Estimates of renal clearance ranged from 4.06 to 6.29 l/h.

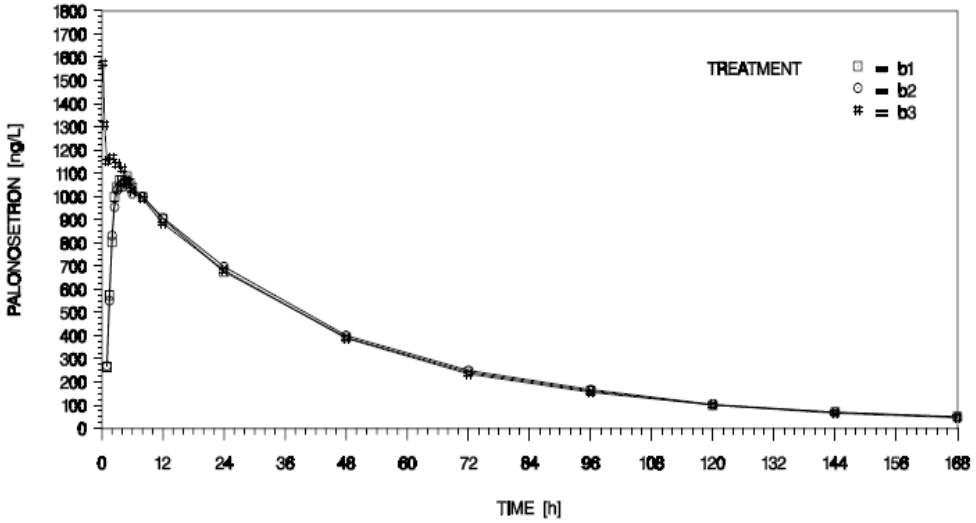
Table 1. PK parameters for palonosetron after a single-dose administration in healthy subjects and cancer patients

Dose	Parameters	Healthy Mean (SD)	Cancer patients Mean (SD)
0.25 mg[1] capsule	C_{max} (ng/ml) T_{max}[2] (h) AUC_{∞} (ng·h/ml)	n/a n/a n/a	0.55 (0.23) 6 (1-47.4) 34.2 (13.6)
0.5 mg capsule	C_{max} (ng/ml) T_{max} [1] (h) AUC_{∞} (ng·h/ml)	0.81 (0.16) 5.0 (2-8) 38.2 (11.7)	0.93 (0.34) 3.5 (1-23.4) 49.7 (12.2)
0.75 mg capsule	C_{max} (ng/ml) T_{max} [1] (h) AUC_{∞} (ng·h/ml)	1.2 (0.32) 4.5 (2-12) 58.3 (18.1)	1.42 (0.36) 4 (1-23.3) 103.3 (37.3)

[1] PK following a 0.25 mg dose capsule administration was not studied in healthy subjects. The closest dose studied in healthy subject was 3 μg/kg which corresponds to 0.21 mg (70 kg BW) using an oral solution.
[2] median (min-max)

The absolute bioavailability of palonosetron after 0.75mg oral capsule administration was 97%. The C_{max} of palonosetron after oral administration was 28% lower than after intravenous administration. Following oral absorption, the elimination profile of palonosetron was similar to those after IV injection (Figure 1).

Figure 1. Arithmetic mean concentration time curves for 0.75 mg capsule: formulations a (phase 3; b1) and b (to-be-marketed*; b2) and 0.75 mg IV palonosetron



b1:0.75 mg palonosetron softgel capsule (Formulation A; phase 3 clinical trial formulation)
b2:0.75 mg palonosetron softgel capsule (Formulation B; proposed commercial formulation)
b3:0.75 mg intravenous palonosetron (reference, 3 x 0.25 mg i.v. Aloxi®)

* Proportionally similar with the proposed to-be-marketed formulation for 0.5 mg strength

Pharmacokinetic characteristics after oral administration of palonosetron HCl was studied only in white subjects except one phase 1 PK study in Japanese male subjects. According to cross-study comparisons the 25% higher apparent total body clearance of palonosetron was observed in Japanese males than in white males.

The mean AUC of palonosetron is approximately 20-38% higher in females compared to males. The mean AUC of a metabolite M9 was 10-30% higher in females but 15% higher in males than in females for the elderly. The M4 exposure was variable and there was no consistent difference in M4 exposure by gender. No dosage adjustment based on gender is needed.

Following oral administration of 0.75 mg palonosetron under fasting, the mean AUC of palonosetron in elderly subjects aged over 65 years was similar to younger subjects aged 18-45 years and the mean Cmax was 13% lower than in the young. There is no need for dosage adjustment in the elderly.

The to-be-marketed formulation (TBM) was modified from a clinical trial formulation used in the phase 3 trial and some phase 1 and 2 trials to improve the shelf-stability. The total formulation change of (b) (4) was agreed to be SUPAC-IR level 2 change in a previous communication with the Agency. The bioequivalence between TBM and trial formulation was demonstrated in a two-way crossover in vivo bioequivalence study. The 90% confidence interval of point estimate ratio for AUC and Cmax fell within the bioequivalence criteria of 80-125% (table 2).

Table 2. ANOVA CVs, point estimates, 90% confidence intervals for (log-transformed) palonosetron pharmacokinetic parameters; Bioequivalence Assessment (N=36 subjects)

Pharmacokinetic parameter palonosetron	Ratio	ANOVA CV [%]	Point estimate Test/Ref. ratio	90% Confidence interval
$AUC_{(0-t)}$ [ng·h/L]	b_2 / b_1	8.7	102.3	98.9 - 105.9
$AUC_{(0-\infty)}$ [ng·h/L]	b_2 / b_1	8.7	102.0	98.6 - 105.6
C_{max} [ng/L]	b_2 / b_1	7.9	103.7	100.5 – 107.0

b1: oral administration of 0.50 mg palonosetron as a softgel capsule (formulation A, clinical trial formulation)
b2: oral administration of 0.50 mg palonosetron as a softgel capsule (formulation B, proposed commercial formulation)
Source: Final Report PALO-06-16, Table 11.4-8.

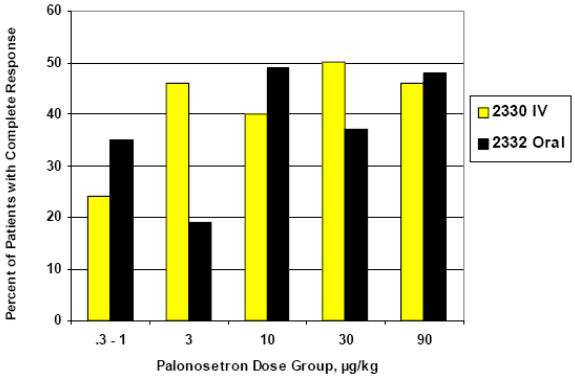
Concomitant antacid (Maloxx®) and high fat diet did not affect AUC and Cmax of palonosetron. Therefore, palonosetron can be taken without regard of meal intake.

Exposure (Dose)-Response Relationship

Efficacy- *The dose of 0.25 mg was the lowest effective dose among doses studied in phase 3 trial for the prevention of acute CINV while the efficacy for the prevention of delayed CINV has not been demonstrated in a statistically meaningful manner and is still under discussion.*

In study 2332, dose-response relationship for efficacy over doses 0.3, 1, 3, 10, 30 and 90 μg/kg was studied in chemotherapy naïve patients who were scheduled to receive their first doses of highly emetogenic chemotherapy. The primary endpoint was the proportion of patients with no emetic episodes and no rescue medication for a period of time i.e. 0-24 hours (CR 0-24) for acute CINV and 24-120 hours (CR 24-120) for delayed CINV after the initiation of chemotherapy. Only CR 0-24 was collected in the phase 2 trial. The clinical response appeared to reach a plateau at a dose of 10 μg/kg (approximately 0.7 mg for 70 kg BW). The dose-response relationship for CR 0-24 of oral administration was comparable for three high doses with IV administration while the lowest oral dose cohort had a higher CR 0-24 and 3 μg/kg oral dose cohort had a significantly lower CR 0-24 than IV administration (Figure 2). The doses of 0.25 mg, 0.5 mg and 0.75 mg were chosen for the phase 3 trial since the efficacy of 0.25 mg was proven in the IV development program for moderately emetogenic chemotherapy (MEC) and the absolute BA of oral administration was greater than 90%.

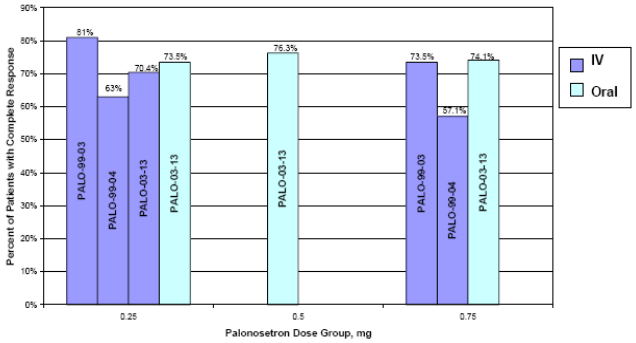
Figure 2: Comparison of complete response for 0-24 hours post-chemotherapy between oral and IV palonosetron



In phase 3 study PALO-03-13, the non-inferiority of all three oral doses 0.25, 0.5 and 0.75 mg was demonstrated to 0.25 mg palonosetron IV administration for CR0-24 i.e. the prevention of acute nausea and vomiting associated with moderately emetogenic chemotherapy. The percentage of patients with CR 0-24 was 73.5%, 76.3% and 74.1% for 0.25 mg, 0.50 mg and 0.75 mg oral doses, respectively. No dose-response relationship among oral doses was observed, which was similar to observed after IV administration as dose-response between 0.25 mg and 0.75 mg IV administration was not observed for the same endpoint in previous study (NDA 21-372) (Figure 3). On the other hand, none of three doses met the pre-specified non-inferiority criteria for the key secondary endpoint CR 24–120 i.e. the prevention of delayed CINV. The sponsor conducted an exploratory post-hoc analysis for the CR 24-120 using a pooled historic data for IV administration to increase the comparator arm and based on the exploratory analysis proposes the dose of 0.5 mg as a recommended dose for the prevention of acute (b) (4) CINV. (b) (4)

The sponsor communicated with the Agency previously and proposed to support the NDA by a sole pivotal efficacy trial based on similar dose-response curves for oral and IV palonosetron over the doses. As indicated above, the dose-response relationship of oral palonosetron was found to be similar to IV palonosetron for the prevention of acute CINV based on CR 0-24 and the dose of 0.25 mg was effective for the prevention of acute CINV (b) (4)
Thus the dose of 0.25 mg is more appropriate than 0.5 mg for the prevention of acute CINV.

Figure 3. Percentage of patients with CR0-24 after oral and IV administration



Safety-*The safety evaluations did not reveal dose-related increases in adverse events.*
Overall, palonosetron was well tolerated in phase 1 and 2 studies at single doses ranging from 0.1 µg/kg to 90 µg/kg. The most frequent adverse events were headache, constipation, abdominal pain, and transient elevation of liver enzymes, none of which appeared to be dose related. Adverse events were generally mild to moderate in intensity, and all recovered without sequelae. The most frequently occurred adverse events (AEs) in phase 3 studies were headache, constipation, diarrhea and dizziness as shown in the table below (Table 3). The incidence of most frequently occurred AEs was comparable between oral administration and IV administration in phase 3 trial. No significant differences in the incidence of AEs for the various

oral doses were observed. Overall, the safety evaluations for this group of studies did not reveal dose-related increases in adverse events. (For details, please see the clinical review by Dr. Nancy Snow of Division of Gastroenterology Products)

A thorough QT study was conducted to evaluate the ECG effects of IV administered palonosetron at a single dose level of 0.25 mg, 0.75 mg or 2.25 mg in 221 healthy subjects. The study demonstrated no significant effect on any ECG interval including QTc duration (cardiac repolarization) at doses up to 2.25 mg. (the label of the Aloxi for injection, NDA 21-372 (b) (4).

Table 3. Adverse events occurred higher than 1% incidence in phase 3 studies

	0.25 mg po N=157	0.5 mg po N=161	0.75 mg po N=375	0.25 mg I.V. N=163
constipation	7/4.5%	12/7.5%	29/7.7%	11/6.7%
headache	19/12.1%	26/16.1%	58/15.5%	24/14.7%
diarrhea	6/3.8%	9/5.6%	16/4.3%	11/6.7%
dizziness	5/3.2%	4/2.5%	4/1.1%	1/0.6%

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

A single-dose of 0.25 mg Aloxi (palonosetron) for injection (NDA 21-372) has been approved for the prevention of acute and delayed CINV with moderately emetogenic chemotherapy and the prevention of acute CINV with highly emetogenic chemotherapy. Based on that IV palonosetron was already approved the sponsor conducted one phase 3 pivotal efficacy trial (PALO 03-13) in total 639 patients (157-163 patients for each dose cohort). In addition, one repeat-cycle open label phase 3 trial (PALO 03-14) at 0.75 mg dose was conducted for safety and sustained efficacy for the oral palonosetron. At an End-of-Phase 2 meeting, the Agency commented that the sponsor's proposal may be sufficient if the dose-response relationship for the IV and oral formulations are similar and that to obtain approval for the prevention of acute (b) (4) nausea and vomiting, efficacy must be shown in (b) (4) the acute (0-24 hour) (b) (4) intervals post-chemotherapy.

Pharmacokinetic characteristics of palonosetron in subjects with mild, moderate and severe hepatic insufficiency or renal insufficiency was evaluated after IV administration. No dosage adjustment based on hepatic or renal function is recommended in the label of Aloxi for injection. Study in subjects with the end-stage-renal disease was not conducted. A thorough QT study was conducted for doses of 0.25 mg, 0.75 mg and a supra-therapeutic dose of 2.25 mg after IV administration. These studies were submitted in support of IV formulation (NDA 21-372) and the results are currently reflected in the label of Aloxi for injection. No additional studies were needed since the dose of oral palonosetron was covered in the previous TQT study and the Cmax after oral administration is expected to be lower than the IV administration for the same dose. In vitro drug interaction studies and protein binding studies were conducted in support of IV formulation and reflected in the label of Aloxi for injection and the same labeling claim was proposed for the oral product.

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

Chemically, palonosetron hydrochloride is: (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 (Figure 4). The empirical formula is

C19H24N2O.HCl, with a molecular weight of 332.87 g/mole. Palonosetron hydrochloride exists as a single isomer and has the following structural formula:

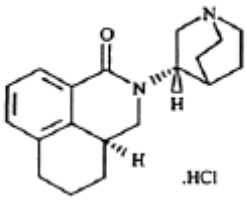


Figure 4. Structure of palonosetron hydrochloride

The bioequivalence between the phase 3 trial formulation and the to-be-marketed formulation was demonstrated in an in vivo BE study.

For oral administration of palonosetron HCl, three different formulations were used during the clinical development program. For early phase 1 and 2 dose-escalation studies, palonosetron was administered as a oral solution using IV formulations either a phosphate-buffered saline based formulation with pH 7 by Syntex or a citrate-buffered aqueous formulation with pH 5 by Helsinn. For phase 3 trials and some phase 1 and 2 trials, liquid-filled oral softgel capsules were used. The liquid formulation in the capsule was solution using a mono- and di-glyceride of capryl/capric acid (b) (4) as a (b) (4) (Table 4). For the marketing, the level of (b) (4) was reduced from (b) (4) and (b) (4) mono- and di-glycerides was increased from (b) (4) from that of the phase 3 clinical trials softgel capsule formulation to optimize shelf-life stability. The bioequivalence between the phase 3 trial formulation and the to-be-marketed formulation was demonstrated by in vivo BE study.

Table 4. Composition of the trial formulation and the to-be-marketed formulation

Names of Ingredients	Reference to standards	Clinical Trial Formulation (mg per capsule)			Proposed Commercial Formulation (mg per capsule)
		0.25 mg	0.50 mg	0.75 mg	0.50 mg
Active drug substance					
Palonosetron HCl	internal	(b) (4)			0.56[b]
Excipients					
Purified water	USP / Ph Eur	(b) (4)			
Glycerin (b) (4)	USP / Ph Eur				
Butylated hydroxyanisole (BHA)	NF / Ph Eur				
Polyglyceryl oleate (b) (4)[d]	FCC				
Mono- and di-glycerides of Capryl/Capric Acid (b) (4)	internal				
(b) (4)	NF				
Theoretical fill weight		133.00 mg	133.00 mg	133.00 mg	133.00 mg

(b) (4)

a corresponding to 0.25 mg free base
b corresponding to 0.50 mg free base
c corresponding to 0.75 mg free base
d Reference is made to (b) (4) supporting the manufacture of the softgel capsules.
* Indicates the only differences between the proposed commercial formulation and the phase 3 formulation.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Palonosetron HCL is a potent serotonin receptor subtype 3 (5-HT3) antagonist. Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 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.

This NDA is filed in support of oral palonosetron HCL at a dose of 0.50 mg, for the prevention of acute (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy. The proposed dosage administration is to take a single-dose of 0.5 mg palonosetron HCL at an hour prior to the initiation of chemotherapy.

2.2 General Clinical Pharmacology

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

In early phase 1 and phase 2 trials, the weight-based doses ranged from 0.3 to 90 µg/kg were given using an oral solution. The weight based doses were converted to fixed dose increments using oral capsule formulation for all subsequent clinical trials including phase 3 trials.

Phase 1

Study PALO-03-07 was conducted in 6 healthy Caucasian males (age 30-54 years) to define the mass balance and the metabolic profile of palonosetron given as a single oral dose of 0.75 mg [^{14}C]-palonosetron. The PK profile of the palonosetron and M9 metabolite was evaluated in plasma and urine. Whole blood and plasma concentrations of total radioactivity and cumulative excretion of radioactivity in urine and feces were evaluated.

Study 2236 was a dose-escalating randomized, double-blind, placebo-controlled study to determine the safety and PK of a single ascending oral dose of palonosetron in healthy Caucasian males (age 19 to 45 years). Groups of six subjects received a single oral dose of 3, 10, 20, 40, or 80 µg/kg palonosetron or placebo. Blood samples were collected 30 minutes pre-dose and up to 168 hours post-dose.

Study 0101 was a double-blind, placebo-controlled, ascending dose study conducted to determine the safety and PK of oral palonosetron in Japanese. Thirty-two healthy Japanese males aged 20 to 32 years, were enrolled in the study and received a single oral dose of 3, 10, 30, or 90 µg/kg, or placebo. Serial blood and urine samples for pharmacokinetic analysis were collected at scheduled intervals of time before dosing up to 168 hours post-dose.

Study PALO-04-04 was a randomized, open-label, three-way crossover study conducted in 36 healthy Caucasian subjects (male and female, age 18-45 years) to assess bioequivalence between clinical trial formulation and the to-be-marketed formulation and to assess the absolute bioavailability of the two formulations in comparison with palonosetron IV at 0.75 mg strength. The blood samples for PK analysis were collected up to 240 hours.

Study PALO-06-16 was a two-way crossover in-vivo bioequivalence study between the to-be-marketed formulation and clinical trial formulation at 0.50 mg strength. Thirty six healthy Caucasian subjects (18 males, 18 females, age 18-45) were enrolled and completed the trial and blood samples were collected up to 120 hours.

In **study PALO 04-02** the effect of a high fat meal and antacid administration on the PK profile of a single oral dose of 0.75 mg palonosetron in healthy Caucasian volunteers aged 18-45 years was evaluated in a single-center, randomized, three-way crossover study. Under fed condition, a standard high fat meal was ingested followed by palonosetron administration within 30 min. Antacid was taken 5 min prior to the drug administration. Because at the time of the study, phase 3 trial was on-going, the sponsor chose the highest dose for the study.

In **study PALO 04-01**, the PK profile of a single oral dose of 0.75 mg palonosetron in healthy Caucasian elderly subjects over 65 years of age was evaluated under fasting condition and compared with the PK parameters of younger subjects obtained under fasting condition from PALO-04-02.

Phase 2

Study 2332 was a randomized, double-blind, dose ranging study to evaluate the efficacy, safety, and pharmacokinetics of five oral doses of palonosetron in the prevention of CINV following highly emetogenic chemotherapy. Doses ranged from 0.3 µg/kg to 90 µg/kg (corresponding to fixed doses of approximately 0.025 mg to 6.25 mg) were studied subjects who were chemotherapy-naive with histologically proven cancer. Palonosetron (IV formulation by Syntex) was administered orally 30 minutes before the start of scheduled chemotherapy and dispensed in dosing cups diluted to a total volume of 25 ml by adding sterile water. The dosing cup was rinsed with an additional 25 ml of sterile water and this volume was swallowed. A total of 169 subjects (107 males and 62 females, aged 27 to 83 years) were enrolled and serial blood samples were collected from a subset of 41 patients at 30 minutes pre-dose and through to 168 hours post-dose.

Study 04-03 was conducted in Romania to assess the PK profile including dose proportionality of three doses (0.25 mg, 0.50 mg, and 0.75 mg, clinical trial formulation) of palonosetron in 36 cancer patients (age 33-75 years; 26 males, 10 females; 12 subjects per dose level) receiving moderately emetogenic chemotherapy under fasting conditions. The patients were treated with the single palonosetron dose on Day 1, 60 minutes prior to moderately emetogenic chemotherapy. In addition, all patients received 8 mg of IV dexamethasone on Day 1, 30 minutes before chemotherapy (for patients receiving paclitaxel, doxetaxel or pemetrexed, 20 mg IV dexamethasone could be used instead of 8 mg). Blood samples for PK analysis were collected at pre-dose and up to 192 hours post-dose at pre-determined interval (1, 2, 3, 4, 5, 6, 7, 24, 48, 72, 96, 168, and 192 hours).

Phase 3

In **study PALO-03-13**, subjects received a single oral dose of 0.25 mg, 0.50 mg or 0.75 mg 60 minutes before the start of moderately emetogenic chemotherapeutic agent or an IV dose of 0.25 mg palonosetron 30 minutes before moderately emetogenic chemotherapy (30 seconds bolus) as active control in a randomized, balanced, parallel group, double-dummy and stratified design. Randomization was stratified by gender and previous chemotherapy history (naïve or non-naïve to cancer chemotherapy) producing four strata. Total 639 patients were randomized and 157-163 patients were treated under each dose cohort. Each subject was randomized in balanced fashion (1:1:1:1) to receive one of the four treatments following an adaptive randomization algorithm which considered the strata. In each group, half of the subjects were randomized to receive 8 mg IV dexamethasone and the other half to receive IV saline solution as placebo for dexamethasone, on Day 1. The trial was a non-inferiority study versus approved IV palonosetron 0.25 mg.

Study PALO-03-14 was an open-label, uncontrolled study to evaluate mainly safety and additionally continued efficacy after multiple cycles at 0.75 mg dose. A single-dose palonosetron in clinical formulation was given 60 minutes before the start of the first moderately emetogenic chemotherapy and this treatment could be repeated up to a maximum of 4 consecutive cycles with 7 days of interval between each cycle.

2.2.2 What are the clinical endpoints measured in clinical pharmacology and clinical studies?

For phase 3 trials, the primary efficacy endpoint was the proportion of subjects with complete response (CR 0-24), defined as no emetic episode or retching during the first 24 hours after chemotherapy. Key

secondary efficacy endpoint was the proportion of subjects with complete response (CR 24-120) for the 24-120 hour interval after chemotherapy. Other secondary efficacy endpoints included, among others, severity of nausea (4-point Likert scale), the time to the first emetic episode; time to administration of rescue therapy; time to treatment failure (either first emesis or need for rescue medication, whichever occurred first); proportion of subjects with complete control (CC) of emesis, defined as no emesis, no rescue medication and only mild or no nausea; and global rating of satisfaction.

For the phase 2 trial 2332, only CR 0-24 was measured not CR 24-120 because preventive anti-emetic medications were allowed after 24 hours at principle investigators' discretion.

2.2.3 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Palonosetron was the main active moiety and measured in plasma by adequately validated bioanalytical assay methods and one of primary metabolites, M9 was measured in study 2332. The contribution of metabolites to response was not expected to be significant because the pharmacological activity of primary metabolites was reported to be less than 1% of palonosetron (the label of Aloxi for injection) and the systemic exposure was less than 20% of palonosetron.

2.2.4 Exposure-Response Evaluation

2.2.4.1 What are the characteristics of the exposure (dose)-response relationships for efficacy?

In phase 2 study (study 2332), dose-response relationship for efficacy was studied in chemotherapy naïve patients who were scheduled to receive their first doses of highly emetogenic chemotherapy e.g. cisplastin (>- 70 mg/m^2) or cyclophosphamide (>1100 mg/m^2). All patients included in efficacy analysis were received cisplastin-based chemotherapy while all patients were included in safety analysis.

Reviewer's comments: *The proposed indication is the prevention of CINV associated with moderately emetogenic chemotherapy.*

Twenty-six to 35 patients were treated with one of the doses of 0.3, 1, 3, 10, 30 and 90μg/kg. Because the lowest dose of 0.3 μg/kg was discontinued during the study due to apparent lack of efficacy, its results were combined with 1 μg/kg dose cohort. For analysis purposes, the efficacy of each dose was compared with the efficacy of the lowest dose (the combined cohort of patients treated with 0.3 or 1 μg/kg). The clinical response appeared to reach a plateau at a dose of 10 μg/kg (corresponding to 0.7 mg for 70 kg BW) and the clinical response at 10 μg/kg was higher than two lower dose cohorts, 0.3-1 μg/kg and 3 μg/kg (corresponding to 0.21 mg for 70 kg BW) (Figure 2 in page 4). The doses of 0.25 mg, 0.5 mg and 0.75 mg were chosen for the phase 3 trial since the efficacy of 0.25 mg was proven in the IV development program for moderately emetogenic chemotherapy (MEC) and the absolute BA of oral administration was greater than 90%.

In phase 3 study PALO-03-13, the percentage of patients with CR 0-24 after moderately emetogenic chemotherapy was 73.5%, 76.3% and 74.1% for 0.25 mg, 0.50 mg and 0.75 mg oral doses, respectively (Figure 3 in page 5). All three oral doses 0.25, 0.5 and 0.75 mg for CR 0-24 was shown to be non-inferior to 0.25 mg palonosetron IV administration. Nonetheless, the dose-response relationship among 0.25 mg, 0.5 mg and 0.75 mg was not evident. For the prevention of delayed CINV as defined by CR 24-120, none of the three doses met the pre-specified non-inferiority criteria to 0.25 mg IV administration. (b) (4) (For details, please, see the clinical review by Dr. Nancy Snow in Division of Gastroenterology Product).

In general, males showed a higher response CR 0-24 rate than females and in male patients, there was a slight increase in the percentage of patients with CR 0-24 with increasing dose (87.5%, 90.5% and 93.2% respectively for 0.25 mg, 0.50 mg and 0.75 mg), but not as consistently for CR 24-120. In female patients,

no dose dependence was evident regarding the percentage of patients with CR; all treatment groups had similar CR 0-24 and 24-120.

The sponsor proposes to support the NDA by the sole pivotal efficacy trial considering similar dose-response curves for oral and IV palonosetron over the doses and similar ADME of palonosetron between oral and IV administration as clinical safety and efficacy data of Aloxi for injection (NDA 21-372) are substantially applicable to oral palonosetron.

***Reviewer's comments**: Please, see the section 2.2.4.4. for discussion*

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

For details, please, see the clinical review by Dr. Nancy Snow in Division of Gastroenterology Product.
Overall, palonosetron was well tolerated in phase 1 and 2 studies at single doses ranging from 0.1 µg/kg to 90 µg/kg. The most frequent adverse events were headache, constipation, abdominal pain, and transient elevation of liver enzymes, none of which appeared to be dose related. Adverse events were generally mild to moderate in intensity, and all recovered without sequelae.

The most frequently occurred AEs in phase 3 study were constipation, headache, diarrhea and dizziness as shown in the table below. The incidence of most frequently occurred AEs was comparable between oral administration and IV administration in phase 3 trials (Table 4). No significant differences in the incidence of AEs over various doses were observed. Notably, PALO 03-14 an open-label safety study, the incidence of AEs was decreased with repeat chemotherapy.

Table 4. Adverse events occurred higher than 1% incidence in phase 3 studies: PALO 03-13 and PALO 03-14

	0.25 mg po N=157	0.5 mg po N=161	0.75 mg po N=375	0.25 mg I.V. N=163
constipation	7/4.5%	12/7.5%	29/7.7%	11/6.7%
headache	19/12.1%	26/16.1%	58/15.5%	24/14.7%
diarrhea	6/3.8%	9/5.6%	16/4.3%	11/6.7%
dizziness	5/3.2%	4/2.5%	4/1.1%	1/0.6%

When combined with phase 2 and phase 3 trials, the incidence of AEs and SAEs was higher for doses > 0.75 mg and < 0.25 mg compared to doses 0.25 mg, 0.5 mg and 0.75 mg (Table 5).

Table 5. The incidence of any adverse events in phase 2/3 trials

Dose*	<0.25mg	0.25 mg	0.5 mg	0.75 mg	> 0.75mg	Total	0.25 mg IV palonosetron
SAEs	25.8% (8/31)	5.4% (11/203)	5.5% (10/339)	3.6% (15/414)	16.2% (11/68)	6.1% (55/898)	0.6% (1/163)
Any AEs	74.2% (23/31)	54.7% (111/203)	51.6% (94/339)	54.1% (224/414)	79.4% (54/68)	56.3% (506/583)	47.9% (78/163)

*Body-weight based doses in phase 2 were converted to fixed doses
( ): number of patients with AE/total number of patients

***Reviewer's comments**: The doses <0.25 mg and >0.75 mg were studied exclusively for highly emetogenic chemotherapy in chemotherapy naïve patients whereas doses 0.25 mg, 0.5 mg and 0.75 mg were studied mainly for moderately emetogenic chemotherapy in both chemotherapy naïve and non-naïve patients..*

A thorough QT study demonstrated no effect of palonosetron on ECG of IV administration of 0.25 mg, 0.75 mg and 2.25 mg (the label of Aloxi for injection; NDA 21-372/S008).

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response?

The dose-response relationship of oral administration for the prevention of CINV in acute phase was found to be similar for CR 0-24 to IV administration.

In phase 2 study (study 2332), the dose-response relationship for CR 0-24 at the three higher doses was similar between oral and IV palonosetron while at the two lowest doses it seemed different. The sponsor noted an unexpectedly high response rate for the lowest 0.3-1 μg/kg dose cohort and it also seems that the 3 μg/kg had unexpectedly lower response rate compared to other dose cohorts. The percentage of free from emetic episodes up to 12hr post-dose was similar between the two low doses (69.2% for 0.3-1μg/kg and 71.9% for 3 μg/kg) while it was 88.6%, 80% and 84.8% for 10, 30, and 90 μg/kg, respectively. On the other hand the percentage of free from emetic episodes for the 3 μg/kg dose cohort dropped significantly to 25% between 12 to 24h while for other doses including the lowest dose cohort the percentage was 46.7 to 57.6%. This was unlikely due to pharmacokinetics since the plasma concentration of PAL at 24 h obtained from a subset of patients increased generally in a dose-proportional manner. Rather the difference in gender distribution in subjects may have contributed to either unexpected high or low response rate in two lower doses. The **3** μg/kg dose cohort had more females (52%) while the lowest dose 0.3-1 μg/kg dose cohort had a significantly less females (19%) compared to other dose cohorts (38-42%) and about 20% higher response rate in males than in females for all treatments was observed in phase 3 study. Furthermore, the response rate at 0.25 mg oral administration was comparable with IV administration within a study and across studies rendering the difference of the response rate at **3** μg/kg between oral administration and IV administration insignificant (Table 6).

Table 6. Patients with complete response by gender during 0-24 and 24-120 after start of chemotherapy

	Oral Palonosetron 0.25 mg (n=155)	Oral Palonosetron 0.50 mg (n=160)	Oral Palonosetron 0.75 mg (n=158)	I.V. Palonosetron 0.25 mg (n=162)
CR 0-24 (95% CI)				
Total	73.5% (65.8-80.2)	76.3% (68.8-82.5)	74.1% (66.4-80.5)	70.4% (62.6-77.1)
Male	87.5% (72.4-95.3)	90.5% (76.5-96.9)	93.2% (80.3-98.2)	82.2% (67.4-91.5)
Female	68.7% (59.3-76.8)	71.2% (62-79)	66.7% (57.1-75)	65.8% (56.4-74.2)
CR 24-120 (95% CI)				
Total	59.4% (51.2-67.1)	62.5% (54.5-69.9)	60.1% (52-67.7)	65.4% (57.5-72.6)
Male	72.5% (55.9-84.9)	85.7% (70.8-94.1)	77.3% (61.8-88)	75.6% (60.1-86.6)
Female	54.8% (45.3-64)	54.2% (44.8-63.4)	53.5% (44-62.8)	61.5% (52.1-70.2)

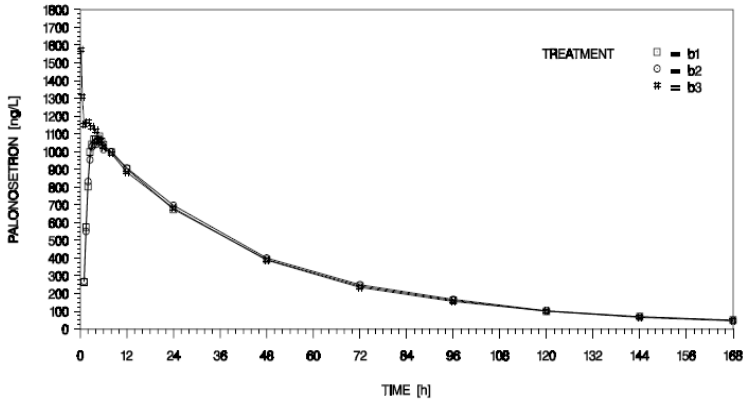
The proposed dose for prevention of acute (b) (4) CINV is 0.5 mg based on the analysis that 0.5 mg met the pre-specified non-inferiority criteria to 0.25 mg IV administration while dose of 0.25 mg is the lowest effective dose for prevention of acute CINV. However, 0.5 mg dose met the criteria only after post-hoc exploratory analysis by combination of historic IV controls to increase a number of subjects in a comparator arm (For details, please see the clinical review by Dr. Nancy Snow). As such for the efficacy of oral palonosetron for the prevention of delayed CINV has not been demonstrated in a statistically meaningful manner and the dose of 0.25 mg is appropriate for the prevention of acute CINV as an effective dose.

2.2.5 Pharmacokinetic Characteristics

2.2.5.1 What are the PK characteristics of the drug and its major metabolite?

The pharmacokinetic profile of palonosetron is characterized by a rapid initial decline of plasma concentration following single intravenous doses, with secondary peaks observed in some subjects approximately two to four hours post-dose. After oral dosing, the peak plasma concentrations were achieved between three and six hours and the plasma concentrations of palonosetron-time profile after Tmax was almost superimposable to the IV profile (Figure 5A and 5B). The mean half-lives are of the order of 40 hours in healthy volunteers and ranged 40-60 hours in patients. In dose-escalation studies using oral solution, plasma concentrations of palonosetron generally increased proportionally with doses over the range of 0.3 to 80 µg/kg for Cmax and AUC after oral administration (Table 7). No significant evidence of changes in clearance or volume of distribution with increasing dose was seen.

Figure 5A. Plasma concentration of Palonosetron-time profile following a single-dose of 0.75 mg oral palonosetron by the trial formulation (b1) and the to-be-marketed formulation (b2) and 0.75 mg IV palonosetron (b3)



b1:0.75 mg palonosetron softgel capsule (Formulation A; phase 3 clinical trial formulation)
b2:0.75 mg palonosetron softgel capsule (Formulation B; proposed commercial formulation)
b3:0.75 mg intravenous palonosetron (reference, 3 x 0.25 mg i.v. Aloxi®)

Figure 5B. Plasma concentration of Palonosetron-time profile following a single-dose of 0.75 mg oral palonosetron by the trial formulation (b1) and the to-be-marketed formulation (b2) and 0.75 mg IV palonosetron (b3) over 24 hours

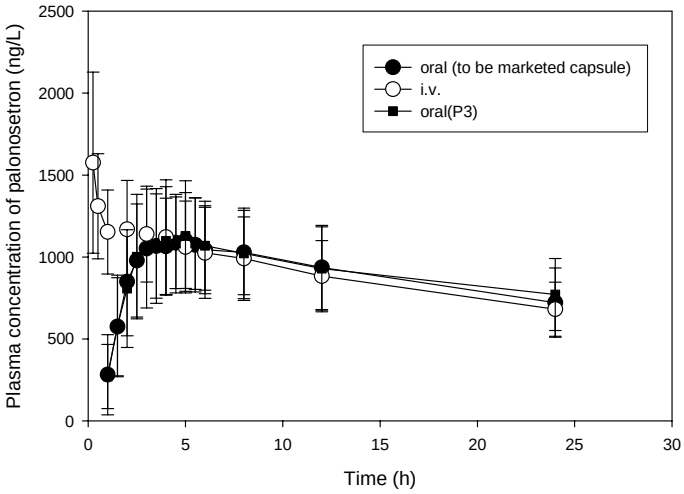


Table 7. Summary of PK parameters of palonosetron following a single administration in dose-escalating studies in white (study 2236) and Japaneses (study 0101) using oral solution

Study	Dose	Route	N	C_{max}		T_{max}		$AUC_{0-\infty}$		$t_{1/2}$		CL/F		CL_r		Vd/F		Comments
				ng/ml	% CV[a]	h	% CV[a]	ng·h/ml	% CV[a]	h	% CV[a]	ml/min	% CV[a]	ml/min	% CV[a]	l/kg	% CV[a]	
2236	(µg/kg)	Oral	(29)									(ml/min/kg)						Healthy volunteers
	3		6	0.422	± 0.085	5.67	± 1.51	18.6	± 5.34	37.5	± 7.09	2.83	± 0.604	NC		8.92	± 1.34	
	10		6	1.57	± 0.432	3.83	± 0.408	63.5	± 12.9	38.1	± 10.6	2.73	± 0.603			8.70	± 1.81	
	20		6	3.08	± 0.746	4.17	± 1.47	127	± 11.7	41.1	± 6.92	2.65	± 0.269			9.42	± 1.75	
	40		5	6.37	± 1.34	4.80	± 2.17	264	± 60.6	38.7	± 3.72	2.63	± 0.578			8.81	± 2.10	
	80		6	14.1	± 3.42	4.36	± 1.36	545	± 169.0	36.0	± 4.22	2.61	± 0.656			8.11	± 2.28	
0101	(µg/kg)	Oral	(24)									(ml/min/kg)		(ml/min/kg)				Healthy Japanese volunteers
	3		6	0.348	± 0.0453	4.33	± 0.816	14.5	± 3.81	31.7	± 5.12	3.63	± 0.899	0.726[b]	± 0.330	9.84	± 2.61	
	10		6	1.48	± 0.297	4.67	± 0.816	64.7	± 19.2	35.3	± 3.74	2.78	± 0.885	0.937[b]	± 0.298	8.33	± 2.00	
	30		6	3.68	± 0.570	4.67	± 0.516	133	± 27.0	30.6	± 3.12	3.89	± 0.712	1.21[b]	± 0.249	10.2	± 1.57	
	90		6	12.4	± 2.61	3.00	± 1.10	476	± 123.0	35.0	± 4.73	3.35	± 0.908	1.09[b]	± 0.233	9.92	± 2.09	

NC = Not calculated.
a Note: standard deviation (± SD) is reported where % CV was not calculated.
b Urine collection is 0 to 168 hours.

In oral ADME study (Study PALO-03-07) concentrations of total radioactivity after administration of 0.75 mg [^{14}C] palonosetron in whole blood generally paralleled those in plasma. The total radioactivity recovered in the urine accounted for a mean of 90.3% (range 85 to 93%) of the administered dose over a period of 288 hr post-dose and the excretion of the total radioactivity via faces accounted for a mean of 5.9% (range 4.4-8%) of the administered dose over a period of 240 hr post-dose. Mean recovery of total radioactivity was 96.1% with a range of 92.9 to 98.7%. There are two principal biotransformation routes, oxidation at the nitrogen to form the N-oxide metabolite, M9, and hydroxylation to form 6-S-hydroxy-palonosetron metabolite, M4. The mean total amount of palonosetron and M9 recovered in urine over the collection period of 144 hours corresponds to 41.1% and 12% of the administered dose, respectively. The mean total amount of M4 recovered in the urine was 17% of the administered dose (Table 8). These metabolites have about 1% of pharmacologic activity of the parent drug tested by 5-HT_3 antagonism activity in an ileal guinea pig model. Therefore, the contribution of the metabolites to the overall efficacy of oral palonosetron is negligible.

Table 8. Radio-HPLC summary table of metabolites present in the urine (0-144h) following a single oral administration of 0.75 mg [^{14}C] palonosetron in Caucasian males

Pool	Urine Sample		Assignment	Retention Time (min)	% Area	% Dose
	% Dose	% Procedural Recovery				
A (001M)	77.26	93.9	M4*	24.2	22.87	16.59
			M6*	29.9	2.73	1.98
				32.1	2.06	1.49
			08-Palo/M9#	36.9	14.12	10.25
			Palonosetron#	38.6	58.22	42.24
B (002M)	83.95	93.2	M4*	24.1	23.46	18.35
			M6*	29.7	2.79	2.18
				32.1	2.85	2.23
			08-Palo/M9#	36.8	17.06	13.35
			Palonosetron#	38.5	53.84	42.13
C (003M)	85.77	92.3	M4*	24.0	20.04	15.87
				25.4	1.39	1.10
				29.6	4.96	3.93
			M6*	32.1	1.63	1.29
			08-Palo/M9#	36.9	17.43	13.80
			Palonosetron #	38.5	54.57	43.20
D (004M)	85.28	90.6	M4*	23.9	17.94	13.86
			M6*	29.5	3.40	2.63
				32.3	1.76	1.36
			08-Palo/M9#	36.9	14.96	11.56
			Palonosetron#	38.5	61.94	47.86
E (005M)	86.69	90.7	M4*	24.7	22.48	17.68
			M6*	30.0	4.49	3.53
				32.1	3.66	2.88
			08-Palo/M9#	36.9	12.28	9.66
			Palonosetron#	38.5	57.09	44.89
F (006M)	80.59	83.1	M4*	23.9	31.41	21.03
			M6*	29.7	6.88	4.61
				32.1	1.77	1.19
			08-Palo/M9#	36.8	21.05	14.10
			Palonosetron#	38.4	38.89	26.05

* Assigned following LC-MS analysis and with reference to Inveresk Summary Report 21356
\# Assigned following LC-MS analysis, with reference to Inveresk Summary Report 21356 and confirmed by co-chromatography with an authentic reference standard

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. In plasma, a higher pre-systemic metabolism was indicated by higher exposure of M9 and M4 after oral administration and a shorter time to achieve the peak concentration of M9 and M4 after oral administration

than after IV administration (Table 9, Figure 11). The systemic exposure of M9 was 94% higher in terms of AUCt and 10% higher for Cmax after oral administration than after IV administration. On the other hand, mean Cmax of M4 was 37% higher while mean AUCt of M4 remained unchanged after oral administration.

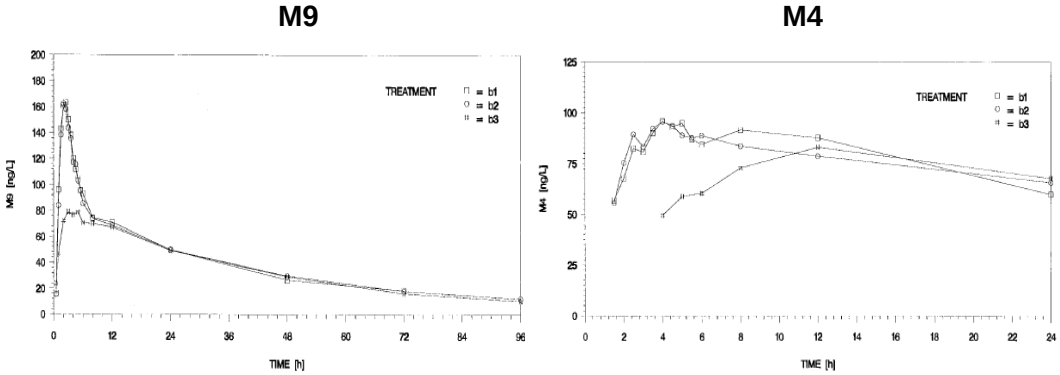
***Reviewer's comment**: The shorter tmax and higher Cmax of M9 suggested that the pre-systemic intestinal metabolism occurs after oral administration. Although increase in Cmax of and AUC, the overall systemic exposure to M9 remained less than 10% of palonosetron. In addition, according to the label of Aloxi for injection, after a single intravenous dose of 10 μg/kg [^{14}C]-palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine with palonosetron representing approximately 40% of the administered dose and approximately 50% metabolized to form two primary metabolites. Similarly after oral administration of 0.75 mg [^{14}C]-palonosetron, about 40% of the administered total radioactivity was recovered in the urine as unchanged palonosetron. This suggests that the pre-systemic metabolism in the intestine is not significant. Therefore, the drug-drug interaction potential via pre-systemic metabolism appears to be lower.*

Table 9. Mean (SD) of PK parameters for palonosetron and metabolites after oral and iv administration of palonosetron

		0.75 mg Oral Trial formulation	0.75 mg Oral To-be-marketed formulation	0.75 mg IV Administration (3X 0.25mg IV Aloxi)
PAL	AUCt (ng h/L)	53835 (17961)	55235 (17817)	53088 (15233)
	AUC_{∞}(ng h/L)	57403 (17898)	58285 (18110)	56480 (15343)
	Cmax(ng/L)	1224 (348)	1200 (324)	1665 (528)
	Tmax* (h)	4.5 (2-8)	4.8 (2-12)	0.25 (0.25-4)
M4	AUCt (ng h/L)	2336 (1499)	2365 (1529)	2275(1671)
	Cmax(ng/L)	121.7(40.7)	115.3(36.7)	94.9(23.0)
	Tmax* (h)	4.7 (2.5-12)	4.5 (2-24)	12 (5-24)
M9	AUCt (ng h/L)	3817 (1569)	3855 (1397)	3443 (1249)
	AUC_{∞}(ng h/L)	4850 (2105)	4783 (1574)	4426 (1300)
	Cmax(ng/L)	175.6 (91.6)	170 (68.7)	90.8 (31.2)
	Tmax* (h)	2.5 (1.5-5.6)	2.0 (1.5-5)	4.5 (2-12)

* median (min-max)

Figure 11. Mean Concentration Time Curves of major metabolites, M9 and M4 for 0.75 mg Capsule: Trial formulation (b1) and to-be-marketed* (b2) and 0.75 mg IV palonosetron (b3)



* Proportionally similar formulation with the proposed to-be-marketed formulation for 0.5 mg strength

2.2.5.3. What are the single dose and multiple dose PK parameters?

Following a single administration of 0.5 mg and 0.75 mg palonosetron in the to-be-marketed formulation in healthy subjects, the Cmax was 810 ± 166 pg/ml and 1200 ± 324 pg/ml, respectively and median Tmax was 4-5 hours (Table 10, 11). The mean AUC was 38.2 ± 11.7 ng·h/ml and 55.2 ±17.8 ng·h/ml after 0.5 mg and 0.75 mg dosing, respectively. Pharmacokinetics for 0.25 mg dose using oral capsule was evaluated only in cancer patients not in healthy subjects.

Multiple dose PK was not studied in support of oral administration of palonosetron but was conducted for IV administration. According to the label for Aloxi for injection, following IV administration of palonosetron 0.25 mg once daily for 3 days in 12 healthy subjects, the mean (± SD) increase in plasma palonosetron concentration from Day 1 to Day 3 was 110 ±45%

Reviewer's comments: *Because palonosetron will be given as a single-dose prior to chemotherapy regimen, a lack of multiple-dose PK is not considered a major deficiency. Nonetheless, it is noted that the sponsor proposed the use of oral palonosetron for repeated chemotherapy and conducted an open-label safety and efficacy study for up to 4 cycles of chemotherapy with 7 day-interval between cycles. With the mean half-life about 40-60 hours for palonosteron, the majority of palonosteron is expected be eliminated from the body during 7 day dosing interval for chemotherapy.*

Table 10. Summary of PK parameters of palonosetron following 0.5 mg oral administration of capsule formulation

Pharmaco-kinetic parameter Palonosetron [unit]		0.50 mg Palonosetron oral administration (formulation A) N=36	0.50 mg Palonosetron oral administration (formulation B) N=36
AUC_{0-t} [ng·h/L]	Mean (SD)	34076 (9874)	35106 (11012)
	Geo. Mean (Geo. SD)	32766 (1.33)	33530 (1.36)
	Median	33641	34981
	Minimum-Maximum		
$AUC_{0-\infty}$ [ng·h/L]	Mean (SD)	37099 (10141)	38176 (11698)
	Geo. Mean (Geo. SD)	35834 (1.30)	36555 (1.35)
	Median	36859	37627
	Minimum-Maximum		
C_{max} [ng/L]	Mean (SD)	785.241 (182.437)	810.176 (165.985)
	Geo. Mean (Geo. SD)	765.702 (1.25)	793.900 (1.23)
	Median	750.344	816.457
	Minimum-Maximum		(b) (4)
t_{max} [h]	Median	5.500	5.000
	Minimum-Maximum		(b) (4)
$t_{1/2\lambda z}$ [h]	Mean (SD)	36.248 (9.565)	37.264 (12.015)
	Median	34.378	35.262
	Minimum-Maximum		(b) (4)

Form A: trial formulation; Form B: To-be-marketed formulation

Table 11. Summary of PK parameters of palonosetron following 0.75 mg oral administration of capsule formulation

Pharmaco-kinetic parameter Palonosetron [unit]		0.75 mg Palonosetron oral administration (formulation A) N=33	0.75 mg Palonosetron oral administration (formulation B) N=33	0.75 mg Palonosetron intravenous administration (3 x 0.25 mg i.v. Aloxi®) N=30
$AUC_{(0-t)}$ [ng·h/L]	Mean (SD)	53835 (17961)	55235 (17817)	53088 (15233)
	Geo.Mean (Geo.SD)	50716 (1.44)	52536 (1.39)	50793 (1.37)
	Median	50978	53325	50984
	Minimum-Maximum	16971 - 96273	20951 - 111916	20609 - 78424
$AUC_{(0-\infty)}$ [ng·h/L]	Mean (SD)	57403 (17898)	58285 (18110)	56480 (15343)
	Geo.Mean (Geo.SD)	54539 (1.40)	55638 (1.37)	54324 (1.34)
	Median	54614	56802	54011
	Minimum-Maximum	18773 - 100234	24473 - 114765	24142 - 81547
C_{max} [ng/L]	Mean (SD)	1223.985 (348.324)	1200.620 (324.606)	1665.314 (527.638)
	Geo.Mean (Geo.SD)	1178.670 (1.32)	1160.078 (1.31)	1588.758 (1.37)
	Median	1208.136	1133.115	1628.480
	Minimum-Maximum			(b) (4)
t_{max} [h]	Median	4.520	4.530	0.250
	Minimum-Maximum			(b) (4)

2.2.5.3 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Following a single-dose administration of oral palonosetron, the systemic exposure in patients was generally dose-proportional over 0.3-90 μg/kg dose range (study 2332) (Table 12,13). The total body clearance in the cross-study comparison, the clearance was generally lower in patients (1.12-1.78

ml/min/kg) than in healthy subjects (2.61-2.83 ml/min/kg). Following 0.5 mg and 0.75 mg administration mean AUC was 28% and 86% higher in cancer patients, respectively and mean Cmax was 14% and 22% higher in cancer patients, respectively (Table 14). The median t_{max} ranged from 3.5 -6 hours. The mean half-life of palonosetron was 50 and 48 hours for the dose of 0.25 mg and 0.5 mg, respectively and it was 64 ± 35 hours after 0.75 mg palonosetron oral administration.
For metabolites, the mean ratio of AUCt of M9 to palonosetron was 5.6-7.7% with individual values ranging between 1.52 and 15.02%. For doses of 0.5 and 0.75 mg, the mean ratio of AUCt of M4 to palonosetron was 9.4 % with individual values ranging between 0.5 to 23%. Concentrations of M4 were not measurable in most patients receiving 0.25 mg and when measurable were highly variable. The biotransformation to M4 and M9 was generally similar between in healthy subjects and patients.

Reviewer's comments: *The plasma concentrations of M4 were calculated using a standard curve of M9 due to unavailability of a reference standard at the time of analysis and subsequently converted to M4 using a detector response ratio between M4 and M9. Because QC was not performed for M4 assay during the run, the M4 measurements for study PALO 04-03 were not adequately validated.*

Table 12. Summary of PK parameters of palonosetron after a single-dose administration of oral solution in cancer patients who received highly emetogenic chemotherapy

RS-25259 Parameter		Mean (± SD)				
	0.3 µg/kg (n = 1)	1 µg/kg (n = 6)	3 µg/kg (n = 6)	10 µg/kg (n = 8)	30 µg/kg (n = 8)	90 µg/kg (n = 12)
C_{max} (ng/mL)	0.134	0.178 (0.0847)	0.423 (0.277)	2.09 (1.29)	5.83 (1.77)	16.3 (7.18)
T_{max} (hr)	4.00	14.7 (10.7)	7.78 (7.98)	5.49 (7.58)	6.20 (9.11)	4.15 (6.51)
Half-life (hr)	NC	66.6 (34.8)	64.9 (24.3)	72.8 (32.7)	45.4 (11.0)	60.8 (41.3)
AUC_{0-24} (ng•hr/mL)	2.35	2.94 (1.71)	7.64 (4.51)	35.3 (23.4)	76.4 (43.1)	268 (126)
Total AUC (ng•hr/mL)	NC	15.9 (4.46)	37.2 (15.8)	156 (87.6)	363 (187)	978 (426)
Clearance (mL/min/kg)	NC	1.12 (0.308)	1.52 (0.579)	1.48 (0.926)	1.70 (0.753)	1.78 (0.677)
Volume (L/kg)	NC	6.49 (3.73)	7.77 (1.27)	8.85 (5.55)	6.09 (1.62)	8.64 (5.65)

NC = not calculable due to missing or BQL plasma concentrations

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Table 13. Summary of PK parameters of palonosetron after a single-dose administration of oral capsules in cancer patients who received a moderately emetogenic chemotherapy

Dose	Statistic	t_{max} (h)	C_{max} (ng/L)	AUC_{0-t} (h*µg/L)	AUC_{0-72} (h*µg/L)	$AUC_{0-\infty}$ (h*µg/L)	$t_{1/2z}$ (h)	Cl/F (L/h)	V_z/F (L)
0.25 mg N=12	n	12	12	12	12	12	12	12	12
	Mean	13.10	553.4	26.81	20.24	34.22	49.91	8.45	553.4
	SD	14.28	230.8	13.52	6.49	13.62	19.52	3.27	205.4
	Min	(b) (4)							
	Median	6.00	571.0	21.10	18.25	30.85	49.95	8.21	559.5
	Max	(b) (4)							
	Geom. Mean	-	507.8	24.04	19.31	31.81	-	7.86	516.3
	CV (%)	-	46.8	50.7	33.0	41.7	-	41.7	41.8
0.50 mg N=12	n	12	12	12	12	11	11	11	11
	Mean	5.12	927.6	44.09	33.22	49.65	48.25	10.65	724.9
	SD	5.93	343.9	12.93	7.67	12.18	19.02	2.80	283.4
	Min	(b) (4)							
	Median	3.50	869.0	43.30	31.35	48.40	43.60	10.30	732.0
	Max	(b) (4)							
	Geom. Mean	-	876.5	42.31	32.41	48.30	-	10.35	673.7
	CV (%)	-	35.4	31.2	23.7	25.3	-	25.4	42.8
0.75 mg N=12	n	12	12	12	12	12	12	12	12
	Mean	9.86	1419	87.89	55.86	103.3	64.73	8.04	656.7
	SD	9.81	364.1	21.17	10.43	37.26	35.73	2.47	149.6
	Min	(b) (4)							
	Median	4.00	1435	85.10	53.70	95.25	50.80	7.94	656.0
	Max	(b) (4)							
	Geom. Mean	-	1375	85.60	55.01	97.88	-	7.66	641.5
	CV (%)	-	27.1	24.3	18.3	34.4	-	34.4	22.8

Reviewer's comment: *In study 2332, the total body clearance appeared to be lower and the half-lives were longer than in PALO 04-03. Studies 2332 and PALO 04-03 conducted in patients differed for*

bioanalytical assay (LC/MS for 2332 and LC/MS/MS for PALO 04-03), dosage form (oral solution for 2332 and capsule LC/MS/MS) and the region of study (US versus Romania). Because of these differences, the cross-study comparison has a limited value.

Table 14. Cross-study comparison for PK parameters of palonosetron in healthy subjects and cancer patients

Dose[1]	Parameters	Healthy Mean (SD)	Cancer patients Mean (SD)	Ratio of Mean
3 μg/kg solution	Cmax (ng/ml) AUC_∞ (ng·h/ml)	0.422 (0.085) 18.6 (5.34)	0.423 (0.28) 37.2 (15.8)	1 2
0.5 mg capsule	Cmax (ng/ml) AUC_∞ (ng·h/ml)	0.81 (0.16) 38.2 (11.7)	0.93 (0.34) 49.65 (12.2)	1.14 1.26
0.75 mg capsule	Cmax (ng/ml) AUC_∞ (ng·h/ml)	1.2 (0.13) 58.3 (18.1)	1.42 (0.36) 103.3 (37.3)	1.22 1.86

[1] Data from study 2236 (3 μg/kg for healthy subjects, male only), study 2332 (3 μg/kg for patients), PALO 06-16 (0.5 mg for healthy subjects), study PALO 04-04 (0.75 mg for healthy subjects), PALO 04-03 (0.5 mg, 0.75 mg for patients)

Reviewer's comment:*It was noted that two subjects in PALO 04-03 study appeared to have a lag time of 2-4 hours for unexplained reasons (subjects 150 and 160). It was also noted that some patients had long half-lives greater than 100 hours. This could be in part due to insufficient sampling duration or assay sensitivity indicated by greater than 20 % difference of AUC_∞ and AUC_{last}.*

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

Renal insufficiency and hepatic insufficiency

No dosage adjustment is currently recommended for patients with mild to moderate hepatic impairment or renal impairment in the current labeling of Aloxi for injection. Study was not done for subjects with the end-stage renal impairment.

CYP2D6 polymorphism

Clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates (the label of Aloxi for injection).

Age

The only special population study performed during the oral development program was an evaluation of palonosetron PK in healthy elderly subjects. The pharmacokinetics of palonosetron and M9 in elderly subjects are similar to young subjects after oral administration of the softgel capsule, however, Cmax appears slightly lower by 13% in the elderly (Figure 12, Table 15). Exposure to M9 is approximately 12% of the parent drug in both populations. M4 concentrations appear somewhat higher in the elderly compared to young subjects; M4 exposure in elderly subjects is slightly less than 4% while it is essentially immeasurable in young subjects (04-02 subjects). No dosage adjustment for age is necessary.

Table 15. Point estimate of PK parameters of elderly/young and associated 90% CI for palonosetron

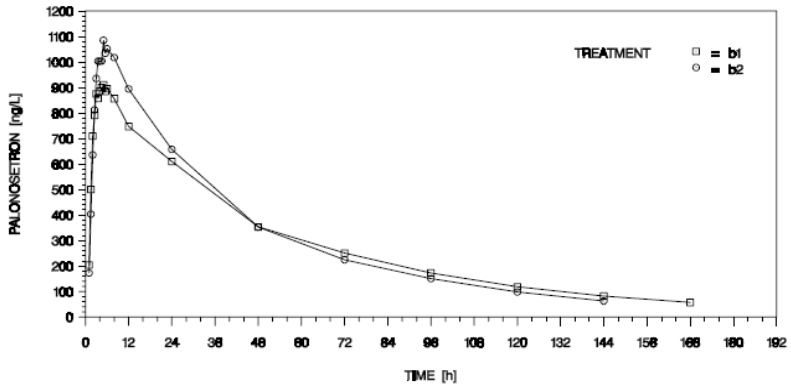
Gender	Pharmacokinetic parameter	Point estimate Test/Ref.	90% Confidence interval
Total	$AUC_{(0-t)}$	98.82	85.58 - 114.09
	$AUC_{(0-\infty)}$	101.08	87.33 - 116.98
	C_{max}	87.09	78.44 - 96.70

Test: 0.75 mg palonosetron given under fasting condition to the elderly
Reference: 0.75 mg palonosetron given under fasting condition to the young

Reviewer's comment: *Measurement of M4 concentration was initially based on the standard curve of M9 due to unavailability of reference standard M4 at the time of assay. Later a detector response ratio was determined for M9 versus M4 after the analytical reference for M4 became available by the detector*

response ratio and used to convert M4 concentrations. Because the QC for M4 assay was not conducted during the run, the measurements of M4 were not validated. It is unknown why plasma M4 levels in the young group are considerably lower than in other young group from different studies.

Figure 12. Plasma concentration-time curve of palonosetron following a single dose of 0.75 mg palonosetron under fasting condition

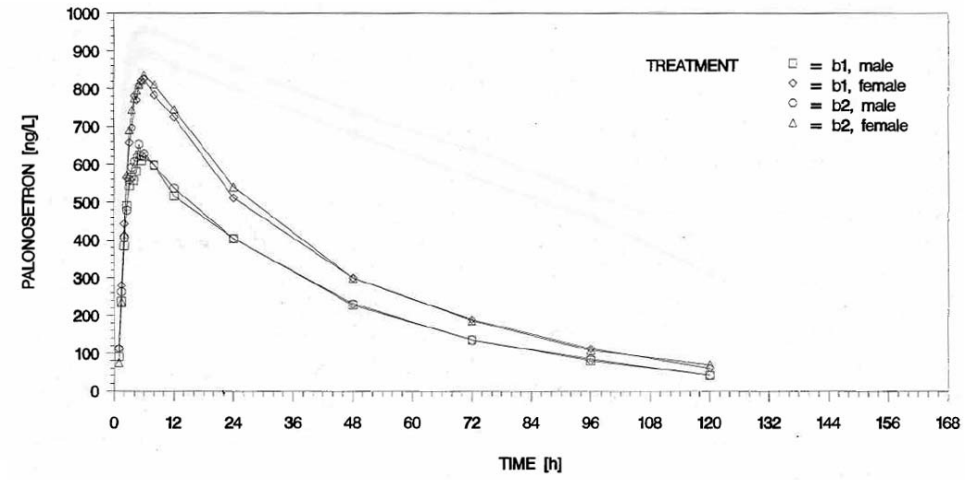


b1: 0.75 mg palonosetron (phase 3 formulation) given under fasting conditions (test, elderly, N=18)
b2: 0.75 mg palonosetron (phase 3 formulation) given under fasting conditions (reference, young, N=17)

Gender

Gender effect was observed in systemic exposure to palonosetron (Table 16, Figure 13). Across three studies exposure to palonosetron was 20-38% higher in females compared to males regardless of age and route of administration. This difference may be due to the lower body weight for females. M9 exposure was 10-30% higher in females for the young but 15% higher in males for the elderly. Difference in M4 exposure by gender was not consistent across studies.

Figure 13. Plasma concentration-time curve of palonosetron by gender following a single dose of 0.50 mg palonosetron



b1: ORAL ADMINISTRATION OF 0.50 mg PALONOSETRON AS A SOFTGEL CAPSULE (REFERENCE, FORMULATION A)
b2: ORAL ADMINISTRATION OF 0.50 mg PALONOSETRON AS A SOFTGEL CAPSULE (TEST, FORMULATION B)

Revewer's comments: *Despite the generally lower exposure of palonosetron, the efficacy response rate in phase 3 study was generally higher in males. The incidence of any AEs was similar between gender groups at various dose levels (Table 17). No dosage adjustment based on gender is necessary. (For details, please see a clinical review by Dr. Nancy Snow of Division of Gastroenterology Products)*

Table 16. The mean AUCt [ng·h/L] by gender following a single-dose of 0.5 mg capsule in healthy subjects

	Male (n=18)	*Female (n=18)*
Palonosetron	*29463 (8026)*	*40749 (10855)*
*M4**	*1192(923)*	*854(664)*
M9	*1775 (834)*	*2238 (1252)*

** male (n=13); female (n=15)*

Table 17. The incidence of adverse events in phase 2/3 trials

	Gender	<0.25mg	0.25 mg	0.5 mg	0.75 mg	> 0.75 mg	Total	IV palnosetron
Any AEs	Total	74.2% (23/31)	54.7% (111/203)	51.6% (94/339)	54.1% (224/414)	79.4% (54/68)	56.3% (506/583)	47.9% (78/163)
	Male	72% (18/25)	50% (32/64)	45.5% (25/55)	56.96% (74/130)	80.5% (33/41)	57.8% (182/315)	44.4% (20/45)
	Female	83.3% (5/6)	56.8% (79/139)	54.3% (69/284)	52.8% (150/284)	77.8% (21/27)	55.6% (324/583)	49.2% (58/118)

Race

The total body clearance was 26% higher in Japanese subjects and the Cmax was slightly lower in Japanese than in Caucasian. In Japanese male subjects, the total body clearance was 2.7-3.9ml/min/kg and it was 2.6-2.8 ml/min/kg in Caucasian males. The dose normalized mean Cmax was 0.14-0.18 ng/ml in Japanese and 0.12-0.15 ng/ml in Caucasian. PK was not characterized in other race.

Reviewer's comments: *In the label of Aloxi for injection, the consistent trend was observed after IV administration such that total body clearance was 25% higher in Japanese subjects compared to Whites. However, no dose adjustment is recommended. For the combined phase 2/3 trials, the proportion of Caucasian, Black, Hispanic, Asian and other race subjects was approximately 70%, 3%, 25% 1% and 1%, respectively.*

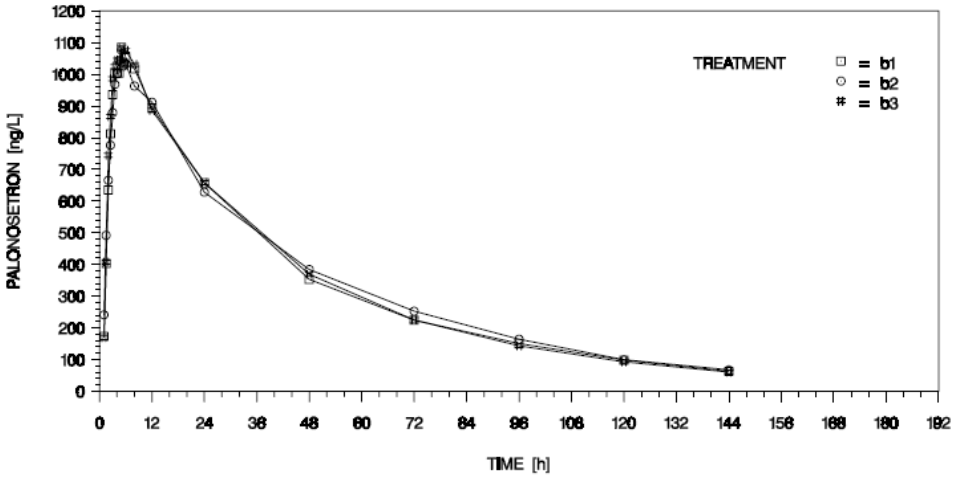
2.4 Extrinsic Factors

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

High fat diet-

Effect of high fat diet was evaluated for the clinical trial softgel capsule formulation using the FDA recommended high fat meal. A high fat diet was ingested within 30 min of drug administration. For palonosetron, all 90% CIs for AUC and Cmax parameters obtained under fasting or fed conditions were within the 80-125% range. As such high fat diet did not affect PK of Palonosetron (Figure 14, Table 18). As for metabolites, high fat meal did not affect AUC of M9 (90% CI: 87.80-112.06) but decreased the peak concentration of M9 about 15% (90% CI: 79.3-93.0) and M4 could not be assessed.

Figure 14. Palonosetron plasma concentrations (arithmetic mean) following palonosetron 0.75 mg after fasted (b1), fed (b2), and concomitant antacid administration (b3). N=17 (PALO-04-02)



***Reviewer's comments**: Although it is less likely for cancer patients who are scheduled to receive emetogenic chemotherapeutics to have a high fat meal close to the initiation of chemotherapy, the food effect study indicates that patients may take oral palonosetron with any type of meal if desired.*

Table 18. Summary of pharmacokinetic parameters for palonosetron by treatment

Pharmacokinetic parameter Palonosetron [unit]		0.75 mg Palonosetron under fasting conditions (Reference) N=17	0.75 mg Palonosetron after high-fat breakfast (Test 1) N=17	0.75 mg Palonosetron + antacid under fasting conditions (Test 2) N=17
$AUC_{(0-t)}$ [ng*h/L]	Mean (SD)#	47915 (1.26)	49163 (1.27)	48087 (1.20)
	Median	51666	53562	48400
	Range			(b) (4)
$AUC_{(0-\infty)}$ [ng*h/L]	Mean (SD)#	51274 (1.26)	52326 (1.26)	51668 (1.19)
	Median	54941	56847	52045
	Range			(b) (4)
AUC_{ext} [%]	Mean (SD)#	6.2 (1.41)	5.7 (1.37)	6.7 (1.31)
	Median	6.2	5.8	6.5
	Range			(b) (4)
C_{max} [ng/L]	Mean (SD)#	1156 (1.19)	1132 (1.17)	1151 (1.23)
	Median	1173	1187	1162
	Range			(b) (4)
t_{max} [h]	Median	4.5	5.0	5.0
	Range			(b) (4)
λz [1/h]	Mean (SD)#	0.018 (1.29)	0.019 (1.20)	0.018 (1.18)
	Median	0.018	0.019	0.019
	Range			(b) (4)
$t_{1/2\lambda z}$ [h]	Mean (SD)#	37.5 (1.29)	36.9 (1.20)	38.0 (1.18)
	Median	38.2	37.3	37.1
	Range			(b) (4)

#geometric mean

Antacid

The effect of concomitant administration of an antacid on PK of palonosetron (clinical trial formulation) was evaluated in healthy volunteers (Figure 14, Table 18). Antacid, Maloxx® was taken 5 minutes prior to palonosetron administration under fasting condition. No effect of concomitant administration of antacids on the pharmacokinetics of palonosetron was observed. Results indicated that for palonosetron and M9 similar PK profiles were obtained when palonosetron was administered alone or in combination with an antacid. Point estimates and 90% confidence intervals for palonosetron and M9 lie within the range of 80-125% confirming no significant drug interaction. M4 was not quantifiable in a number of samples and highly variable.

2.4.2 Drug-Drug Interactions

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

In vitro studies were previously conducted and reflected in the Aloxi IV label. Other than effect of concomitant antacid, no studies were conducted for oral palonosetron administration.

***Reviewer's comments**: A mass balance study for oral administration indicated that metabolic profile of orally administered palonosetron is similar to that after intravenous administration and the contribution of pre-systemic metabolism is not significant based on the comparable recovery of unchanged palonosetron in the urine (about 40% of administered dose over 144 hours post-dose) after oral and IV administration. A higher pre-systemic metabolism after oral administration was indicated by higher exposure of M9 and M4 and a shorter time to achieve the peak concentration of M9 and M4 than after IV administration. The systemic exposure of M9 was 94% higher in terms of AUCt and 10% higher in terms of Cmax after oral administration than after IV administration. On the other hand, mean Cmax of M4 was 37% higher while mean AUCt of M4 remained unchanged after oral administration. Although increase in Cmax of and AUC, the systemic exposure to M9 remained less than 10% of palonosetron. As such the pre-systemic metabolism was not significant and the drug-drug interaction potential via pre-systemic metabolism appears to be low.*

2.5 General Biopharmaceutics

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility and permeability support this classification?

Palonosetron hydrochloride is freely soluble in water (Aloxi for injection label) and high solubility of palonosetron was demonstrated at various pH conditions (Table 19).

Table 19. Analytical Results of pH-Solubility Profile of Palonosetron

Aqueous Medium	Sampling	Solubility1 (mg/mL)	Dose/Solubility2 mL	Dose/Solubility3 Volume ≤ 250mL (yes/no)
pH 1.2 HCl buffer	after 4h	0.0043	174	Yes
	after 24h	0.0038	197	Yes
pH 5.0 Acid Phthalate buffer	after 4h	0.0045	167	Yes
	after 24h	0.0040	188	Yes
pH 8.0 Phosphate buffer	after 4h	0.0041	183	Yes
	after 24h	0.0043	174	Yes

[1] Solubility limit value 0.003 mg/mL according to FDA guidance entitled, "Waiver for In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System".
[2] The highest phase 3 oral dosage strength, 0.75 mg, was used. Calculation of Dose/Solubility = 0.75 mg/Solubility in mg/mL in accordance with FDA guidance entitled, "Immediate Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation".
[3] According to BCS classification, high solubility drugs are those with a Dose/Solubility Volume of less than or equal to 250 mL. Accordingly palonosetron HCl is classified as a high solubility drug.

The permeability of palonosetron HCl was addressed based on absolute bioavailability resulted from study PALO-04-04. PK data from this study indicate that oral palonosetron has 96.6% and 97.3% relative bioavailability for AUC0-t and AUC0-∞, respectively, for the 0.75 mg oral dosage form (phase 3 softgel capsule formulation) relative to 0.75 mg administered IV. High permeability of palonosetron is also supported by the findings that 90% (83-93%) of administered total radioactivity was recovered in the urine in the mass balance study. Based on these in-vivo data, palonosetron is considered a highly permeable drug. These data serve as the basis for designating palonosetron HCl as a BCS Class 1, highly soluble and highly permeable drug.

***Reviewer's comment:** For the mass balance study, palonosetron dissolved in sterile water was administered. As such the observed high absolute BA of oral palonosetron product appears to be mainly attributed to intrinsic properties of palonosetron.*

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

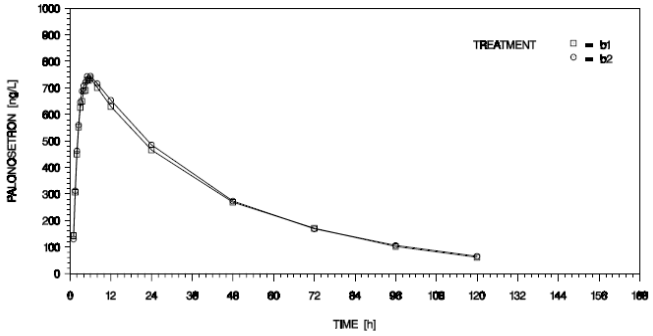
The to-be-marketed formulation and the trial formulation are bioequivalent

The to-be-marketed (TBM) formulation was modified from the phase 3 trial formulation to improve shelf-life stability by (b) (4) the formulation change was determined as SUPAC-IR level 2 change in a previous communication between the sponsor and the Agency.

The two formulations of 0.5 mg strength were compared in a two-way cross-over in vivo bioequivalence study. Thirty-six healthy subjects were enrolled (18 males and 18 females) and all of them completed the study. The ratio of AUCt and AUC_{∞} of PAL after administration of TBM and the phase 3 trial formulation (trial formulation hereafter) was 102.3% (90% CI: 98.9-105.9%) and 102.0% (90% CI: 98.6-105.6%), respectively and the ratio of Cmax of PAL after administration of TBM and the phase 3 formulation was 103.7% (90% CI: 100.5-107.0%) (Figure 15, Table 22-23). As such the comparison of pharmacokinetic parameters met the bioequivalence criteria, 90% CI: 80-125% and the bioequivalence between TBM and trial formulation was demonstrated.

The bioequivalence was also demonstrated between trial formulation and the TBM for 0.75 mg strength such that the ratio Cmax and AUC_{∞} of TBM to trial formulation were 98.4% (90% CI: 93.4-103.6%) and 102% (96.5-107.8) respectively.

Figure 15. Arithmetic Mean Concentration versus Time profiles for palonosetron Formulation b1= phase 3 clinical formulation and b2= commercial formulation (PALO-06-16, 0.50 mg Capsule Strength)



Source: Final Report PALO-06-16, Figure 11.4-1

The sponsor also conducted BE and absolute BA study with 0.75 mg strength, the highest phase 3 trial dose and the sponsor conducted a pivotal BE study with 0.5 mg strength because it is a proposed commercial dose.

Reviewer's comment: *This reviewer think that this pivotal BE study for the commercial strength after conducting at a higher strength could have been waived because PK in the range is dose-proportional, the formulation is proportionally similar such that the formulation change due to the active ingredient content as a free base is less than 0.3% of total filled liquid weight which remained constant.*

Table 22. PK parameters following a single-dose of 0.5 mg palonosetron oral capsule

Pharmaco-kinetic parameter Palonosetron [unit]		0.50 mg Palonosetron oral administration (formulation A) N=36	0.50 mg Palonosetron oral administration (formulation B) N=36
AUC_{0-t} [ng·h/L]	Mean (SD)	34076 (9874)	35106 (11012)
	Geo. Mean (Geo. SD)	32766 (1.33)	33530 (1.36)
	Median	33641	34981
	Minimum-Maximum	(b) (4)	
$AUC_{0-\infty}$ [ng·h/L]	Mean (SD)	37099 (10141)	38176 (11698)
	Geo. Mean (Geo. SD)	35834 (1.30)	36555 (1.35)
	Median	36859	37627
	Minimum-Maximum	(b) (4)	
C_{max} [ng/L]	Mean (SD)	785.241 (182.437)	810.176 (165.985)
	Geo. Mean (Geo. SD)	765.702 (1.25)	793.900 (1.23)
	Median	750.344	816.457
	Minimum-Maximum	(b) (4))	
t_{max} [h]	Median	5.500	5.000
	Minimum-Maximum	(b) (4)4)	
$t_{1/2\lambda z}$ [h]	Mean (SD)	36.248 (9.565)	37.264 (12.015)
	Median	34.378	35.262
	Minimum-Maximum	(b) (4)	

Table 23. ANOVA CVs, point estimates, 90% confidence intervals for (log-transformed) palonosetron pharmacokinetic parameters; bioequivalence assessment (N=36 subjects)

Pharmacokinetic parameter palonosetron	Ratio	ANOVA CV [%]	Point estimate Test/Ref. ratio	90% Confidence interval
$AUC_{(0-t)}$ [ng·h/L]	b_2 / b_1	8.7	102.3	98.9 - 105.9
$AUC_{(0-\infty)}$ [ng·h/L]	b_2 / b_1	8.7	102.0	98.6 - 105.6
C_{max} [ng/L]	b_2 / b_1	7.9	103.7	100.5 – 107.0

b1: oral administration of 0.50 mg palonosetron as a softgel capsule (formulation A, clinical trial formulation)
b2: oral administration of 0.50 mg palonosetron as a softgel capsule (formulation B, proposed commercial formulation)
Source: Final Report PALO-06-16, Table 11.4-8.

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

The sponsor did not request a waiver of in vivo BE study.

Reviewer's comments: *Because the formulation change is categorized as SUPAC-IR level 2 change* (b) (4) *the in vivo BE was not required as such the above two formulations could have been bridged in adequate in vitro studies. The formulation changes to this extent are not expected to significantly influence on bioavailability of palonosetron, which is highly soluble and highly permeable drug.*

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

For the clinical trial formulation, high fat diet did not affect PK of Palonosetron and AUC of M9 (90% CI: 87.80-112.06) but decreased the peak concentration of M9 about 15% (90% CI: 79.3-93.0). On the other hand, M4 could not be assessed.

The food effect study was conducted with the clinical trial formulation not with the to-be-marketed formulation, the sponsor proposed for a labeling claim for meal intake instruction in relation to medication based on the study done with the trial formulation because palonosetron is considered a BCS Class 1, highly soluble and highly permeable drug and the bioequivalence has been demonstrated between the trial formulation and TBM formulation.

Reviewer's comment*: Palonosetron HCl is freely soluble (Aloxi for injection label) and indirectly shown to be highly permeable based on the absolute bioavailability greater than 90% criteria. The stability of palonosetron in the intestinal lumen is also evident by the absolute bioavailability of palonosetron. As such palonosetron HCl is considered in BCS I class. In general, important food effects on BA are unlikely to occur with rapidly dissolving, immediate release drug products containing highly soluble and highly permeable drug substances (BCS Class I). (Guidance for industry: Food-Effect Bioavailability and Fed*

Bioequivalence Studies). No significant food effect was observed with the clinical trial formulation and the food effects on BA of palonosetron are expected to be similar if any for trial formulation and TBM formulation. In phase 3, palonosetron was taken without regard of food intake. As such, it is unlikely to expect significantly different food effects for TBM from the trial formulation and therefore the food effect on the trial formulation is applicable to TBM. Thus no further food effect study on TBM is necessary and palonosetron oral capsule can be taken without regard of food intake.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Three analytical methods have been used to evaluate palonosetron and M9 (primary metabolite) plasma in the course of the development program: HPLC-RIA, LC/MS and LC/MS/MS (Table 24). The sponsor submitted assay validation study reports for HPLC-RIA method for PAL and M9 in plasma (Study IAR-B-1009), an HPLC method for PAL and M9 in human urine (study IAR-B-1050), HPLC/MS method for Pal and M9 in human plasma (Study IAR-B-1058) and an LC/MS/MS method for PAL and M9 in human plasma and urine (study PALO-99-09)).

The same study reports for bioanalytical assay validation were submitted in original submission for palonosetron i.v. formulation dated 09/27/2002 (NDA 21-372, IAR-B-1058, March 1998, PALO-99-09 July 2001) and reviewed by the office of clinical pharmacology and found adequate (For details, please see Clinical Pharmacology and Biopharmaceutics Review by Drs. Sue-Chih Lee and Suliman Al-Fayoumi).

All PK analysis for oral capsule administration was conducted using LC/MS/MS while LC/MS was used for oral solution administration in some phase 1 and 2 studies. No cross-validation between LC/MS and LC/MS/MS was conducted. The analytical assay run for palonosetron and M9 was adequately validated and analytical assay run for M4 was adequately validated for BA and BE studies (PALO 04-04, 06-16). However, adequate in-run QC was not conducted for during the actual sample analysis for M4 in studies PALO 04-01, 04-02, 04-03, as such bioanalytical run for these studies for M4 was not adequately validated.

Table 24. Summary of in vivo analytical methods

Method	Sensitivity of Method	Specificity (parent/metabolites)	Used in Study Nos
HPLC-RIA[a]	Plasma 35 pg/ml palonosetron 75 pg/ml M9	Specific	2236
LC/MS[b]	Plasma 20 pg/ml palonosetron 50 pg/ml M9 Urine 5000 pg/ml palo and M9	Specific	0101 2332 2502
LC/MS/MS[c]	Plasma 50 pg/ml palonosetron 10 pg/ml M9 50 pg/ml M4 Urine 500 pg/ml palonosetron 439 pg/ml M9	Specific	PALO-03-07 PALO-04-01 PALO-04-02 PALO-04-03 PALO-04-04 PALO-04-13 PALO-06-16

HPLC-RIA Method for Determination of Palonosetron and M9

In this method, a plasma sample was subjected to HPLC for purification and isolation of the individual analytes. Small amounts of tritiated RS-25259 (Palonosetron) and RS-17825 (M9) were added to each plasma sample before HPLC to provide a determination of procedural recovery of each analyte. A portion of each HPLC fraction 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 method had lower limits of quantification for palonosetron and M9 of 35 pg/ml and 75 pg/ml, respectively.

LC/MS Methods for Determination of Palonosetron and M9
The analytes were extracted from plasma and concentrated using solid phase extraction column prior to injection onto an HPLC system. The separation of the metabolite from the parent was accomplished with a reverse phase C18 column and an appropriate mobile phase. Detection of the analytes was by positive electrospray mass spectrometery. The method had lower limits of quantification in plasma for palonosetron and M9 of 20 pg/ml and 50 pg/ml, respectively.

LC/MS/MS Methods for Determination of Palonosetron, M9 and M4
In brief, palonosetron, M9 and the internal standard were isolated from human plasma by solid-phase extraction. An aliquot of the extract was injected into the HPLC system and analysed by reversed phase HPLC with tandem mass spectrometry detection in the positive electrospray ionization mode (ESI(+)). The limit of quantification was approximately 50 pg/ml for palonosetron and 10 pg/ml for M9. Along with palonosetron, M9 and an internal standard, aliquots were injected and analyzed in the HPLC MS/MS detection system described above. The limit of detection for M4 was approximately 50 pg/ml.

For studies, PALO 04-01, 04-02 and 04-03, M4 concentrations were calculated using a standard curve for M9 due to unavailability of a reference standard M4 and subsequently converted to M4 based on MS detector response for M4 vs. M9. Four different M4 concentrations spiked in human plasma and the concentrations were calculated with M9 calibration standards. The mean conversion factor was 0.44 among factors determined at four different M4 concentrations were used to retrospectively convert M4 concentration in studies.

***Reviewer's comments**: Because adequate QC was not conducted for bioanalytical assay for M4 during the actual sample run for the measurements of M4 for studies PALO 04-01, 04-02, 04-03, were not adequately validated. However, given the low pharmacological activity of M4 (<1% of palonosetron) and a relative low systemic exposure compared to the parent drug (~10%), deficiency of QC for M4 during the sample analysis run does not deter the clinical pharmacology and biopharmaceutics program.*

2.6.2 Which metabolites have been selected for analysis and why?

The most significant metabolites were the M9 (N-oxide) and the M4 (hydroxy) metabolites. Pharmacological activity of M9 and M4 as a serotonine 5-HT3 antagonist is 1% of parent drug measured. It was recommended previously to assess the systemic exposure of metabolites after oral administration since the route of administration was to be changed from intravenous to oral.

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

The linear range of the standard curve was established from 43.9 ng/L to 2153.6 ng/L for palonosetron for palonosetron and from 11 ng/L to 539.4 ng/L for M9. The in-run QC was adequately conducted for palonosetron and M9 (Table 22). The overall precision of M9 at the lowest QC for valid batches was 24.5% indicating the measurements of M9 at the concentration may be inconsistent. The sponsor submitted assay validation study M4 in plasma as an appendix of the final report of "determination of the concentrations of palonosetron and its metabolites M4 and M9 in human plasma" for study PALO-04-03. The bioanalytical assay validation was adequately conducted with acceptable precision and accuracy (Table 23 for M4 and for details of Palonosetron and M9 assay validation, please see clinical pharmacology and biopharmaceutics review by Drs. Sue-Chih Lee and Suliman Al-Fayoumi).

Table 22. LC/MS/MS bioanalytical QC for palonosetron and M9 in human plasma (PALO 06-16)

Palonosetron QC (ng/L)	111.06	1075.454	1729.162
Precision (%) Accuracy (%)	8.19 5.32	9.94 4.32	6.35 3.77
M9 QC (ng/L)	27.73	268.52	431.73
Precision (%) Accuracy (%)	24.5 -1.81	14.58 -0.97	8.89 -3.56

Table 23. LC/MS/MS bioanalytical assay validation for M4 in human plasma

Parameter (M4):	Result:
Calibrated Range [ng/L]	49.975-2226.595
Defined LLOQ [ng/L]	49.975
Precision [%] at the LLOQ	10.46
Accuracy [%] at the LLOQ	6.41
Precision [%] at the lowest QC	9.56
Accuracy [%] at the lowest QC	1.65
Stability freeze thaw cycle, 3 times	stable
Stability in high performance liquid chromatography (HPLC) autosampler at approximately +4°C	approximately 22 days
Stability in matrix at ambient temperature/influence of light	stable for approximately 24 h
Stability in plasma at approximately -20°C	approximately 9 months
Stability in water at approximately +4°C	approximately 10 months
Recovery [%]	60
Recovery internal standard [%]	(b) (4)
Matrix effect [%]	-47
Matrix effect internal standard [%]	(b) (4)
Precision [%] of the matrix effect tested on different matrices	19
Carry over [%]	9
Selectivity	proven
Conversion factor (M4 concentrations calculated with M9 calibration standards)	0.44

3 Detailed Labeling Recommendations

Please, see appendix 4.1. for the proposed package insert with reviewer's recommended revision

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DRAFT LABELING

4.2. Individual Study Synopsis

2.7.6.1 Tabular Listing of All Clinical Studies

Study Identifier	Location of Study Report (Volume)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects	Healthy Subjects or Diagnosis of Patients (Location)	Duration of Study (Treatment)	Study Status; Type of Report
Bioavailability Studies								
PALO-04-04	5.3.1.1.1 Vols. 1-6	Absolute bioavailability and bioequivalence	Open-label, single center, three treatment, single dose crossover	0.75 mg PO (clinical trial softgel capsule) vs. 0.75 mg PO (proposed commercial softgel capsule) vs. 0.75 mg IV (FDA approved IV commercial formulation)	17M 18F	Healthy Volunteers (Germany)	Aug 2006 to Oct 2006 (single dose; 3 period crossover)	Complete; Full report
Bioequivalence Studies								
PALO-06-16	5.3.1.2.1 Vols. 6-11	Definitive bioequivalence study	Open label, single center, two treatment randomized crossover single dose study	0.50 mg PO (clinical trial softgel capsule) vs 0.50 mg proposed commercial softgel capsule	18M 18F	Healthy volunteers (Germany)	Jan 2007 to Apr 2007 (single dose, 2 period crossover)	Complete; Full report

Study Identifier	Location of Study Report (Volume)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects	Healthy Subjects or Diagnosis of Patients (Location)	Duration of Study (Treatment)	Study Status; Type of Report
Pharmacokinetic Studies (continued)								
PALO-04-03	5.3.3.2.1 Vols. 18-21	PK, dose proportionality and safety in CINV patients	Phase 2, single dose, open label randomized, parallel group PK study	0.25 mg, 0.50 mg 0.75 mg PO (clinical trial softgel capsule)	26M 10F	CINV patients-moderately emetogenic chemo (Romania)	Feb 2006 to May 2006 (single dose)	Complete; Full report
Efficacy and Safety Studies								
PALO-03-13	5.3.5.1.1 Vols. 41-67	Efficacy and Safety	Multicenter, randomized, balanced, stratified, double blind double dummy active control non-inferiority study	0.25 mg, 0.50 mg, 0.75 mg PO (clinical trial softgel capsule) vs 0.25 mg IV (FDA approved commercial formulation)	171 M 464 F	CINV patients receiving moderately emetogenic chemo (Europe/US/ Mexico)	June 2005 to Aug 2006 (single dose)	Complete; Full report
PALO-03-14	5.3.5.2.1 Vols. 68-85	Safety and Efficacy after multiple cycles	Multicenter, open-label, repeated cycle, uncontrolled study	0.75 mg PO (clinical trial softgel capsule)	54 M 163 F	CINV patients receiving moderately emetogenic chemo (Europe/US/ Mexico)	June 2005 to Apr 2006 (repeat cycle)	Complete; Full report

Study Identifier	Location of Study Report (Volume)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects	Healthy Subjects or Diagnosis of Patients (Location)	Duration of Study (Treatment)	Study Status; Type of Report
Efficacy and Safety Studies (continued)								
2332	5.3.4.2.1 Vols. 30-40	Safety, efficacy and PK in CINV patients	Phase 2 double-blind, single dose, dose-ranging	S0.3, 1, 3, 10, 30 or 90 µg/kg (oral solution	107 M 62 F (entire study population, not only PK cohort)	CINV patients-highly emetogenic chemo (USA)	Apr 1994 to Mar 1995 (single dose)	Complete; Full report
PALO-07-35	5.3.5.1.1.4 Vol. 67	Efficacy	Post hoc analysis	0.25 mg, 0.50 mg, 0.75 mg PO (clinical trial softgel capsule) vs 0.25 mg IV (FDA approved commercial formulation		CINV patients receiving moderately emetogenic chemo (Europe/US/ Mexico)	----	Full report
PALO-07-36	5.3.5.1.1.5 Vol. 67	Efficacy	Post hoc analysis	0.25 mg, 0.50 mg, 0.75 mg PO (clinical trial softgel capsule) vs 0.25 mg IV (FDA approved commercial formulation		CINV patients receiving moderately emetogenic chemo (Europe/US/ Mexico)	----	Full report

PALO 04-04

NAME OF COMPANY: Helsinn Healthcare SA NAME OF FINISHED PRODUCT: NAME OF ACTIVE INGREDIENT(S): Palonosetron	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of study: The effect of high fat meal and antacid administration on the pharmacokinetic profile of a single oral dose of 0.75 mg palonosetron in healthy volunteers: a single center, open, randomized, three-way cross-over study		
Principal Investigator:	Matthias Grossmann, MD, PhD	
Investigators:	[redacted] (b) (4)(4)	
Study center:	[redacted] (b) (4)	
Publication (reference):	None	
Study period (years): **Date of first subject enrolled:** **Date of last subject completed:**	2005 10 October 2005 25 November 2005	**Development phase of the study:** I
Objectives: **Primary objective:** To investigate the effects of (1) a high fat meal and (2) the co-administration of an antacid product (Maalox®) on the pharmacokinetics of oral administered palonosetron and its main metabolites M4 and M9 in healthy male and female subjects. **Secondary objectives:** To evaluate safety and tolerability of a single oral dose of palonosetron 0.75 mg in healthy male and female volunteers under fasting conditions, following a high fat meal and coadministered with Maalox®, an antacid containing aluminum hydroxide and magnesium hydroxide.		
Methodology: Open label, single-center, single-dose, three-treatment (b_1 to b_3), three-periods (a_1 to a_3) cross-over study with randomized assignment of male and female subjects to one of six treatment sequences (c_1 to c_6).		

NAME OF COMPANY: Helsinn Healthcare SA **NAME OF FINISHED PRODUCT:** **NAME OF ACTIVE INGREDIENT(S):** Palonosetron	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(FOR NATIONAL AUTHORITY USE ONLY)**
Title of study: Bioequivalence and absolute bioavailability of a single oral dose of two formulations of 0.75 mg palonosetron in healthy volunteers: a three-treatment, three-period, two-sequence cross-over study		
Principal Investigator:	Sybille Baumann-Noss, MD CRS-Mannheim GmbH	
Investigators:	(b) (4)(4)	
Study center:	(b) (4)	
Publication (reference):	None	
Study period (years): **Date of first subject enrolled:** **Date of last subject completed:**	2006 30 August 2006 27 October 2006	**Development phase of the study:** I
Objectives: **Primary objective:** 1. To investigate the bioequivalence of two oral softgel palonosetron 0.75 mg capsules (formulation A and formulation B) 2. To investigate the absolute bioavailability of two oral softgel palonosetron 0.75 mg capsules (formulation A and formulation B) as compared to the intravenous formulation (i.v.) (test/reference). **Secondary objectives:** To evaluate the safety and tolerability of two oral softgel palonosetron 0.75 mg capsules (formulation A and formulation B) and of palonosetron 0.75 mg i.v. administered as single doses in healthy male and female subjects under fasting conditions.		
Methodology: Randomized, open-label, three-treatment (b_1, b_2, b_3), three-period (a_1, a_2, a_3), two-sequence (c_1, c_2) cross-over design. Each subject received Treatment b_3 in period 3 and Treatments b_1 and b_2 in randomized order in periods 1 and 2.		

Number of subjects (planned and analyzed):	Planned: 36 Screened: 65 (including 29 screening failures) Randomized: 36 Drop-outs: 6 Analyzed: 33 (bioequivalence) 30 (absolute bioavailability) 35 (safety)
Main criteria for inclusion:	Male and female subjects between 18 and 45 years of age, in good general health and with a body weight within 20% of ideal weight for height, frame and age according to the 1983 Metropolitan Life Insurance Tables
Products, dose and mode of administration, batch nos.: A single dose of palonosetron in the form of oral softgel capsules was administered as follows: Treatment b_1 (formulation A, Clinical Trial formulation): Dose: 0.75 mg Mode of administration: oral Batch No.: 04JM-261 Treatment b_2 (formulation B, Proposed Commercial formulation): Dose: 0.75 mg Mode of administration: oral Batch No.: 06JM-124	
Reference product (bioavailability analysis), dose and mode of administration, batch no.: A single dose of palonosetron was administered as i.v. bolus injection (Aloxi®, 0.25 mg/5 mL) Treatment b_3: Dose: 3 x 0.25 mg palonosetron Mode of administration: i.v. solution for injection Batch No.: P00019	
Duration of treatment: The study was carried out over three periods of eleven study days each. The administration of the study treatments was performed on Study Day 1 of each period.	

NAME OF COMPANY: Helsinn Healthcare SA NAME OF FINISHED PRODUCT: NAME OF ACTIVE INGREDIENT(S): Palonosetron	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Criteria for evaluation:

Primary pharmacokinetic parameters (derived from plasma concentrations):
$AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for palonosetron.

Secondary pharmacokinetic parameters (derived from plasma concentrations):
t_{max}, $t_{1/2\lambda z}$, and λ_z for palonosetron. C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2\lambda z}$, λ_z as well as $AUC_{0-\infty,m/p}$ for M4 and M9, as data permit.

Safety:
Physical examination, vital signs, electrocardiogram (ECG), adverse events (AEs), clinical chemistry, hematology, urinalysis and overall tolerability.

Statistical methods:
Pharmacokinetics:
The primary and secondary model-independent pharmacokinetic characteristics for palonosetron, M4 and M9 were calculated using non-compartmental procedures. For both metabolites, the parameters (including $AUC_{0-\infty m/p}$) were calculated as data permitted.
Natural log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} data as well as untransformed (or raw) t_{max} and $t_{1/2\lambda z}$ data were analyzed using an analysis of variance (ANOVA) model containing sequence, period and treatment as fixed effects, and subject within sequence as random effect.
The two oral treatments b_1 and b_2 were considered bioequivalent if the 90% confidence intervals for the $AUC_{0-\infty}$ (or AUC_{0-t}) and C_{max} treatment ratios of palonosetron lie within a range of 80% to 125%. AUC_{0-t} was used for deciding bioequivalence instead of $AUC_{0-\infty}$ if the extrapolated part AUC_{ext} [%] was above 20% for at least one subject and one of the oral palonosetron formulations (Treatments b_1 and b_2).
Absolute bioavailability of the oral palonosetron formulations was defined as the geometric mean of the corresponding treatment ratio (b_1/b_2 or b_2/b_3) for $AUC_{0-\infty}$. AUC_{0-t} was used for absolute bioavailability instead of $AUC_{0-\infty}$ if the extrapolated part AUC_{ext} [%] was above 20% for at least one subject and one of the treatments involved in a ratio.

Statistical methods:
Safety:
Results of all safety measurements were listed individually and, if appropriate, described by descriptive statistics.
Descriptive statistics were calculated for continuous laboratory parameters, vital signs including body weight and oral body temperature and ECG parameters. Changes from baseline were summarized. Qualitative data were summarized by means of frequency tables.
If appropriate, shift-tables were used for describing change of baseline values relevant to laboratory normality/abnormality.
Medical Dictionary for Regulatory Activities (MedDRA; Version 9.0) coding was used for adverse events, previous and concomitant diseases and drug indication.
All adverse events were listed together with information on onset, duration, frequency, intensity, seriousness, relationship to investigational medicinal product, outcome and action taken. Frequency tables per System Organ Class and Preferred Term were provided.
Intensity, seriousness and relationship of adverse events as well as assessment of overall tolerability by the Investigator were summarized using frequency tables.
The results of the physical examinations were listed.

Results and Conclusions were discussed in QBR

PALO 06-16

NAME OF COMPANY: Helsinn Healthcare SA **NAME OF FINISHED PRODUCT:** Not applicable **NAME OF ACTIVE INGREDIENT(S):** Palonosetron	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(FOR NATIONAL AUTHORITY USE ONLY)**
Title of study: Bioequivalence of a single oral dose of two formulations (Formulation A and Formulation B) of palonosetron 0.50 mg softgel capsule in healthy male and female subjects. (A two treatments, two periods, two sequences, open label, randomized, cross-over study).		
Principal Investigator:	Kai Mehltretter, MD CRS-Mannheim GmbH	
Investigators:	(b) (4)	
Study center:	(b) (4)	
Publication (reference):	None	
Study period (years): **Date of first subject enrolled:** **Date of last subject completed:**	2007 29 January 2007 04 April 2007	**Development phase of the study:** I
Objectives: **Primary objective:** To investigate the bioequivalence of two oral softgel palonosetron 0.50 mg capsules (Formulation A and Formulation B). **Secondary objectives:** To evaluate the safety and tolerability of two oral softgel palonosetron 0.50 mg capsules (Formulation A and Formulation B) administered as single dose in healthy male and female subjects under fasting conditions.		
Methodology: Randomized, open-label, two-treatment (b_1, b_2), two-period, two-sequence cross-over design. Each subject received Treatments b_1 and b_2 in randomized order in Periods 1 and 2.		
Number of subjects (planned and analyzed):	Planned: 36 Randomized: 36 Analyzed: 36 (Bioequivalence) 36 (Safety)	

Main criteria for inclusion:	Male and female subjects between 18 and 45 years of age, in good general health and with a body weight within 20% of ideal weight for height, frame and age according to the 1983 Metropolitan Life Insurance Tables.

Products, dose and mode of administration, batch nos.:

Treatment b_1 (Formulation A, clinical trial formulation):

Dose:	single dose of 0.50 mg
Mode of administration:	oral
Batch No.:	04JM-260

Treatment b_2 (Formulation B, proposed commercial formulation):

Dose:	single dose of 0.50 mg
Mode of administration:	oral
Batch No.:	06JM-122

Duration of treatment:

The study was carried out over two periods of eleven study days each. The administration of the study treatments was performed on Study Day 1 of each period.

Criteria for evaluation:

Pharmacokinetics:

Primary pharmacokinetic parameters (derived from plasma concentrations):

$AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for palonosetron.

Secondary pharmacokinetic parameters (derived from plasma concentrations):

t_{max}, $t_{1/2\lambda z}$, and λ_z for palonosetron. C_{max}, t_{max}, AUC_{0-t} $AUC_{0-\infty}$, $t_{1/2\lambda z}$, λ_z as well as $AUC_{0-\infty,m/p}$ for M4 and M9, as data permitted.

Safety:

Physical examination, vital signs, electrocardiogram (ECG), adverse events (AEs), clinical chemistry, hematology, urinalysis, and overall tolerability.

NAME OF COMPANY: Helsinn Healthcare SA **NAME OF FINISHED PRODUCT:** Not applicable **NAME OF ACTIVE INGREDIENT(S):** Palonosetron	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(FOR NATIONAL AUTHORITY USE ONLY)**

Statistical methods:

Pharmacokinetics:

The primary and secondary model-independent pharmacokinetic characteristics for palonosetron and metabolites M4 and M9 were calculated using non-compartmental procedures. For both metabolites, the parameters (including $AUC_{0-\infty,m/p}$) were calculated as data permitted.

Natural log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} data as well as untransformed (or raw) t_{max} and $t_{1/2\lambda z}$ data were analyzed using an analysis of variance (ANOVA) model containing sequence, period and treatment as fixed effects, and subject within sequence as random effect.

The two oral treatments b_1 and b_2 were considered bioequivalent, if the 90% confidence intervals for the $AUC_{0-\infty}$ (or AUC_{0-t}) and C_{max} treatment ratios of palonosetron were within the limits of 80% to 125%. AUC_{0-t} was used for deciding bioequivalence instead of $AUC_{0-\infty}$ if the extrapolated part AUC_{ext} [%] was above 20% for at least one subject and one of the oral palonosetron formulations (Treatments b_1 and b_2).

Safety:

Results of all safety measurements were listed individually and, if appropriate, described by descriptive statistics.

Descriptive statistics were calculated for continuous laboratory parameters, vital signs including body weight and oral body temperature and ECG parameters. Changes from baseline were summarized. Qualitative data were summarized by means of frequency tables.

If appropriate, shift-tables were used for describing change of baseline values relevant to laboratory normality/abnormality.

Medical Dictionary for Regulatory Activities (MedDRA; Version 9.1) coding was used for adverse events.

All adverse events were listed together with information on onset, duration, frequency, intensity, seriousness, relationship to investigational medicinal product, outcome and action taken. Frequency tables per System Organ Class and Preferred Term were provided.

Intensity, seriousness and relationship of adverse events as well as assessment of overall tolerability by the Investigator were summarized using frequency tables.

The results of the physical examinations were listed.

Results and conclusions were discussed in QBR

Study 0101

BEST AVAILABLE COPY

SUMMARY

Title of Study: A Single-Dose Safety and Pharmacokinetics Study of RS-25259 (Oral Solution) in Healthy Volunteers

Study No. and RS No.: 25259S0101 and RS-25259

Investigator and Study Center: Munetetsu Tei, M.D., (b) (4)4) (b) (4)

Study Period: November 1994–March 1995

Clinical Phase: I

Objective: The objective of this study was to determine the safety, tolerability, and pharmacokinetics of a single, oral dose of RS-25259 in healthy, male, Japanese adult volunteers.

Methodology: This was a double-blind (by cohort), placebo-controlled, ascending-dose study. The subjects enrolled in four sequential cohorts of 8 volunteers each, 6 of whom received active RS-25259 and 2 of whom received placebo. The volunteers in each cohort were monitored for 7 days (168 hours) after their oral dose, and the next cohort was not started until the principal investigator had reviewed all of the safety data from the subjects in the previous cohort and declared that dose safe. Blood and urine specimens collected before and periodically during the 168-hour postadministration period were assayed for RS-25259 and its major metabolite RS-17825, from which the pharmacokinetics of RS-25259 were evaluated.

Number of Subjects: Thirty-two volunteers enrolled in the study: 8 received placebo, and 24 received active RS-25259. They were all Japanese men. Their mean (± SD) age was 23.0 (± 2.4) years (range, 20–32), mean (± SD) weight was 64.2 (± 7.6) kg (range, 48.6–76.7), and mean (± SD) height was 171 (± 5.4) cm (range, 156.1–182.8). All completed the study normally, and all were included in the pharmacokinetic and safety analyses.

Diagnosis and Criteria for Inclusion: The volunteers for this study were all Japanese males between 20 and 32 years of age with body weight not more than 80 kg and within 15% of the following formula: [Height (in cm) - 100] × 0.9. They had no abnormalities apparent from the results of physical examinations, 12-lead electrocardiograms (ECGs), and routine clinical laboratory profiles performed or obtained within 4 weeks before study initiation, and they all tested negative for human immunodeficiency virus (HIV), hepatitis, and syphilis.

Test Product, Dose and Mode of Administration, Formulation No., Batch/Lot No.: RS-25259 (Formulation No. F25259-006, Lot No. 25259-197-1021881) was supplied in vials containing 5 mL of oral solution at a concentration of 500 µg/mL of free base. RS-25259 doses administered in this study were 3, 10, 30, and 90 µg/kg of body weight. The amount of RS-25259 required for each volunteer was calculated based on his body weight on the day of administration and for ease of administration further diluted with physiological saline (JP) to a total volume of 50 mL. The diluted drug solution was dispensed in a plastic medication cup for consumption of a single oral dose of RS-25259

Reference Therapy, Dose and Mode of Administration, Formulation No., Batch/Lot No.: Placebo (Formulation No. F25259-001, Lot No. 25259-197-12035) was supplied in vials containing 5 mL of oral solution (vehicle) not containing RS-25259. Two volunteers in each cohort received a single oral dose of placebo, which was prepared and administered in exactly the same way as the RS-25259 doses.

Duration of Treatment: Each volunteer received a single oral dose of RS-25259 or placebo and was observed for at least 168 hours after receiving the dose.

Criteria for Evaluation: *Pharmacokinetics:* All of the plasma samples collected from the volunteers were assayed to determine their concentrations of RS-25259 and RS-17825 (its main metabolite, the N-oxide of RS-25259). From these data, the values of the following computed parameters were calculated for or from each analyte: Time to maximum observed concentration in plasma (T_{max}), maximum observed concentration in plasma (C_{max}); plasma half-life ($t_{1/2}$); areas under the plasma concentration vs. time curve calculated from 0 to 24 hours (AUC_{0-24}), from Time 0 to the postdose time at which the last measurable analyte concentration was observed (AUC_{0-LOCT}), and from Time 0 to infinity (AUC_{inf}). In addition, the ratio of the value of AUC_{inf} for RS-17825 to the value of AUC_{inf} for RS-25259 (AUC ratio) was also calculated. For RS-25259, the following additional pharmacokinetic parameters were calculated: clearance (Cl) and volume of distribution (V_{ss}). All of the urine specimens from all of the volunteers were assayed for RS-25259 and RS-17825, and the cumulative amounts of RS-25259 and RS-17825 excreted were calculated for each collection interval. *Safety:* Safety parameters evaluated included adverse events, electrocardiograms (ECGs), physical examination results, and routine clinical laboratory test (hematology, blood chemistry, urinalysis) results.

Statistical Methods: Pharmacokinetics: Plasma concentrations, computed pharmacokinetic parameters, and urinary recoveries were listed and statistically summarized for each dose group; individual and mean plasma concentrations were plotted versus time; and computed parameters were analyzed for a dose relationship (e.g., dose proportionality, dose linearity). Safety: Safety evaluations are presented in summary tables and listings. No statistical analyses were performed.

Results and conclusion are discussed in QBR

Study 2236

SUMMARY

Title of Study: Single Ascending-Dose Safety and Pharmacokinetics Study of an Oral Solution of RS-25259-007 in Healthy Volunteers

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Study No. and RS No.: RGR/25259s2236/USA and RS-25259-007

Investigator and Study Center: Randall R. Stoltz, M.D., (b) (4) (b) (4))

Publications: None

Study Period: August 1993–November 1993

Clinical Phase: I

Objectives: The objectives of this study were to monitor the safety, determine the maximum dose tolerated through a range of doses, and study the pharmacokinetics of single oral doses of RS-25259-007.

Methodology: This was a randomized, double-blind, placebo-controlled safety and pharmacokinetic study of single ascending oral solution doses of RS-25259-007. Subjects were randomized in the ratio of 3:1 to receive either study drug or placebo. Safety data, including Holter electrocardiogram (ECG) examinations for 72 hours after dosing, were reviewed at each dose level before proceeding to the next level. Blood samples for pharmacokinetic analysis were taken from each subject before dosing and at various times up to 168 hours after dosing. The plasma portion was assayed for RS-25259 and RS-17825 (the N-oxide metabolite) concentrations, from which pharmacokinetic parameters were computed.

Number of Subjects: Thirty-nine healthy men, 19–45 years of age, were enrolled. All subjects completed the protocol normally.

Diagnosis and Criteria for Inclusion: Subjects were within 15% of the average weight for their sex, age, and height and had no clinically significant medical history or abnormalities on physical examination or laboratory testing, including two 24-hour Holter ECG examinations and screening tests for human immunodeficiency virus (HIV), hepatitis, and drugs of abuse.

Test Product, Dose and Mode of Administration, Formulation No., Batch/Lot No.: Oral RS-25259-007 was provided as a lyophilized cake in amber glass vials, reconstituted with acetate buffer pH 5.0, and diluted with distilled water to produce a 100-mL solution for administration at doses of 3, 10, 20, 40, and 80 µg/kg (Formulation Nos. F25259-021, -022, and -031; Batch Nos. 25259-007-12393, -12365, and -12364).

Reference Therapy, Dose and Mode of Administration, Formulation No., Batch/Lot No.: Oral placebo solution consisted of acetate buffer pH 5.0 in amber glass vials similar in appearance to the vials of RS-25259 and diluted with distilled water to produce a 100-mL solution (Formulation No. P25259-032; Batch No. 25259-007-12361).

Duration of Treatment: Subjects received a single oral solution dose of RS-25259-007 or placebo.

Criteria for Evaluation: Clinical Data—physical examination and vital signs data, cardiac telemetry and Holter monitor data, laboratory findings, and adverse event data; Pharmacokinetic Data—plasma concentrations and computed pharmacokinetic parameters for parent drug (RS-25259) and the N-oxide metabolite (RS-17825)

Statistical Methods: Demographic and safety data were summarized; plasma concentrations and computed pharmacokinetic parameters were listed and statistically summarized by dose group; individual and mean plasma concentrations versus time were plotted; and computed parameters were analyzed for a dose relationship (e.g., dose proportionality, dose linearity).

Results are discussed in QBR

PALO 03-07

Name of Sponsor/Company: Helsinn Healthcare SA	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: [^{14}C]-Palonosetron	Volume:	
Name of Active Ingredient: Palonosetron	Page:	

Title of Study: A Phase I Study to Investigate the Absorption, Metabolism and Excretion of [^{14}C]-Palonosetron Following a Single Oral Administration to Healthy Male Volunteers

Principal Investigator: J E A Dickson MBChB

Study Centres: Clinical phase: (b) (4) (b) (4))

Analytical Phase: (b) (4)

Publication (Reference): None

Studied Period (Clinical Phase):	**Phase of Development:**
08 August to 19 September 2003	Phase I

Objectives: The aims of this study were to define the mass balance and the metabolic profile, including the presence or absence of RS-42358, of [^{14}C]-palonosetron given as a single oral dose of 0.75 mg to healthy male volunteers. The pharmacokinetic (PK) profile of the parent compound and its N-oxide metabolite, M9, were to be evaluated in plasma and urine. Other metabolites and faecal evaluations were to be performed as appropriate. The tolerability of the administered dose was to be assessed.

Methodology: Single-centre, open-label, absorption, distribution, metabolism and excretion study.

Number of Subjects (planned and analysed): Planned: 6 subjects; Enrolled: 6 subjects; Analysed: 6 subjects.

Diagnosis and Main Criteria for Inclusion: Subjects were non-smoking healthy males, aged 30 to 55 years, with a body weight within 30% of ideal weight according to the 1983 Metropolitan Height/Weight Tables, and with average bowel movements of at least one every 48 h. Subjects were in good health based on physical examination, laboratory evaluation, electrocardiogram (ECG) and vital signs assessments.

Test Product Dose and Mode of Administration, Batch Number:
0.75 mg containing 50 μCi of [^{14}C]-palonosetron, administered as an oral solution.
Radiolabelled palonosetron batch number: CFQ13108.
Non-radiolabelled palonosetron batch number: 21000567.

Duration of Treatment: Single dose.

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable.

Criteria for evaluation:

Absorption and Excretion Kinetics, Metabolite Profiling and Palonosetron and M9 Metabolite Concentrations: Whole blood and plasma concentrations of total radioactivity and cumulative excretion of radioactivity in urine and faeces were evaluated. Detailed chromatographic analyses of composite urine and plasma samples were performed. Plasma and urine concentrations of palonosetron and M9 were determined using a validated LC/MS/MS assay.

Pharmacokinetics: The following PK parameters were evaluated: Cmax(obs), Tmax(obs), AUC(0-t), AUC(0-∞) and T½el were evaluated for total radioactivity (in plasma and whole blood); Cmax(obs), Tmax(obs), AUC(0-t), AUC(0-∞), T½el, CL/F, Vd/F, CumARec, Total ARec, CLr, and % Rec for palonosetron;. and Cmax(obs), Tmax(obs), AUC(0-t), AUC(0-∞), T½el, CumARec and Total ARec for M9.

Safety: Assessment of adverse events, haematology, clinical chemistry and urinalysis, vital signs, ECG and physical examination.

Statistical Methods: No formal statistical analysis was performed. Descriptive or categorical summary statistics were produced, as appropriate. All data were listed.

Results are discussed in QBR

PALO 04-03

NAME OF SPONSOR Helsinn Healthcare S.A.	**INDIVIDUAL STUDY TABLE REFERRING TO PART (..) OF THE DOSSIER** **VOLUME:** **PAGE:**	**(FOR NATIONAL AUTHORITY USE ONLY)**
NAME OF FINISHED PRODUCT Aloxi®		
NAME OF ACTIVE INGREDIENT Palonosetron hydrochloride		

TITLE OF STUDY
A randomised two-period cross-over study to evaluate pharmacokinetics and tolerability of a single oral dose of palonosetron (0.75 mg) in fasted and fed healthy males and females

INVESTIGATOR
Principal investigator: Huub R A Van Paaschen MD

STUDY CENTRE
(b) (4)

PUBLICATION (REFERENCE)
Not applicable

STUDY PERIOD	**PHASE OF DEVELOPMENT**
First subject first visit: 17 AUG 2004 Last subject last visit: 13 OCT 2004	Phase I

OBJECTIVES
- To assess the effect of food on the pharmacokinetics of palonosetron orally administered as drinkable solution in healthy male and female volunteers;
- To assess the safety and tolerability of palonosetron orally administered as drinkable solution in healthy male and female subjects.

METHODOLOGY
The study was designed to determine the preliminary pharmacokinetics of palonosetron 0.75 mg given as a single oral dose (drinkable solution) under fasting and fed conditions. This was a randomised, two-period cross-over, open label study in six healthy male subjects and six healthy female subjects. Each subject was to receive palonosetron both in fasted and fed state, in a randomised order. Between Day 1 of the two consecutive study periods the washout time was 14 days.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED)
A number of six healthy male subjects and six healthy female subjects was planned. Five men and seven women were enrolled and analyzed. The PK population consisted of all 12 subjects (all had PK measurements available). However, one subject was excluded from all summary statistics and statistical tests, as he did not complete both treatments

MAIN CRITERIA FOR INCLUSION
Healthy male and female volunteers, aged 18 to 45 years (inclusive); subjects had to voluntarily sign a written informed consent agreement approved by the Independent Ethics Committee after explanation of the nature and objectives of the study and prior to any study specific procedure; women of childbearing potential were to use adequate contraceptives; body weight was to be within 30% of ideal weight for height, frame and age according to the 1983 Metropolitan Height/Weight Tables; subjects were to be non-smokers or have refrained from smoking the last 12 months before screening, were to be in general good health, were to be able to communicate well with the investigator, and to be able to comply with the requirements of the entire study.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER
INN: Palonosetron hydrochloride; dosage: 0.25 mg/ 5 ml IV (Aloxi®); Lot no: HPA024. NOTE: the three IV vials were administered as drinkable solution (0.75 mg) by the oral route as the final formulation (i.e., soft-gel capsule) was not yet available.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER
Not applicable

DURATION OF THE STUDY
Screening within 28 days before Day 1 of the first period; Admission period three days; Sampling period 11 days; Washout between consecutive periods was 14 days (between Day 1 of the two consecutive periods); Follow-up 11 days after second dose; Maximum total duration 53 days.

CRITERIA FOR EVALUATION – PHARMACOKINETICS
The parameters to be analyzed were t_{lag}, C_{max}, t_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, λ_Z, $t_{1/2Z}$.

CRITERIA FOR EVALUATION – SAFETY
Criteria for safety evaluation were monitoring of adverse events, haematology, biochemistry and urine laboratory parameters, physical examination, ECG, and vital signs.

STATISTICAL METHODS
Descriptive statistics were calculated for demographics and safety data.
Summary statistics (i.e. n, mean, standard deviation, minimum, median and maximum) were presented for all pharmacokinetic parameters by treatment. Geometric means and coefficients of variation (based on the logarithmically transformed data) were presented for C_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, CL/F and V_Z/F.
Estimated mean ratios of C_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, with 90% confidence intervals were presented for the comparisons of data obtained in fed and fasted condition. All estimates were derived from an ANOVA model, using the ln-transformed AUC and C_{max} data obtained after each of the two treatments; the fixed effect terms in the model were treatment (fed/fasted), gender and subject. Interaction terms were not included in view of the explorative nature of the study. The mean ratios and 90% Confidence Interval of the mean ratios were used to evaluate the relative bioavailability of palonosetron in the fed state.

Results are discussed in QBR

PALO 04-02

NAME OF COMPANY: Helsinn Healthcare SA **NAME OF FINISHED PRODUCT:** **NAME OF ACTIVE INGREDIENT(S):** Palonosetron	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(FOR NATIONAL AUTHORITY USE ONLY)**
Title of study: The effect of high fat meal and antacid administration on the pharmacokinetic profile of a single oral dose of 0.75 mg palonosetron in healthy volunteers: a single center, open, randomized, three-way cross-over study		
Principal Investigator:	Matthias Grossmann, MD, PhD (b) (4)	
Investigators:	(b) (4) (b) (4)	
Study center:	(b) (4)	
Publication (reference):	None	
Study period (years): **Date of first subject enrolled:** **Date of last subject completed:**	2005 10 October 2005 25 November 2005	**Development phase of the study:** I
Objectives: **Primary objective:** To investigate the effects of (1) a high fat meal and (2) the co-administration of an antacid product (Maalox®) on the pharmacokinetics of oral administered palonosetron and its main metabolites M4 and M9 in healthy male and female subjects. **Secondary objectives:** To evaluate safety and tolerability of a single oral dose of palonosetron 0.75 mg in healthy male and female volunteers under fasting conditions, following a high fat meal and coadministered with Maalox®, an antacid containing aluminum hydroxide and magnesium hydroxide.		
Methodology: Open label, single-center, single-dose, three-treatment (b_1 to b_3), three-periods (a_1 to a_3) cross-over study with randomized assignment of male and female subjects to one of six treatment sequences (c_1 to c_6).		

Number of subjects (planned and analyzed):	Planned: 18 Screened: 41 (including 23 screening failures) Randomized: 18 Drop-outs: 1 Analyzed: 17 (Pharmacokinetics) 18 (Safety)
Main criteria for inclusion:	Male and female subjects between 18 and 45 years of age, in good general health and with a body weight within 20% of ideal weight for height, frame and age according to the 1983 Metropolitan Height/Weight Tables

Test products, dose and mode of administration, batch nos.:

Palonosetron given 30 minutes after start of the high fat content breakfast (Treatment b_2)
Dose: 0.75 mg
Mode of administration: oral
Batch No.: 04-JM-261

Palonosetron given under fasting conditions concomitantly with an antacid (Maalox®, 5 minutes before palonosetron (Treatment b_3))
Dose palonosetron: 0.75 mg
Mode of administration: oral
Batch No.: 04-JM-261

Reference product, dose and mode of administration, batch no.:
Palonosetron given under fasting conditions (Treatment b_1)
Dose: 0.75 mg
Mode of administration: oral
Batch No.: 04-JM-261

Other product, dose and mode of administration, batch no.:
Dose Maalox®: 30 ml suspension (10 mL suspension corresponding to 900 mg aluminium hydroxide and 600 mg magnesium hydroxide)
Mode of administration: oral
Batch No: PS 40010

Duration of treatment:
The study was carried out over three periods, with nine study days in each period and administration of the treatments on Study Day 1 of each period.

Criteria for evaluation:

Primary pharmacokinetic parameters (derived from plasma concentrations):
$AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for palonosetron.

Secondary pharmacokinetic parameters (derived from plasma concentrations):
t_{max}, $t_{1/2\lambda z}$, and λ_z for palonosetron. C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2\lambda z}$, λ_z as well as $AUC_{0-\infty,\ m/p}$ for M4 and M9, as data permit.
Safety:
Physical examination, vital signs, electrocardiogram (ECG), adverse events (AEs), clinical chemistry, hematology, urinalysis, and overall tolerability.

Statistical methods:
Pharmacokinetics:
The primary and secondary model-independent pharmacokinetic characteristics for palonosetron, M4 and M9 were calculated using non-compartmental procedures. For both metabolites, the parameters (including $AUC_{0-\infty,m/p}$) were calculated as data permitted.

The following treatment comparisons were performed by means of the pharmacokinetic variables: Oral palonosetron given fed versus oral palonosetron given alone (fasting), and oral palonosetron given with antacid versus oral palonosetron given alone (fasting).
Natural log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} as well as untransformed (or raw) t_{max} and $t_{1/2\lambda z}$ were analyzed using an analysis of variance (ANOVA) model containing sequence, period and treatment as fixed effects, and subject within sequence as random effect.

Statistical methods (continued):
Pharmacokinetics:
For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, the treatment ratio and its 90% confidence interval was estimated. The 90% confidence intervals for the AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} ratios of palonosetron within the equivalence range of 80-125% were utilized to determine the presence of food and antacid effects on the pharmacokinetics of palonosetron compared to fasting state (treatment b_1) as reference.
Safety:
Results of all safety measurements were listed individually and, if appropriate, described by descriptive statistics.
Descriptive statistics were calculated for continuous laboratory parameters, vital signs including body weight and oral body temperature and ECG parameters. Changes from baseline were summarized. Qualitative data were summarized by means of frequency tables.
If appropriate, shift-tables were used for describing change of baseline values relevant to laboratory normality/abnormality.
Medical Dictionary for Regulatory Activities (MedDRA; Version 7.1) coding was used for adverse events, previous and concomitant diseases and drug indication.
All adverse events were listed together with information on onset, duration, frequency, severity, seriousness, relationship to investigational medicinal product, outcome and action taken. Frequency tables per System Organ Class and preferred term were provided.
Intensity, seriousness and relationship of adverse events as well as assessment of overall tolerability by the Investigator were summarized using frequency tables.
The results of the physical examinations were listed.

PALO 04-01

NAME OF COMPANY: Helsinn Healthcare SA **NAME OF FINISHED PRODUCT:** **NAME OF ACTIVE INGREDIENT:** Palonosetron	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(FOR NATIONAL AUTHORITY USE ONLY)**
Title of study: Evaluation of the pharmacokinetic profile of a single oral dose of 0.75 mg palonosetron in healthy elderly volunteers: a single center, single group study.		
Principal Investigator:	Matthias Grossmann, MD, PhD Pathophysiologist and Clinical Pharmacologist (b) (4) [redacted]	
Sub-investigators:	[redacted]	
Study center:	[redacted]	
Publication (reference):	None	
Study period (years): **Date of first subject enrolled:** **Date of last subject completed:**	2005 10 November 2005 24 November 2005	**Development phase of the study:** I
Objectives: **Primary objective:** To investigate the pharmacokinetic profile of palonosetron and its main metabolites M4 and M9 in healthy male and female subjects aged ≥65 years under fasting conditions. **Secondary objectives:** To evaluate safety and tolerability (1) of a single oral dose of palonosetron 0.75 mg in healthy male and female subjects, aged ≥ 65 years under fasting conditions, and (2) comparisons of the pharmacokinetic parameters of young healthy subjects treated under fasting conditions in the study PALO-04-02 performed according to standard methods.		
Methodology: Open-label, single-center, one-treatment (b_1), one-period (a_1) design.		

Number of subjects (planned and analyzed):	Planned: 18 Screened: 40 (including 22 screening failures) Randomized: 18 Drop-outs: 0 Analyzed: 18 (Pharmacokinetics) 18 (Safety)
Main criteria for inclusion:	Male and female subjects, aged ≥65 years, in good general health and with a body weight within 20% of ideal weight for body height, frame and age according to the 1983 Metropolitan Height/Weight Tables

Test product, dose and mode of administration, batch no.:
Palonosetron given under fasting conditions
Dose: 0.75 mg
Mode of administration: oral
Batch No.: 04JM-261

Reference product, dose and mode of administration, batch no.:
None

Duration of treatment:
The study was performed in one period, with one ambulatory day for Screening, three in-house days (Study Day -1 to 2) and 7 daily unit visits for blood sampling and blood pressure/pulse rate measurement every 24 hours up to Day 9 (192 h a.a.). A single oral dose of 0.75 mg palonosetron was administered in the form of a softgel capsule under fasting conditions on Day 1.

Criteria for evaluation:

Primary pharmacokinetic parameters (derived from plasma concentrations):
$AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for palonosetron.

Secondary pharmacokinetic parameters (derived from plasma concentrations):
t_{max}, $t_{1/2\lambda z}$, and λ_z, for palonosetron, and C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2\lambda z}$, and λ_z for M4 and M9 as well as $AUC_{0-\infty,m/p}$.

Safety:
Physical examination, vital signs, electrocardiogram (ECG), adverse events (AEs), clinical chemistry, hematology, urinalysis, overall tolerability.

Statistical methods:
Pharmacokinetics:
Primary target variables for pharmacokinetics were $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for palonosetron. Secondary target variables for pharmacokinetics were t_{max}, $t_{1/2\lambda z}$, and λ_z, for palonosetron, and C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2\lambda z}$, and λ_z, as well as $AUC_{0-\infty,m/p}$ for M4 and M9. Further secondary target variables for pharmacokinetics were the dose and body weight normalized parameters $AUC_{0-\infty,norm}$, $AUC_{0-t,norm}$, $C_{max,norm}$ for palonosetron, M4 and M9.
Comparisons elderly versus young (data from study PALO-04-02) were performed by means of the pharmacokinetic variables derived from plasma concentrations obtained from the oral administration of palonosetron 0.75 mg under fasting conditions.
Log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} as well as non-transformed t_{max} and $t_{1/2\lambda z}$ were analyzed using an analysis of variance (ANOVA) model with age (elderly or young) as fixed effect. A 5% level of significance was used to test for this effect.
For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the ratio elderly/young of the age groups and their 90% confidence interval were estimated. An equivalence range of 80-125% was utilized to determine the effect of age on the pharmacokinetics of palonosetron.
For comparisons (elderly versus young) of t_{max} Hodges-Lehmann shift estimates and corresponding 90% confidence intervals were calculated from non-transformed data.
Frequency tables for t_{max} were drawn up based on the corresponding nominal times; they were given for all subjects as well as by gender.

Safety:
Results of all safety measurements were listed individually and, if appropriate, summarized by descriptive statistics. Descriptive statistics were calculated for continuous laboratory parameters, vital signs including body weight and body temperature, and ECG parameters. Changes from baseline were summarized. Qualitative data were summarized by means of frequency tables.

Results are discussed in QBR

PALO 04-03

Name of Sponsor/Company: **Helsinn Healthcare SA**	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: Palonosetron HCl	Page:	

Title of the study: A Single Dose, Randomized, Open Label, Parallel Group Pharmacokinetic Study of Palonosetron 0.25, 0.50 and 0.75 mg Administered by the Oral Route to Cancer Patients Receiving Moderately Emetogenic Chemotherapy

Investigators: 1 investigator in Romania.

Study Centers:
There was 1 active center in Romania.

Publication (reference): (not applicable)

Study period (years):
First patient enrolled: February 27, 2006
Last patient completed: May 30, 2006

Phase of development: II

Study Objectives:

- To evaluate the pharmacokinetic (PK) profile, including dose proportionality, of a single oral dose of palonosetron 0.25 mg, 0.50 mg, and 0.75 mg in cancer patients receiving a course of moderately emetogenic chemotherapy.
- To evaluate the safety profile and tolerability of orally administered palonosetron 0.25 mg, 0.50 mg, and 0.75 mg in this patient population.

Methodology: This was a phase II, single dose, randomized, open-label, parallel group pharmacokinetic study to assess the pharmacokinetic profile, including dose proportionality, of single 0.25 mg, 0.50 mg, and 0.75 mg oral doses of palonosetron in cancer patients receiving moderately emetogenic chemotherapy. In addition, the safety and tolerability of orally administered palonosetron in this patient population was evaluated.

Number of patients:

Planned: 36 (12 per treatment group)
Enrolled: 41
Randomized 36

Analyzed:		Safety Set	PK Set
	Palonosetron 0.25 mg	12	12
	Palonosetron 0.50 mg	12	12
	Palonosetron 0.75 mg	12	12

Diagnosis and main criteria for inclusion: Male or female patients aged 18 years or older; naïve or non-naïve to cancer chemotherapy; with histologically or cytologically confirmed malignant disease and a Karnofsky index ≥ 50%; who had provided written informed consent and were scheduled to receive a single intravenous (IV) dose moderately emetogenic treatment of the following agents on Study Day 1: oxaliplatin, carboplatin, epirubicin, idarubicin, doxorubicin, ifosfamide, irinotecan or daunorubicin or cyclophosphamide < 1500 mg/m^2 or cytarabine > 1 g/m^2.
Patients with known non-severe hepatic, non-severe renal, or cardiovascular impairment or a known history or predisposition of cardiac conduction interval abnormalities could be enrolled at the discretion of the investigator.
Main criteria for exclusion: Patients who were expected to be non-compliant with the study procedures; had received any investigational drugs within 30 days before the start of study treatment or were scheduled to receive cisplatin, dacarbazine, streptozotocin, carmustine, mechlorethamine, hexamethylmelamine, procarbazine, cyclophosphamide ≥ 1500 mg/m^2, or radiotherapy before study end, or any moderately emetogenic chemotherapeutic agent during Days 2 to 9 of the study were excluded. Patients were also excluded if they had received any antacid drug within 24 hours prior to study drug administration or were scheduled to receive such treatment within 6 hours after study treatment; had any condition that could have been associated with a risk of emesis near or at the time of study drug administration; had a clinically unstable seizure disorder with seizure activity requiring anticonvulsant medication; experienced any vomiting, retching, or National Cancer Institute (NCI) Common Toxicity Criteria grade 2 or 3 or nausea in the 24 hours preceding chemotherapy; had ongoing vomiting from any organic etiology; had diabetes mellitus; had severe renal or hepatic impairment; had positive serology test results; had clinically significant blood loss in the last 30 days; had a known contraindication to 5-HT$_3$ receptor antagonists; were treated with commercially available IV palonosetron (Aloxi®) within 2 weeks prior to start of study treatment or were enrolled in a previous study with palonosetron.

Test product: Palonosetron soft gelatin capsules

		Batch numbers:
Dose:	0.25 mg or	04 JM 259
	0.50 mg or	04 JM 260
	0.75 mg	04 JM 261

Mode of administration: oral

Duration of treatment: single dose

Criteria for evaluation:

Pharmacokinetic evaluation:

PK assessments were performed for all three doses, 0.25 mg, 0.50 mg, and 0.75 mg. The following PK parameters were evaluated for palonosetron and the metabolites M4 and M9 (as data allowed): maximum observed plasma concentration (C_{max}); time to maximum observed plasma concentration (t_{max}); area under the curve (AUC) for the time interval 0 to time of last sample (AUC_{0-t}); AUC 0 to infinity ($AUC_{0-\infty}$); AUC 0 to 72 hours (AUC_{0-72}); terminal elimination rate constant (λ_z); number of points used for estimation of λ_z; lower and upper time point used for estimation of λ_z; terminal phase elimination half-life ($t_{1/2Z}$); Rsquare; % AUC extrapolation ($AUC_{t-\infty}$ as % of $AUC_{0-\infty}$). For palonosetron only, the oral clearance (Cl/F) and the apparent oral volume of distribution (V_z/F) were determined.

Safety evaluation:

Adverse events, vital signs, physical examinations, clinical laboratory parameters, 12-lead electrocardiogram (ECG).

Statistical methods:

PK: Palonosetron, M4 and M9 plasma concentrations were listed, summarized, and presented graphically. Initial calculation of the PK parameters - using a non-compartmental model - was accomplished for all patients with any plasma concentration values available. The PK set was then determined to be all patients who received palonosetron and for whom at least one reliable PK parameter could be derived. Palonosetron PK parameters for the PK set were listed and summarized by dose group for the parameters C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-72}, λ_z, $t_{1/2z}$, oral clearance, and V_z/F. M9 and M4 PK parameters C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-72}, and $t_{1/2z}$ were summarized and listed similarly. For descriptive statistics, mean, standard deviation, minimum, median, maximum, geometric mean and CV(%) of the geometric mean were produced as applicable. Mean and individual plasma concentration versus time plots were provided for palonosetron, M9, and M4.

Safety: The analysis of safety was performed for the safety set, defined as all patients who received palonosetron and had at least one safety assessment after treatment. The results were interpreted in a descriptive manner. Incidence of AEs was calculated overall, by system organ class and by preferred term. In addition, 95% confidence intervals were provided for overall incidences and for incidences of non-related and related AEs.

Physical examination and vital signs data were listed and summarized. For vital signs, differences were calculated compared to baseline.

Laboratory data were analyzed and described considering the age and/or gender dependent normal ranges of the local laboratory. Laboratory data were summarized and listed. Marked abnormalities and assessments concerning clinical relevance for abnormal values were included. Shift tables were used for vital signs and laboratory data to evaluate categorial changes with respect to normal ranges.

Statistical methods (continued):

For all ECGs heart rate, PR, QRS, QT, QTcB and QTcF were analyzed. Summary statistics including mean, median, standard deviation, range and 95% confidence interval for the mean were presented for each visit as well as change from baseline (Visit 2 pre-dose). In addition an outlier analysis was performed.

The number and proportion of patients with ECG abnormalities were presented for each visit. In addition, any new abnormalities recorded at Visit 2 post-dose or Visit 8 which were not present at Visit 2 pre-dose were presented by visit.

Nausea and vomiting: Nausea and vomiting were assessed at each time point for PK sampling after study drug administration. All data on nausea and vomiting were summarized and listed.

Results are discussed in QBR

4.3 OCP Filing Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-233**	**Brand Name**	**Aloxi**
OCP Division (I, II, III)	**DCP3**	**Generic Name**	**Palonosetron hydrochloride**
Medical Division	**Gastroenterology product**	**Drug Class**	
OCP Reviewer	**Insook Kim, Ph.D.**	**Indication(s)**	**Prevention of acute (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy**
OCP Team Leader	**Sue-Chih Lee. Ph.D.**	**Dosage Form**	**0.5 mg capsule**
		Dosing Regimen	**0.5 mg capsule 1 hour prior to the start of chemotherapy**
Date of Submission	**October 24, 2007**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**June 1, 2008**	**Sponsor**	**Helsinn Healthcare SA**
PDUFA Due Date	**August 22, 2008**	**Priority Classification**	**Standard**
Division Due Date	**June 24, 2008**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE	**x**	**13**	**10**	
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary				
Labeling	**x**			
Reference Bioanalytical and Analytical Methods		**1**	**1**	
I. Clinical Pharmacology				
Mass balance:	**x**	**1**	**1**	
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x			
multiple dose:				
Patients-				
single dose:	x			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	5	4	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:		1	1	
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

ethnicity:				
gender:				
pediatrics:				
geriatrics:	x	1	1	
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	1			
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	**x**	**1**	**1**	
Relative bioavailability -				
solution as reference:	x			
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	1	1	
replicate design; single / multi dose:				
Food-drug interaction studies:	**x**	**2**	**1**	
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class	**X**			
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**13**	**10**	

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. Dose-selection** **2.**	
Other comments or information not included above		

Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

CC: NDA XX-XXX, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR

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

/s/

Insook Kim
7/23/2008 10:15:42 AM
BIOPHARMACEUTICS

Sue Chih Lee
7/23/2008 10:42:25 AM
BIOPHARMACEUTICS