

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-233

MEDICAL REVIEW(S)

**Division of Gastroenterology Products
Clinical Review**

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Drug Aloxi® Palonosetron
Therapeutic Class 5HT³ Receptor Antagonist

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Priority Designation S
Formulation Oral Capsule
Dosing Regimen 0.50 mg

Indication Moderately emetogenic cancer
 chemotherapy

Intended Population Adults

Reviewer Dr. Nancy F. Snow
 Medical Officer
 HFD-180

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

In the current NDA submission, the sponsor is requesting approval of Aloxi® (palonosetron) 0.50 mg oral capsules for the prevention of acute (b) (4) chemotherapy induced nausea and vomiting (CINV) associated initial and repeat courses of moderately emetogenic chemotherapeutic agents (MEC). Acute CINV is defined as nausea and vomiting that occur within 24 hours of receiving chemotherapy. (b) (4)

Efficacy in the acute phase for the prevention of CINV was demonstrated for all 3 oral palonosetron doses, based on: (1) the percentage of patients with complete response (CR; no emesis and no rescue medications), (2) non-inferiority to the active control, I.V. palonosetron. In the delayed phase, CR rates were similar to the I.V. formulation, but none of the oral dosage forms demonstrated non-inferiority to the active comparator. Of the three oral dosage forms tested, the 0.50 mg dose came closest to the non-inferiority margin.

Based on demonstrating non-inferiority to the I.V. approved formulation for all three oral dose levels in the acute phase, but failure to show non-inferiority in the delayed phase, the medical reviewer recommends that the 0.50 mg oral capsule be approved for the prevention of nausea and vomiting in the acute (0 to 24 hour) phase (b) (4)

1.2 Recommendation on Postmarketing Actions

From a clinical perspective, no post marketing actions are recommended.

1.2.1 Risk Management Activity

From a clinical perspective, no risk management activity is recommended.

1.2.2 Required Phase 4 Commitments

From a clinical perspective, no risk management activity is recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

In preparation for a type B meeting in March 2007, the sponsor submitted questions to DGP in which they asked about the adequacy of efficacy data from sole pivotal phase 3 study PALO-03-

13, and supporting phase 3 repeat-cycle study PALO-03-14. DGP responded that the pivotal study would need to provide substantial evidence of efficacy, and identify other data sources and studies used for supportive evidence.

Accordingly, PALO-03-13 was submitted as the sole pivotal efficacy trial for this NDA. Two additional analyses, an historical pooled analysis (PALO-07-36) and an exploratory analysis (PALO-07-36) were performed post hoc to support PALO-03-13 results. Phase 2 study (2332) and repeat cycle, Phase 3 open-label study PALO-03-14 are also submitted as supporting studies.

Trial PALO-03-13 was conducted in the United States (15 sites), Mexico (7 sites), Romania (6 sites), Poland (7 sites) and the Czech Republic (11 sites). The 6 Romanian sites were added during the last two months of the trial because, toward the end of the scheduled enrollment period, overall enrollment was behind schedule and some sites were administratively closed. PALO-03-14 was conducted in the United States, Mexico, Poland, and the Czech Republic.

PALO-03-13 was a double-blind, randomized, balanced, parallel-group, stratified, non-inferiority study in which three dose levels of palonosetron capsules were compared to 0.25 mg palonosetron I.V. in the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy

Patients were randomly assigned to one of four treatment groups; the most emetogenic chemotherapeutic agent was administered first on study Day 1. Nitrogen mustard analogues (cyclophosphamide $<1500 \text{ mg/m}^2$) and anthracyclines and related substances (doxorubicin and epirubicin) were the two most frequent chemotherapeutic agents administered. The breakdown of patients is as follows:

- Group 1: oral palonosetron 0.25 mg – 157 enrolled
- Group 2: oral palonosetron 0.50 mg – 161 enrolled
- Group 3: oral palonosetron 0.75 mg – 158 enrolled
- Group 4: I.V. palonosetron 0.25 mg – 163 enrolled

Phase 3 supportive study **PALO-03-14** was a multicenter, open-label, repeat cycle, uncontrolled trial to assess safety and efficacy of single oral doses of palonosetron 0.75 mg in the prevention of MEC in repeated and consecutive moderately emetogenic chemotherapy cycles. It did not study the 0.50 mg (the proposed to-be marketed) dose, and only cycle 1 data was included in the Integrated Summary of Safety for the NDA.

1.3.2 Efficacy

The primary efficacy measure for Phase 3 studies was complete response (no emetic episodes, no rescue medication) during 0 to 24 hours after administration of moderately emetogenic chemotherapy. The key secondary efficacy measure was CR during 24 to 120 hours after MEC. Other secondary efficacy parameters included complete control (CR and no more than mild nausea), daily number of emetic episodes, and time to first emetic episode.

In PALO-03-13 randomization was stratified by gender and previous chemotherapy history (naïve or non-naïve) to produce 4 strata. Within each group patients received one of four palonosetron doses, with or without dexamethasone (two subgroups for each treatment group). The majority of patients were female (73%) , white (69%), and chemotherapy naïve (59%).

Results from PALO-03-13 showed that the number of patients with complete response in the 0 to 24 hour period was comparable in the three oral palonosetron treatment groups (less than 3% difference between the individual oral treatment groups), and slightly higher than with the I.V. formulation. In all 3 oral palonosetron doses the lower limit of the 98.3% CI was above the non-inferiority margin of -15%, implying with reasonable certainty that the proportion of complete responders to palonosetron was no more than 15% less than the proportion seen with the comparator. No clear dose response relationship was observed in the oral palonosetron studies, or in the earlier studies conducted with the I.V. formulation.

During the 24 to 120 hour time frame the highest percentage of patients with CR was seen with I.V. palonosetron (65.4%), followed by the 0.50 mg oral palonosetron dose (62.5%). As with the acute phase, oral doses of palonosetron were compared in a non-inferiority manner to the approved I.V. formulation. Since the lower limit of the CI for the oral doses was below the pre-set threshold of -15%, none of the oral doses were statistically non-inferior. Thus for all oral dose levels studied in the delayed time period, the proportion of complete responders to palonosetron fell outside the -15% margin. The 0.50 mg dose performed best, and came closest to the margin.

1.3.3 Safety

The safety assessment of palonosetron is based primarily on 1061 patients enrolled in Phase 2 or 3 studies: Study 2332, PALO-04-03, PALO-03-13, and the first cycle of chemotherapy in PALO-03-14. A total of 898 (84.%) patients were exposed to oral palonosetron and 163 (15.4%) received I.V. palonosetron. Eleven patients died during these studies. No deaths appear related to the study drug.

In Phase 2 and 3 trials included in the safety review, 56 patients experienced a total of 120 serious adverse events. Of these, 17 were assessed as unrelated to study drug, 30 unlikely, 4 missing/unknown (later considered unrelated in the SAE narratives), and 5 possibly related. In PALO-03-13 there were more SAEs in the 0.50 mg oral dose than in the lower 0.25 mg dose. Half of the SAEs in the 0.50 mg group occurred beyond 2 weeks after receiving chemotherapy and study medication. Each of these SAEs was reviewed, and most appear related to the patient's cancer, chemotherapy, or concomitant conditions.

One of the most concerning of the SAEs was seen in pivotal study PALO-03-13, in the 0.50 mg arm. A patient with a pre-existing left bundle branch block developed second degree heart block and QTc prolongation on Day 2. The patient recovered, but ultimately required pacemaker placement. It is difficult to determine causality, since the patient's history of LBBB, ischemic heart disease, and decreased ejection fraction, in combination with a chemotherapeutic regimen of Avastin (bevacizumab) and Folfiri (irinotecan, folinic acid, fluorouracil), known to have anticholinergic side effects, may have been predisposing factors.

To allay concerns about QTc prolongation with palonosetron, a thorough QT/QTc study (tQT - PALO-03-11, performed under IND 39,797) was conducted by the sponsor. Reviewed as part of NDA 21-372, there were no significant effects of palonosetron administration on the QT interval detected in the study.

Although PALO-03-14 studied the safety of palonosetron in up to 4 cycles of chemotherapy, only cycle 1 data was included in the Integrated Summary of Safety. Overall, the incidence of cycles with adverse events decreased slightly from cycle 1 to cycle 3, and remained about the same in cycle 4.

1.3.4 Dosing Regimen and Administration

Doses studied in the oral development program were selected based on results of oral ADME (absorption, distribution, metabolism and elimination) study, phase 2 oral and I.V. dose-response studies 2332 and 2330, and I.V. palonosetron phase 3 studies PALO-99-03 and PALO-99-04.

The dose of 0.50 mg oral palonosetron was chosen for marketing because, according to the sponsor, it showed a more favorable efficacy profile than the other oral doses studied, and provided safety comparable to the 0.25 mg I.V. palonosetron formulation already on the market.

Medical Officer's Comments:

In the acute phase all three oral dose levels performed in a similar fashion, with little difference between them. In the delayed phase none of the oral dose levels showed non-inferiority to the active comparator. Of the three, the 0.50 mg came closest to the non-inferiority margin of -15%. From a safety perspective there were no major differences in adverse events that would support one dose over another with respect to the 0.25 and 0.50 mg doses.

1.3.5 Drug-Drug Interactions

In-vitro studies conducted during the original development of the I.V. formulation indicate that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5, nor does it induce the activity of CYP1A2, CYP2D6 or CYP3A3/4. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low, as stated in current approved Aloxi® labeling.

1.3.6 Special Populations

Special patient population PK studies involving the I.V. palonosetron formulation indicate that no dosage adjustment is required for elderly patients, or patients with impaired renal or hepatic function. However the pharmacokinetics of palonosetron have not been studied in patients with end-stage renal disease. Because there are no adequate and well-controlled studies in pregnant women and during lactation, palonosetron is not recommended for use during pregnancy or in nursing women.

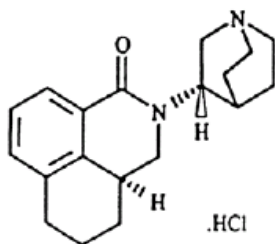
2 INTRODUCTION AND BACKGROUND

Through the current NDA submission the sponsor, Helsinn Healthcare, is seeking approval of an oral capsule dosage form of the approved drug Aloxi® (palonosetron) for the prevention of acute (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. Originally approved July 2003, palonosetron belongs to the drug class of 5-HT₃ receptor antagonists. Palonosetron is currently approved in an I.V. formulation for acute and delayed chemotherapy induced nausea and vomiting (CINV) associated with moderately emetogenic chemotherapy agents, acute chemotherapy induced nausea and vomiting associated with highly emetogenic chemotherapy agents, and post-operative nausea and vomiting (PONV).

The proposed dose is 0.50 mg, to be taken orally 60 minutes before the start of chemotherapy. It is intended to be used in patients 18 years and older.

2.1 Product Information

Trade Name (established name): Aloxi® (Palonosetron HCL)



Proposed Indication:

- Prevention of **acute** nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy

➤ (b) (4)

Proposed Age Group: Adults ≥ 18

Pharmacologic Class: 5-HT₃ Receptor Antagonist

Route of administration: Oral

Proposed Treatment Regimen: One 0.50 mg capsule one hour before chemotherapy

2.2 Currently Available Treatment for Indications

There are four antiemetics of the 5HT-3 receptor antagonist class currently marketed in the United States : ondansetron, granisetron, dolasetron and palonosetron. The following table provides an overview of this drug class.

DRUG	CINV	CINV PEDIATRIC	PONV	PONV PEDIATRIC	RINV
Palonosetron I.V. (Aloxi)	Acute MEC,HEC/ Delayed MEC (age ≥18)		Prevention 0-24 hours		
Palonosetron PO					
Ondansetron I.V. & premixed (Zofran)	Acute CINV	6 m to 18 y	Prevention	1 m to 12 y	
Ondansetron PO (tabs, oral solution, orally disintegrating tabs)	Acute MEC, HEC	4 to 16 y	Prevention		X
Granisetron I.V. (Kytrel)	Emetogenic CINV	2 to 16 y	Prevention & treatment		
Granisetron PO (tabs, solution)					X
Dolasetron I.V. (Anzemet)	Emetogenic CINV	2 to 16 y	Prevention or treatment	2 to 16 y	
Dolasetron PO	MEC	2 to 16 y	Prevention or treatment	2 to 16 y	

Medical Officer's Comments:

The American Society of Clinical Oncologists (ASCO) Guidelines for antiemetics in Oncology recommends a 5-HT₃ receptor antagonist, along with dexamethasone for patients receiving chemotherapy of moderate emetic risk other than anthracycline and cyclophosphamide. A three drug combination of a 5-HT₃ receptor antagonist, dexamethasone, and an NK-1 receptor antagonist is recommended for patients receiving anthracycline and cyclophosphamide, and for highly emetogenic regimens. At no time is palonosetron to be used alone to prevent MEC or HEC.

2.3 Availability of Proposed Active Ingredient in the United States

Palonosetron I.V. has been available in the United States since 2003. The commercial drug products are manufactured at Catalent Pharma (Somerset, NJ), the manufacturing site where the capsules used in the clinical studies were prepared.

2.4 Presubmission Regulatory Activity

NDA 21-372, for I.V. palonosetron, was submitted September 2002, and approved July 2003 for the indication of prevention of acute (MEC and HEC) and delayed (MEC only) CINV. Subsequently, Palonosetron has been approved and marketed in 53 countries worldwide.

In 1995, two Phase 2 CINV studies, Study 2330 (I.V.) and Study 2332 (oral), were completed under IND 39,797 and IND 42,886, respectively, both sponsored by Syntex, the original developer of palonosetron. Phase 2 mass balance and metabolite profiles showed that the I.V. and oral formulation are qualitatively alike and quantitatively similar.

An end-of-phase 2 meeting was held December 15, 2003 during which the sponsor proposed one large Phase 3 pivotal efficacy trial and one large repeat-cycle open label safety and efficacy trial for the oral palonosetron clinical development program. Based on FDA feedback from the meeting the sponsor submitted a Special Protocol Assessment (IND 42,886) and two amendments for pivotal study PALO-03-13.

Study PALO-03-13 was completed in August 2006, and results and questions were submitted to DGP in a pre-NDA background package. Specifically, the sponsor asked about the adequacy of sole pivotal phase 3 study PALO-03-13, and supporting phase 3 repeat-cycle study PALO-03-14. DGP responded that the submission would need to justify the pivotal study and its results as providing substantial evidence of efficacy, and identify other data sources and studies used for supportive evidence.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The Chemistry Reviewer, Dr. Zhengfang Ge, notes that “the sponsor has provided adequate information in the original submission and subsequent amendments to assure identity, strength, purity, and the quality of the drug product. From a CMC perspective, the NDA is approvable, pending satisfactory facility inspections.”

3.2 Animal Pharmacology/Toxicology

Since palonosetron is approved for marketing in the United States, no additional pre-clinical studies were required for this submission. Animal Pharmacology/Toxicology studies are reviewed in the original NDA submission, NDA 21-371 and discussed, as relevant, in the PharmTox review of Dr. David Joseph.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor, Helsinn Healthcare SA, assumed responsibilities for both I.V. and oral palonosetron INDs in 1998 and continued development of I.V. palonosetron through approval in 2003 (NDA 21-273). The present oral palonosetron NDA references the approved I.V. formulation to provide preclinical, PK, and clinical efficacy and safety data support.

PALO-03-13 is the pivotal efficacy trial for this NDA. Two additional analyses, an historical pooled analysis (PALO-07-36) and an exploratory analysis (PALO-07-36) were performed to support the PALO-03-13 data. In addition the phase 2 study (2332) and repeat cycle efficacy data from Phase 3 open-label study (PALO-03-14) are also submitted as supporting studies.

The Phase 3 studies were international trials; PALO-03-13 had sites in the United States (15), Mexico (7), Romania (6), Poland (7) and the Czech Republic (11). PALO-03-14 was conducted in the United States, Mexico, Poland, and the Czech Republic.

4.2 Tables of Clinical Studies

The following tables, taken from the NDA synopses, provide a listing of all studies pertinent to the oral palonosetron development program.

Tables of 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

Pharmacokinetic Studies

0101	5.3.3.1.1 Vols. 12-13	Dose-proportionality, safety and pharmacokinetics	Double-blind, single dose, ascending dose, placebo-controlled	Palonosetron; 3, 10, 30 or 90 µg/kg or placebo; Oral solution	32M	Healthy volunteers (Japan)	Nov 1994 to Mar 1995 (Single dose)	Complete; Full report
2236	5.3.3.1.2 Vols. 14-15	Dose-proportionality, safety and pharmacokinetics	Double-blind, single dose, ascending dose, placebo-controlled	Palonosetron; 3, 10, 20, 40 or 80µg/kg or placebo; Oral solution	39M	Healthy volunteers (USA)	Aug 1993 to Nov 1993 (Single dose)	Complete; Full report
PALO-03-07	5.3.3.1.3 Vols. 16-17	Oral ADME	Open-label, single center, single oral dose ADME study	0.75 mg PO (oral solution-radiolabeled)	6M	Healthy Volunteers (Scotland)	Aug 2003 to Sept 2003 (single dose)	Complete; Full report

(b) (4)

Pharmacokinetic Studies (continued)

PALO-04-02	5.3.3.4.2 Vols. 24-28	Effect of antacids and food (high fat meal) on PK of oral palonosetron	Open label, randomized, single center, three period, crossover, single dose study	0.75 mg PO (clinical trial softgel capsule) Fasted vs 0.75 mg PO (clinical trial softgel capsule) Fed vs 0.75 mg PO (clinical trial softgel capsule) with antacid	9M 9F	Healthy Volunteers (Germany)	Oct 2005 to Nov 2005 (Single dose three period crossover)	Complete; Full report
PALO-04-01	5.3.3.4.1 Vols. 22-24	Pharmacokinetics in elderly	Open label, single center, single treatment study in healthy fasting elderly subjects (Fasting group from study PALO-04-02 used as young comparator group)	0.75 mg PO (clinical trial softgel capsule)	9M 9F	Healthy Volunteers (Germany)	Nov 2005 to Nov 2005 (single dose)	Complete; Full 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
2332	5.3.4.2.1 Vols. 30-40	Safety, efficacy and PK in CINV patients	Phase 2 double-blind, single dose, dose-ranging	50.3, 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

Medical Reviewer's Comments:

PALO-07-35 and PALO-07-36 were post hoc analysis, not pre-specified in the statistical analysis plan for PALO-03-13, the pivotal study for the current submission.

4.3 Review Strategy

The primary emphasis of this review is pivotal trial PALO-03-13, with consideration given to supplemental and supportive studies.

4.4 Data Quality and Integrity

According to the sponsor, the quality and accuracy of the data collected, tabulated and analyzed for the purpose of reporting, have been assured by monitoring of the study, by data management procedures, and by quality assurance audits. Data management and data entry were performed by Kendle, Cincinnati and Munich.

4.5 Compliance with Good Clinical Practices

Palonosetron clinical trials performed under Helsinn sponsorship (1999-2007), which included all phase 3 trials (Studies PALO-03-13 and PALO-03-14), clinical pharmacology trials (PALO-03-07, PALO-04-01, PALO-04-02, PALO-04-03, PALO-04-04, PALO-04-14, PALO-06-16) and I.V. supportive phase 1 studies (Studies PALO-99-34, PALO-99-35, PALO-99-39, PALO-99-51), were conducted in compliance with applicable Institutional Review Board / Institutional Ethic Committee regulations (21CFR Part 56, ICH E6) and Informed Consent regulations (21 CFR Part 50, ICH E6).

4.6 Financial Disclosures

The sponsor has submitted form 3454, certifying that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study, as defined in 21 CFR 54.2(a).

Medical Officer's Comments:

The sponsor has certified that they did not enter into any financial agreement with the clinical investigators whereby the value of their compensation could be affected by the outcome of the studies.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Sponsor Table 2.5:4 summarizes pharmacokinetic results for oral palonosetron from CINV studies. In general, dose-dependent increases in C_{max} and AUC are seen. PALO-04-03 is the only study that provides PK data in cancer patients for the proposed market dose of 0.50 mg.

Table 2.5:4 Mean Pharmacokinetic Parameters of Palonosetron after Single Oral Doses

Dose	C _{max} (ng/ml)	T _{max} (hr)	t _{1/2} (hr)	Total AUC (ng·hr/ml)	Cl (ml/min/kg)	V _d (l/kg)
Study PALO-04-03 (n=36, CINV moderately emetogenic)						
0.25 mg (n=12)	0.553	6.0	49.9	34.2	2.01	7.91
0.50 mg (n=12)	0.927	3.5	48.3	49.7	2.54	10.36
0.75 mg (n=12)	1.42	4.0	64.7	103.3	2.01	9.48
Study 2332 (n=41, CINV highly emetogenic)						
0.3 µg/kg (n=1)	0.134	4.0	NC	NC	NC	NC
1 µg/kg (n=6)	0.178	14.7	66.6	15.9	1.12	6.49
3 µg/kg (n=6)	0.423	7.78	64.9	37.2	1.52	7.77
10 µg/kg (n=8)	2.09	5.49	72.8	156	1.48	8.85
30 µg/kg (n=8)	5.83	6.20	45.4	363	1.70	6.09
90 µg/kg (n=12)	16.3	4.15	60.8	978	1.78	8.64

Source: Final Reports PAOL-04-03, 2332, Table 7.2-a, End-of Text Table 25 respectively.

Note that 3 µg/kg is approximately 0.25 mg and 10 µg/kg; T_{1/2} is reflected as median values. All values have been converted to the same units for comparison.

NC = not calculable

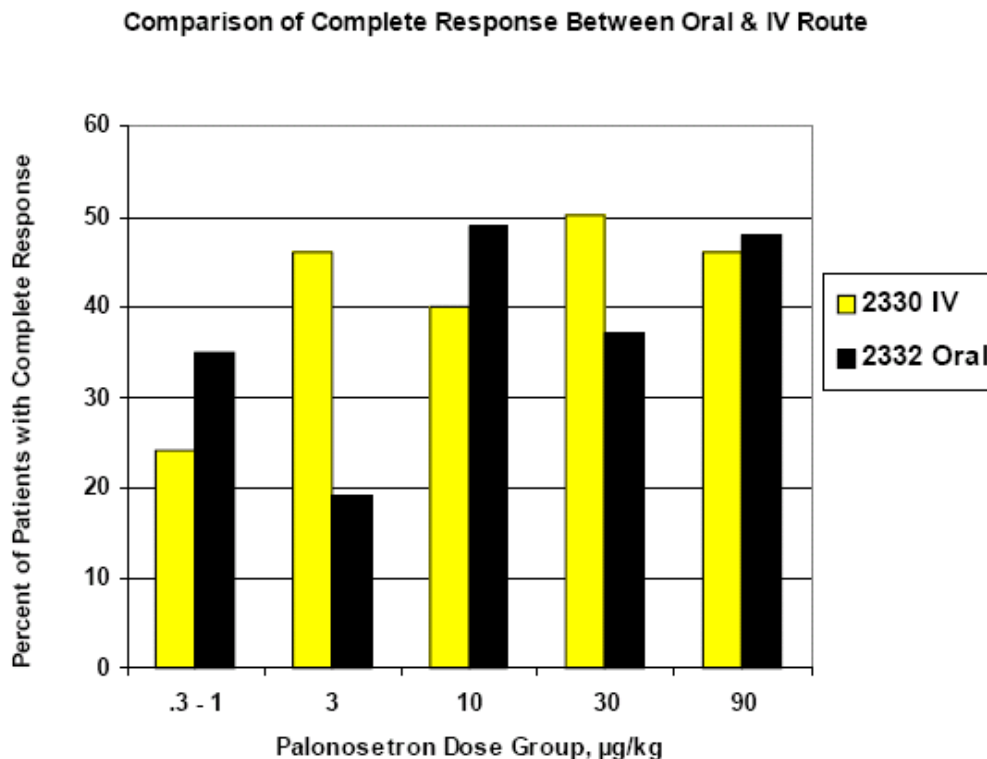
In Phase 1 studies exposure to palonosetron was 20 to 30% higher in females than males. These results were also found in PK studies evaluating the I.V. route of administration. The sponsor notes that “the clinical implications of these gender findings appear to be of limited significance, since the safety margin is large”. In addition, a dose-response relationship has not been demonstrated to be closely linked to plasma concentrations. The reviewer agrees with these explanations.

5.2 Pharmacodynamics

The pharmacological profile of palonosetron is derived from non-clinical models and clinical trials. Preclinical information was submitted in the original NDA. Clinical pharmacodynamic data are derived from pivotal and supportive studies that analyze the anti-emetic efficacy of oral palonosetron.

5.3 Exposure-Response Relationships

The following graph shows dose-response results from phase 2 trials 2330 (I.V.) and 2332 (oral). A wide range of doses were evaluated and similar dose response curves were seen with the oral and I.V. routes.



CR for the lowest oral dose level was higher, and for the second dose level lower than expected. Therefore the sponsor concluded that the lowest fully effective oral dose may lie between 3µg/kg (0.25 mg) and 10 µg/kg (0.75 mg).

6 INTEGRATED REVIEW OF EFFICACY

The following Integrated Review of Efficacy examines efficacy data submitted with NDA22-233.

6.1 Indication

Chemotherapy induced nausea and vomiting is categorized as acute (from 0 to 24 hours after the start of chemotherapy), delayed (from 24 to 120 hours after chemotherapy), and anticipatory (appearing prior to administration of repeat courses of chemotherapy). The current application is being filed in support of acute (b) (4) CINV associated with moderately emetogenic chemotherapeutic agents. The indication, as proposed by the sponsor, is:

- *Moderately emetogenic cancer chemotherapy – prevention of acute (b) (4) nausea and vomiting associated with initial and repeat courses*

Intravenous palonosetron was approved for these indications (along with prevention of acute CINV for highly emetogenic chemotherapeutic agents) in 2003. The current application is for an

oral capsule formulation to be used to prevent nausea and vomiting associated with chemotherapeutic agents of moderate emetogenic potential only.

Medical Officer's Comment:

The indication being sought is for initial and repeat courses of moderately emetogenic chemotherapy. However pivotal trial PALO-03-13 studied a one time administration of oral palonosetron associated with one chemotherapy treatment only. Supportive study PALO-03-14, assessed efficacy in up to 4 chemotherapy cycles, but had no comparator, and did not study the to-be-marketed dose.

6.1.1 Methods

This efficacy review is based primarily on data derived from Phase 3 study PALO-03-13, and to a lesser extent Phase 2 trial 2332, and Phase 3 study PALO-03-14. Study 2332 examined acute CINV associated with highly emetogenic agents, and PALO-03-14 studied the 0.75 mg dose only, in initial and repeat chemotherapy regimens. PALO-03-14 was an open-label study with no comparator. Thus the design of these supportive studies differs in significant ways from pivotal study PALO-03-13.

To augment results from PALO-03-13, and provide support for the secondary efficacy endpoint of complete response (CR) in the delayed phase (24 to 120 hours), further investigations were done, pursuant to 21 CFR 314.126(b)(2)(v).

- Historical pooled analyses, PALO-07-36
- Exploratory analysis, PALO-07-35 (non-inferiority test of proportions)

21 CFR 314.126(b)(2)(v) states:

“Historical control. The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).”

During the course of the review the FDA requested additional information from the sponsor, including historical placebo controlled trials specific to the delayed phase. These items were also reviewed with the NDA and provide further data for the efficacy review.

Medical Officer's Comments:

In NDA 22-233 the most useful and robust data comes from pivotal study PALO-03-13. Supportive Phase 3 study PALO-03-14 provides limited efficacy data since the trial did not

evaluate the 0.50 mg dose and was uncontrolled. Phase 2 study 2332 evaluated CR in the acute phase only, for patients receiving highly emetogenic chemotherapy (HEC).

The supplemental data, which the sponsor submitted to support CR in the delayed phase, pooled data from historical I.V. CINV pivotal trials, with the 0.25 mg I.V. arm in PALO-03-13. These data are useful in so far as they provide a larger database for the active comparator, but since dexamethasone was not the standard of care when these studies were conducted, fewer patients received dexamethasone than in the current studies. In addition this evaluation was not part of the original statistical analysis plan, and was done post-hoc.

The historical placebo data provides additional information about efficacy beyond 24 hours by comparing the percentage of patients on placebo (derived from earlier studies) who did not have emesis with patients receiving 0.50 mg oral palonosetron. Data were presented for days 2, 3, and 4-5. On day two 23% of placebo patients did not have emesis, compared to 75% of palonosetron patients. On day three 40% of placebo patients were emesis-free, compared to 84% observed with palonosetron.

The endpoint measured, no emesis, was not the primary, or key secondary endpoint used in PALO-03-13. Further there were differences with respect to type of cancer treated, chemotherapeutic agent, gender, previous chemotherapy history, and corticosteroid use. In addition, efficacy was measured on single days, rather than for the entire delayed phase of 24 to 120 hours.

6.1.2 General Discussion of Endpoints

The following Table 2.7.3:3 provides a brief overview of efficacy endpoints used in the oral palonosetron CINV trials.

Table 2.7.3:3 Efficacy Endpoints for the CINV Trials

Primary and / or Key Secondary Efficacy Endpoints	Pivotal	Supportive	
	PALO 03-13	PALO 03-14	2332
Primary efficacy endpoint: Complete Response (CR, defined as no emetic episode and no rescue medication) during 0-24 hours after the start of moderately emetogenic chemotherapy administration.	X	X ^a	
Key secondary efficacy endpoint: CR during 24-120 hours after the start of moderately emetogenic chemotherapy administration	X	X ^a	
Primary efficacy endpoint: Complete antiemetic response ^b for 24 hours following highly emetogenic chemotherapy			X ^b
Other Secondary Efficacy Endpoints			
CR daily for the 24-120 hour interval (i.e. 24-48 hour, 48-72 hour, 72-96 hour and 96-120 hour intervals), for cumulative time periods (i.e 0-48 hour, 0-72 hour, 0-96 hour intervals) and for the overall 0-120 hour interval (Days 1-5).	X	X	X ^c
Complete control ^d (CC, defined as CR and no more than mild nausea) daily and cumulative for the 0-120 hour interval, for the overall 0-120 hour interval (Days 1-5) and for the 24-120 hour period.	X	X	X
Number of emetic episodes daily for the 0-120 hour interval and for the overall 0-120 hour interval (Days 1-5).	X	X	
Time to first emetic episode.	X	X	X
Time to first administration of rescue therapy.	X	X	X
Time to treatment failure (time to first emetic episode or to administration of rescue therapy, whichever occurred first).	X	X	X
Severity of nausea (4-point Likert scale) daily for the 0-120 hour interval.	X	X	X

a PALO-03-14 was a safety trial therefore CR (0-24 and 24-120) was an efficacy parameter of major interest

b Although in the 2332 study report CR was defined as "the proportion of patients free from emetic episodes", the more conservative definition of CR as "patients free from emetic episodes and requiring no rescue medication" was adopted during data analyses. Errata Corrigé dated 12 August, 2002.

c Assessed daily over 7 days in study 2332.

d CC definition is given in the 2332 study, Errata Corrigé dated 12 August, 2002.

Table 2.7.3:3 Efficacy Endpoints for the CINV Trials (continued)

Other Secondary Efficacy Endpoints (Continued)	Pivotal	Supportive	
	PALO 03-13	PALO 03-14	2332
Percentage of patients with/without nausea, daily for the 0-120 hour interval, the overall 0-120 hour interval, and for the 24-120 hour interval.	X	X	
Percentage of patients with/without rescue medication, daily for the 0-120 hour interval, the overall 0-120 hour interval, and for the 24-120 hour interval.	X	X	X ^c
Percentage of patients with/without emesis, daily for the 0-120 hour interval, the overall 0-120 hour interval, and for the 24-120 hour interval.	X	X	X ^c
Subject global satisfaction with therapy (VAS; visual analog scale) daily for the 0 to 120-hour interval	X	X	X ^c

a PALO-03-14 was a safety trial therefore CR (0-24 and 24-120) was an efficacy parameter of major interest

b Although in the 2332 study report CR was defined as "the proportion of patients free from emetic episodes", the more conservative definition of CR as "patients free from emetic episodes and requiring no rescue medication" was adopted during data analyses. Errata Corrigé dated 12 August, 2002.

c Assessed daily over 7 days in study 2332.

d CC definition is given in the 2332 study, Errata Corrigé dated 12 August, 2002.

The primary efficacy measure was complete response (no emetic episodes, no rescue medication), during 0 to 24 hours after administration of moderately emetogenic chemotherapy. The key secondary efficacy endpoint was CR during 24 to 120 hours after MEC. Additional secondary efficacy parameters included percentage of patients with/without nausea, percentage of patients with/without rescue medication, and percentage of patients with/without emesis.

To understand the endpoint of CR, it is useful to return to I.V. palonosetron to see how acute and delayed were originally conceived. Sponsor's Table 7, taken from NDA 21-372 (I.V. palonosetron for CINV), shows efficacy endpoints for the I.V. CINV trials used in the original palonosetron approval.

TABLE 7: Efficacy Endpoints for the CINV Trials

	Moderately Emetogenic		Highly Emetogenic	
	PALO-99-03	PALO-99-04	PALO-99-05	2330
Primary Efficacy Endpoint				
Complete response (CR) ^a during the first 24 hours after administration of chemotherapy.	X	X	X	X
Secondary Efficacy Endpoints				
Complete response over 120 h	X	X	X	X
Complete control (CC). ^b	X	X	X	X
Total response (subjects free from emetic episodes, rescue medication, and nausea over time).				X
Number of emetic episodes.	X	X	X	
Time to first emetic episode.	X	X	X	X
Time to rescue medication.	X	X	X	X
Time to treatment failure (time to first emetic episode or administration of rescue medication, whichever occurred first).	X	X	X	X
Severity of nausea (Likert Scale)	X	X	X	X
Subject global satisfaction with therapy (VAS; visual analog scale).	X	X	X	X
Quality of life questionnaire (FLIE; Functional Living Index):	X	X	X	

^a Defined as no emetic episode and no rescue medication.

^b Defined as a complete response and no more than mild nausea.

Source: Final Study Reports: PALO-99-03; PALO-99-04; PALO-99-05, and 2330.

The efficacy endpoints, both primary and secondary, did not specify a “delayed” response. As per the statistical reviewer:

Delayed response was not pre-specified as a primary endpoint, and “delayed” is itself not precisely defined (it could be the overall five day time period, the overall post-24 hour four-day time period, or each of the four post 24-hour days) . The outcome analyzed, however, is the primary one of complete response. The most sensible definition of delayed response is the overall post-24 hour four-day value: it does not include the acute response but does include information from all subsequent days, in particular the final day of observation when the emetogenicity of the chemotherapy is most muted.

In contrast, the current submission for an oral capsule formulation, clearly separates acute from delayed.

Although the definition of CR has changed and evolved over time, it has been defined consistently in palonosetron clinical trials as no vomiting and no rescue medications, without mention of nausea. The definition of acute vs. delayed has varied, as discussed above.

The primary efficacy variable for the current submission was analyzed in a confirmatory manner for the full analysis set (all randomized patients who received study medication and had at least

moderately emetogenic chemotherapy) to demonstrate non-inferiority of at least one oral dose of palonosetron compared to the approved 0.25 mg I.V. formulation.

Validation

To show validity of the study, two comparisons were performed:

- CR of the active comparator (I.V. palonosetron 0.25 mg) in the FAS at 24 hours compared to historical placebo response rate at 24 hours
- CR rate of active comparator without dexamethasone in the FAS at 24 hours compared to historical I.V. palonosetron 0.25 mg without dexamethasone response rates at 24 hours

The historical placebo response rates were derived from a meta-analysis of published literature of clinical trials with placebo and setrons. Historical I.V. palonosetron 0.25 mg response rates were derived from a meta-analysis based on data from two previous palonosetron studies (PALO-99-03 and PALO-99-04).

Sponsor's Table 7.1-h shows results of the validation compared to modeled historical placebo.

Table 7.1-h: Validation of the study: Historical placebo

Modeled historical placebo		Study PALO-03-13 palonosetron 0.25 mg IV	
CR rate at 24 h (%)	95% CI (%)	CR rate at 24 h (%)	95% CI (%)
19.4	[14.6, 25.3]	70.4	[62.6, 77.1]

Source: Appendix B-1.4, Table 43.1
CI = confidence interval, CR = complete response

The CR rate of the active comparator, I.V. palonosetron 0.25 mg, at 24 hours was superior to the historical placebo response rate since the lower limit of the 95% confidence interval of the complete response in the active comparator group (62.6%) was greater than the upper limit of the 95% confidence interval of the complete response rate of the modeled historical placebo (25.3%). The large positive difference of 37.3% between the two above mentioned limits favoring the comparator showed the validity of the study with regard to historical placebo.

Sponsor's Table 7.1-i shows results of the study validation by comparing the active comparator group (without dexamethasone) to historical I.V. palonosetron 0.25 mg (without dexamethasone).

Table 7.1-i: Validation of the study: Historical IV palonosetron

Modeled historical IV palonosetron 0.25 mg (without dexamethasone)		Study PALO-03-13 palonosetron 0.25 mg IV (without dexamethasone)	
CR rate at 24 h (%)	95% CI (%)	CR rate at 24 h (%)	95% CI (%)
76.7	[70.0, 82.2]	57.5	[46.0, 68.3]

Source: Appendix B-1.4, Table 43.2
CI = confidence interval (two-sided), CR = complete response

To validate the study with regard to the historical I.V. palonosetron 0.25 mg, the complete response rate of the active comparator group without dexamethasone at 24 hours in the actual study should have been similar to the historical I.V. palonosetron 0.25 mg response rate without dexamethasone at 24 hours. For this goal, the response rate of the active comparator without

dexamethasone had to be greater or equal to the lower limit of the two sided 95.0% confidence interval of the modeled historical I.V. palonosetron response rate without dexamethasone. This was not the case, as the response rate of study I.V. palonosetron 0.25 mg without dexamethasone (57.5%) was smaller than the lower limit of the confidence interval of the response rate of the historical comparator without dexamethasone (70.0%). Therefore, validation of the study by comparing CR over 24-hours for the active comparator without dexamethasone versus historical IV palonosetron without dexamethasone, was not shown.

The sponsor explains the failure of the validation study as follows:

The complete response rate calculated for the historical I.V. palonosetron 0.25 mg was based on a meta-analysis that used data from only two previous studies and included only 636 patients (rather low for a validation model). Moreover, in one of these studies (PALO-99-03), the complete response rate was high (81.0%), which resulted in an optimistic assumption and model. Thus, the first validation model was not truly representative. Furthermore, based on the historical data, factors had been found that positively influenced the complete response rate, i.e. factors that contributed to a higher response rate. These factors, e.g. percentage of male patients, percentage of patients ≥ 60 years of age and percentage of patients administered chemotherapies other than the AC/EC regimen were represented in even higher numbers in the current population than in the historical population. This resulted in an optimistic estimation of the complete response rate. Additionally, the modeled historical palonosetron had to be compared to complete response for the active comparator of this study in the subgroup of patients without dexamethasone since the historical studies did not include use of dexamethasone. This restriction to the subgroup without dexamethasone resulted in a small sample size. Both the optimistic estimation for the modeled historical palonosetron and the small sample size in the comparator group contributed to the failure to validate the study against historical palonosetron.

For this reason a second study validation model was used. This model was based on data derived from a meta-analysis with historical setrons and was based on the data of a higher number of patients. This is the same model used to obtain the modeled historical placebo response rate. Sponsor's Table 7.1-j summarizes the results of the second model that was applied to the whole population, since the model permits to also adjust for the use of dexamethasone.

Table 7.1-j: Validation of the study: Historical setron

Modeled historical setron		Study PALO-03-13 palonosetron 0.25 mg IV	
CR rate at 24 h (%)	95% CI (%)	CR rate at 24 h (%)	95% CI (%)
66.1	[58.1, 73.3]	70.4	[62.6, 77.1]

Source: Appendix B-1.4, Table 43.3
CI = confidence interval (two-sided), CR = complete response

Applying this model, the response rate of the study I.V. palonosetron 0.25 mg (70.4%) was greater than the lower limit of the two-sided 95.0% confidence interval of the modeled setron response rate (58.1 %). The positive difference of 12.3% between the current response rate and the lower limit of the confidence interval for the modeled response rate showed that the study was validated with this more appropriate second model.

Medical Officer's Comment:

The second validation model shows more convincing results, but both validation models examine only the 0 to 24 hour time period and do not address the delayed phase data.

6.1.3 Study Design

PALO-03-13

PALO-03-13 was a double-blind, randomized, balanced, parallel-group, stratified non-inferiority study in which three doses of oral palonosetron capsules were compared to 0.25 mg I.V. palonosetron in the prevention of acute and delayed CINV associated with moderately emetogenic cancer chemotherapy. (Agents of moderate emetogenic risk include Carboplatin, Cyclophosphamide ($\leq 1.5 \text{ g/m}^2$), Cytarabine ($>1 \text{ g/m}^2$), Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Ifosfamide, Irinotecan, and Oxaliplatin). The protocol for this study was reviewed by the FDA in a Special Protocol Assessment (SPA), in Sept. 2004.

The active comparator, 0.25 mg I.V. palonosetron, is approved for prevention of acute and delayed CINV associated with moderately emetogenic chemotherapy, and prevention of acute CINV associated with highly emetogenic chemotherapy. Approval of I.V. palonosetron was based on a demonstration of non-inferiority of palonosetron to active comparators ondansetron and dolasetron.

The following Study Flow Chart provides an overview of study procedures.

Clinical Review
 Nancy Snow
 NDA 22-233
 Aloxi (Palonosetron)

An overview of the study procedures is given in the Study Flow Chart below.

PALO-03-13						
	Screening Day -7 to 0	Day 1 ^a		Day 2, (24 to 26 hrs) ^b	Days 6 - 8 ^{b, c}	Day 15 ^{c, d}
	Visit 1	Visit 2		Visit 3	Visit 4	Tel. Contact or Visit 5
		Visit 2A	Visit 2B ^e			
Informed Consent	X					
Inclusion / Exclusion Criteria	X	X				
Demography	X					
Past Medical History	X					
Karnofsky Index	X					
Pregnancy Test	X					
Vital Signs	X			X	X	
Physical Examination	X			X ^f	X ^f	
Concomitant Medication	X	X	X	X	X	X
Randomization		X				
Chemotherapy		X				
Study Drug Administration		X				
Patient Diary	Instruction	Covering Days 1 to 5, filled in daily, collected at Visit 4				
Adverse Events		X	X	X	X	X
Blood Chemistry	X			X	X	
CBC with Differential	X			X	X	
Urinalysis	X			X	X	
12-Lead ECG	X ^g		X ^h	X ^h	X ^h	

a) If a patient is randomized at Visit 1 and study medication and chemotherapy can be administered at that time, Visit 1 and Visit 2 procedures can be performed on the same day
 b) After start of chemotherapy on Day 1
 c) If holidays or weekend day, the visit or telephone contact will be scheduled the previous/next business day.
 d) If patient is scheduled for a clinic or hospital visit on this day, this information will be obtained at that time.
 e) Visit 2B is to be performed starting from 3 hours (ECG recording) after oral study medication intake
 f) Limited PE only on these days
 g) At screening, ECG will be performed in triplicate
 h) At Visits 2B, 3 and 4, ECGs will be performed as single readings

At the request of the FDA Visit 2B was added 3 hours after administration of study medication and chemotherapy. A 12-lead ECG was obtained at visit 2B.

Randomization

Randomization was stratified by gender and previous chemotherapy history (naïve or non-naïve) to produce 4 strata. Within each group patients received one of four palonosetron doses with or without dexamethasone (two subgroups for each treatment group). A dynamic adaptive stratification type of randomization method was used that was to balance the four treatment arms with or without dexamethasone. The treatments were balanced across the entire study, and not within each individual site or within each individual country component. To check the randomness of the treatment allocation procedure, the permutation test of Fisher was performed.

Medical Officer's Comment:

The validity of the randomization method is currently under review by the FDA statistician. In a prior special protocol review, the statistician noted that "Stratified randomization is acceptable, using the strata specified above. Dynamic adaptive randomization is controversial. We recommend considering a random treatment assignment with no reweighting as an alternative. If

dynamic adaptive randomization is used, permutation tests based on the allocation scheme as realized in the trial will be required.” .

Patients were enrolled from sites in the United States, Czech Republic, Poland, Romania, and Mexico, although the original protocol did not include Romania. Six sites in Romania were added during the last two months of the study because, according to the sponsor, toward the end of the scheduled PALO-03-13 enrollment period, overall enrollment was behind schedule and some sites were administratively closed. The (b) (4) managing the study advised the sponsor that some sites in Romania were capable of promptly enrolling patients who met the study inclusion/exclusion criteria. Consequently, after site qualification and initiation visits, 6 sites in Romania were added.

The sponsor did not submit an amendment for a change in the protocol to add the Romanian sites based on their interpretation of the regulations, set forth in 21 CFR 312.30(b). (adding Romanian sites in the study did not constitute changing the scope of the study since the addition was not an increase in dose, significant change in study design, increase in number of subjects under study, or addition of a test or procedure). Shortly after initiating the Romanian sites, study-wide enrollment across all active sites, including Romania, reached the planned number of patients for the study and was stopped.

The sponsor notes that “the mean number of patients enrolled per site in Romania is not dissimilar to the range or means for sites in other participating countries”. The following sponsor Table 1, which provides information on enrollment at study sites, shows that the total number of patients and the mean number of patients per site from Romania is consistent with other countries.

Table 1. Mean Number of Patients per Site by Treatment by Country in PALO-03-13 (FAS - Full Analysis Set)

Country	No. of Patients	No. of Sites	Mean No. Pts per Site
US	125	15	8.3
Czech Republic	107	11	9.7
Poland	119	7	17.0
Romania	115	6	19.2
Mexico	169	7	24.1

As per section 5.4.4 of the Clinical Study Report for PALO-03-13, two independent randomization lists were prepared by a statistician not involved in the Helsinn projects, using a validated SAS program prior to the start of the study, to allow for blinding of the four treatment groups and dexamethasone (or its placebo). An additional randomization list for dexamethasone was prepared after the decision to extend the study to Romania, while no additional randomization list for palonosetron was needed.

Medical Officer's Comment:

In this reviewer's opinion, the sponsor has provided adequate justification for adding Romanian sites without submitting a protocol amendment.

Demographics

Sponsor's Table 2.7.3:5 provides an overview of patients in PALO-03-13, as well as in PALO-99-03 and PALO-99-04, pivotal studies in the original CINV submission. The majority of patients were female, white, and chemotherapy naïve. The use of corticosteroids was not similar between current and earlier studies since steroids were not the standard of care in moderately emetogenic chemotherapy at the time the earlier studies were done. The sponsor notes that the use and non-use of steroids was an important consideration in the logistical regression historical pooled analysis and the analysis and model was adjusted accordingly. A further discussion of the historical pooled analysis appears elsewhere in this review.

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Table 2.7.3:5 Demographics and Baseline Characteristics for Phase 3 Oral Study PALO-03-13 (FAS), PALO-99-03 and PALO-99-04 Intravenous Palonosetron 0.25 mg Treatment Arms and for Pooled Analysis PALO-07-36							
	PALO-03-13				PALO-99-03	PALO-99-04	Pooled
	Palo PO 0.25 mg (N = 155)	Palo PO 0.50 mg (N = 160)	Palo PO 0.75 mg (N = 158)	Palo IV 0.25 mg (N = 162)	IV 0.25 mg (n=187)	IV 0.25 mg (n=189)	IV 0.25 mg (n=538)
Age							
Mean ± SD	57.1 ± 11.9	56.1 ± 12.3	55.8 ± 12.7	57.7 ± 12.7	56.1 ± 11.7	53.3 ± 13.1	55.6 ± 12.6
Gender, n (%)							
Male	40 (26)	42 (26)	44 (28)	45 (28)	54 (29)	34 (18)	133 (25)
Female	115 (74)	118 (74)	114 (72)	117 (72)	133 (71)	155 (82)	405 (75)
Height (cm)							
Mean ± SD	161.7 ± 11.3	162.2 ± 8.8	161.9 ± 9.4	163.2 ± 10.7	165.0 ± 7.2	159.7 ± 9.6	162.6 ± 9.5
Weight (kg)							
Mean ± SD	71.4 ± 15.6	69.6 ± 15.0	70.8 ± 14.8	72.3 ± 15.7	71.6 ± 13.3	71.3 ± 17.2	71.7 ± 15.5
Race, n (%)							
White	109 (70)	112 (70)	106 (67)	114 (70)	184 (98)	57 (30)	355 (66)
Black	2 (1)	1 (1)	2 (1)	0 (0)	0 (0)	12 (6)	12 (2)
Hispanic	43 (28)	44 (28)	49 (31)	45 (28)	1 (1)	115 (61)	161 (30)
Asian	1 (1)	1 (1)	0 (0)	2 (1)	2 (1)	3 (2)	7 (1)
Other	0 (0)	2 (1)	1 (1)	1 (1)	0 (0)	2 (1)	3 (1)
Chemotherapy history n (%)							
Naïve	95 (61)	91 (57)	93 (59)	96 (59)	75 (40)	124 (66)	295 (55)
Non-naïve	60 (39)	69 (43)	65 (41)	66 (41)	112 (60)	65 (34)	243 (45)
Use of dexamethasone n (%)							
Yes	78 (50)	79 (49)	80 (51)	82 (51)	0 (0)	11 (6)	93 (17)
No	77 (50)	81 (51)	78 (49)	80 (49)	187 (100)	178 (94)	445 (83)

SD = Standard deviation.

N = Number of subjects per treatment group

n (%) = Number and percentage of subjects.

N/A = Not applicable.

Source: Final Study Reports PALO-03-13, Table 6.4-b; PALO-07-36, Table 1

Patients eligible for the study were randomly assigned to one of the four treatment groups.

- Group 1: oral palonosetron 0.25 mg _ 157 enrolled
- Group 2: oral palonosetron 0.50 mg – 161 enrolled
- Group 3: oral palonosetron 0.75 mg – 158 enrolled
- Group 4: I.V. palonosetron 0.25 mg – 163 enrolled

The most emetogenic chemotherapeutic agent was administered first on study Day 1. In each group half of the patients were randomized to receive 8 mg I.V. dexamethasone, and the other half to receive a matching I.V. placebo (saline solution) in a double-dummy fashion 30 minutes before the start of chemotherapy. Sponsor's Table 2.7.3:6 shows that cyclophosphamide (moderate emetic risk, 31-90%) was administered on study Day 1 in over 50% of patients in all treatment arms.

Table 2.7.3:6 Chemotherapy Treatment Administered on Study Day 1 (According to the Protocols) for Moderately Emetogenic CINV Study PALO-03-13 (FAS) and Historical Studies PALO-99-03 and PALO-99-04 IV Palonosetron 0.25 mg Treatment Arms (ITT)

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Substance ^a (WHO-DRL)	PALO-03-13								PALO-99-03		PALO-99-04	
	Palo PO 0.25 mg (N = 157)		Palo PO 0.50 mg (N = 161)		Palo PO 0.75 mg (N = 158)		Palo IV 0.25 mg (N = 163)		Palo IV 0.25 mg (N = 189) ^d		Palo IV 0.25 mg (N=189)	
	n	%	n	%	n	%	n	%	n	%	n	%
Cyclophosphamide	92	(58.6)	94	(58.4)	94	(59.5)	98	(60.1)	119	(63.0)	138	(73.0)
Doxorubicin	71	(45.2)	80	(49.7)	79	(50.0)	76	(46.6)	97	(51.3)	91	(48.1)
Epirubicin	17	(10.8)	11	(6.8)	17	(10.8)	15	(9.2)	13	(6.9)	39	(20.6)
Fluorouracil	62	(39.5)	69	(42.9)	68	(43.0)	60	(36.8)	0	(0)	0	(0)
Carboplatin	39	(24.8)	40	(24.8)	34	(21.5)	45	(27.6)	15	(7.9)	30	(15.9)
Oxaliplatin	16	(10.2)	9	(5.6)	13	(8.2)	14	(8.6)	0	(0)	0	(0)
Methotrexate	0	(0)	0	(0)	0	(0)	0	(0)	23	(12.2)	7	(3.7)
Cisplatin	0	(0)	0	(0)	0	(0)	0	(0)	36 ^h	(19.0) ^b	14 ^c	(7.4) ^c

Palo = Palonosetron.

WHO-DRL = World Health Organization-Drug Reference List.

n (%) = Number and percentage of subjects.

a Subject may have received more than one substance.

b The median cisplatin dose was 37 mg/m²; source: PALO-99-03, Table 6.4.3-b.

c The median cisplatin dose was 40 mg/m²; source: PALO-99-04, Table 6.4.3-b.

d The N includes 2 patients who did not receive 0.25 mg IV and were not part of the pooled analysis. Data in this column are taken from the study report, not the pooled analysis dataset which consisted of 2 subjects less.

Source: Final Study Reports PALO-03-13, table 6.4-e; PALO-99-03, Table 6.4.3-a; and PALO-99-04, Table 6.4.3-a.

Chemotherapy was administered 60 minutes after oral study medication, and 30 minutes after administration of the I.V. formulation. The duration of treatment with the most emetogenic agent was not to extend four hours.

Nitrogen mustard analogues (cyclophosphamide) and anthracyclines and related substances (doxorubicin or epirubicin) were the two most frequent chemotherapeutic agents administered in the pivotal phase 3 study, and also in studies PALO-99-03 and PALO-99-04

Patients remained in the hospital for a minimum of three hours after administration of the oral study medication. Visit 2B was begun at 3 hours, and included ECG recording, adverse event recording, and administration of concomitant medication.

Patients returned to the study site approximately 24 hours after the start of chemotherapy, which was defined as Visit 3. At this visit physical examination, completion of 24 hour efficacy evaluation, and adverse event monitoring was done. Visit 4 (Day 6-8) was similar to visit 3 and included physical exam, concomitant medication, adverse events, 12 lead ECG, labs, and

retrieval of diary. At the final Visit 5 (or via telephone contact) the patient was queried about adverse events and concomitant medications.

PALO-03-14

PALO-03-14 was a multicenter, open-label, repeated cycle, uncontrolled trial to assess safety and efficacy of single oral capsules of palonosetron 0.75 mg in the prevention of MEC in repeated and consecutive moderately emetogenic chemotherapy cycles. Patients enrolled were allowed to continue in the study until a maximum of four consecutive chemotherapy cycles per patient had been evaluated, and until at least 600 cycles were available as a total.

Oral palonosetron 0.75 mg was administered on Study Day 1 in an open-label fashion in the form of a soft gelatin capsule 60 minutes before the start of the first emetogenic chemotherapeutic agent. A single I.V. or oral 8 mg dose of dexamethasone could be given at the discretion of the investigator 30 minutes before the start of chemotherapy. If a patient received dexamethasone during the first study cycle, he/she was to continue to receive dexamethasone with subsequent cycles. The interval between 2 consecutive study drug administrations was at least 7 days.

The following flow-chart shows patients enrolled in each cycle of the study. As indicated, patients enrolled were allowed to continue in the study protocol until a maximum of four consecutive cycles per patient had been evaluated.

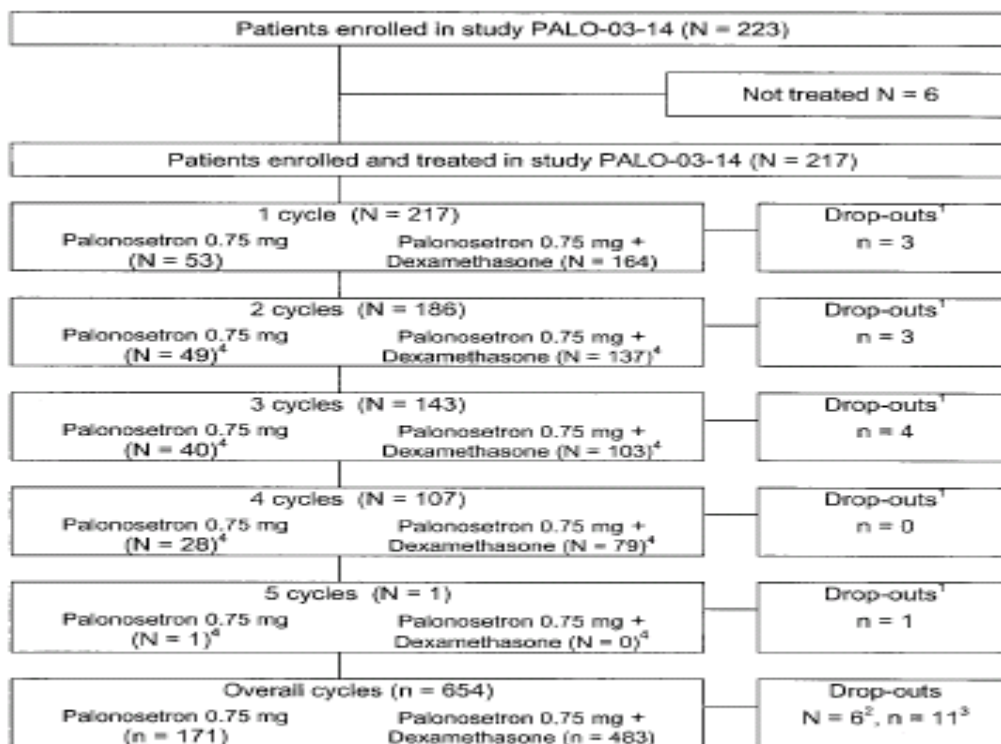


Figure 6.1-a: Description of patients during the course of the study

N = number of patients, n = number of cycles, ¹ cycle prematurely terminated, ² number of patients treated in at least 1 cycle with last cycle prematurely terminated, ³ number of cycles with study drug administration and at least one cycle prematurely terminated, ⁴ as treated in the respective n-th cycle.

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The most frequently administered chemotherapeutic agents were anthracyclines and related substances and nitrogen mustard analogues, but differences were seen by country/region. The following sponsor table 6.4-d shows chemotherapeutic treatment administered on Day 1.

Table 6.4-d: Chemotherapeutic treatment¹ administered on Day 1 (based on cycles) (Full analysis set, N = 654)

ATC level 4 Ingredient (WHO-DRL 04/2004)	Palonosetron 0.75 mg (N = 171)		Palonosetron 0.75 mg + Dexamethasone (N = 483)		Total (N = 654)	
	n	%	n	%	n	%
Any Chemotherapeutic treatment administered on Day 1	171	100.0	483	100.0	654	100.0
Anthracyclines and related substances	118	69.0	301	62.3	419	64.1
Doxorubicin	97	56.7	150	31.1	247	37.8
Epirubicin	21	12.3	151	31.3	172	26.3
Nitrogen mustard analogues	118	69.0	297	61.5	415	63.5
Cyclophosphamide	118	69.0	297	61.5	415	63.5
Pyrimidine analogues	42	24.6	246	50.9	288	44.0
Fluorouracil	38	22.2	237	49.1	275	42.0
Gemcitabine	4	2.3	7	1.4	11	1.7
Capecitabine	0	0.0	2	0.4	2	0.3
Platinum compounds	52	30.4	155	32.1	207	31.7
Carboplatin	37	21.6	99	20.5	136	20.8
Oxaliplatin	15	8.8	56	11.6	71	10.9
Taxanes	0	0.0	65	13.5	65	9.9
Paclitaxel	0	0.0	42	8.7	42	6.4
Docetaxel	0	0.0	23	4.8	23	3.5
Vinca alkaloids and analogues	17	9.9	20	4.1	37	5.7
Vinorelbine	17	9.9	9	1.9	26	4.0
Vinblastine	0	0.0	11	2.3	11	1.7
Other antineoplastic agents	12	7.0	21	4.3	33	5.0
Irinotecan	12	7.0	18	3.7	30	4.6
Bevacizumab	2	1.2	3	0.6	5	0.8
Podophyllotoxin derivatives	2	1.2	13	2.7	15	2.3
Etoposide	2	1.2	13	2.7	15	2.3
Folic acid analogues	1	0.6	8	1.7	9	1.4
Methotrexate	1	0.6	8	1.7	9	1.4
Purine analogues	0	0.0	5	1.0	5	0.8
Fludarabine	0	0.0	5	1.0	5	0.8

Source: Appendix B-1.1, Table 16.2

¹ multiple answers were possible

N = Number of cycles in specific group

n = Number of cycles in the relevant category

% = Percentage based on N

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At each cycle efficacy was assessed daily by the patient during the 0 to 120 hour time period from the administration of chemotherapy. Patient diaries were used to record emetic episodes, use of rescue medication, severity of nausea, and patients' global satisfaction with anti-emetic therapy.

Phase 2 Trial (Syntex 2332)

This was a randomized, double-blind, parallel-group, phase 2, dose-ranging, multicenter study to assess the efficacy, safety, and pharmacokinetics of five dose levels of oral palonosetron administered to cancer patients for the prevention of nausea and vomiting associated with highly

emetogenic chemotherapy. One hundred sixty-nine patients (107 males, 62 females) 27-83 years of age were enrolled. All patients were included in safety evaluation, but 13 patients were excluded from efficacy analysis.

PALO-07-36 Historical Pooled Analysis

PALO-07-36 pooled efficacy data on palonosetron 0.25 mg I.V. from PALO-03-13 (current submission pivotal efficacy trial) and phase 3 studies PALO-99-03 and PALO-99-04, pivotal studies for the original CINV approval. The aim of this analysis was to compare the effect of single oral doses of palonosetron 0.25 mg, 0.50 mg and 0.75 mg against 0.25 mg I.V. on complete response during the 0-24, 24-120 and 0-120 hour time periods. Both the current phase 3 pivotal trial and phase 3 trials from the earlier submission used a non-inferiority design, and the same primary endpoints.

Pooling of the historical data was modeled using a logistic regression equation, which allowed for the assessment and adjustment of differences in major potential influential factors seen between the historical and the PALO-03-13 study data.

The datasets used for this analysis were the original PALO-03-13 efficacy datasets, (i.e., the same unchanged datasets used for the original P ALO-03-13 analysis and study report), pooled with data from the 0.25 mg I.V. palonosetron dose arms from historical studies PALO-99-03 and PALO-99-04. The ITT / FAS population from each study was pooled and evaluated. Only the 0.25 mg I.V. dose was added since it was the only arm which used the same dose and route of administration as PALO-03-13.

PALO-07-35 Exploratory Analysis

The objective of the exploratory analysis was to compare the effect of single oral doses of palonosetron 0.25 mg, 0.50 mg and 0.75 mg versus a single I.V. dose of palonosetron 0.25 mg on CR during 0-24, 24-120, and 0-120 hours after the start of moderately emetogenic chemotherapy administration, and on other secondary efficacy variables using CIs and an equivalence test of proportions (EquivTest/PK statistical software). This study was not included in the statistical analysis plan (SAP), but was done, according to the sponsor, because pivotal study 03-13 was underpowered for secondary efficacy endpoint evaluation.

Medical Officer's Comments:

- *PALO-03-13 protocol was submitted and agreed to by DGP pursuant to a Special Protocol Assessment*
- *PALO-3-14 did not evaluate the proposed to-be-marketed dose of 0.50 mg, had no comparator, and evaluated repeated and consecutive moderately emetogenic chemotherapy cycles*
- *Trial 2332 evaluated acute CINV with highly emetogenic chemotherapeutic agents from 0 to 24 hours*
- *The historical pooled analysis and exploratory analysis were post hoc*

6.1.4 Efficacy Findings

As noted, the primary and key secondary efficacy endpoints were complete response in the acute (0 to 24 hour) time period, and delayed (24 to 120 hour) time period. Efficacy analysis of PALO-03-13 was based on the hypothesis that for at least 1 dose of oral palonosetron the proportion of complete responders was no more than 15% less than the proportion of complete responders seen with the I.V. comparator.

The calculation of the CI for the differences between proportions and the CI for the proportions were provided as stated in the Statistical Analysis Plan.

The key secondary efficacy variable (the proportion of patients with CR during the 24 to 120 hour time period), and other secondary efficacy variables, were examined using the same statistical methods as for the primary efficacy variable (two-sided 98.3% confidence intervals).

Medical Officer's Comments:

A margin of -15% was used in the initial submission for I.V. palonosetron. Although the FDA agreed to the -15% margin for the current submission, it is higher than the margin generally used in non-inferiority studies.

Prevention of Acute CINV

The following sponsor's Table 7.1-a shows the results for the primary efficacy analysis of CR 0 to 24 hours.

Table 7.1-a: Patients with complete response during the first 24 hours after start of chemotherapy (Full analysis set, N = 635)

Oral Palonosetron 0.25 mg (N = 155)			Oral Palonosetron 0.50 mg (N = 160)			Oral Palonosetron 0.75 mg (N = 158)			IV Palonosetron 0.25 mg (N = 162)		
n	%	95% CI (%)	n	%	95% CI (%)	n	%	95% CI (%)	n	%	95% CI (%)
114	73.5	[65.8, 80.2]	122	76.3	[68.8, 82.5]	117	74.1	[66.4, 80.5]	114	70.4	[62.6, 77.1]

Source: Appendix B-1.2.1, Table 15.1.1, Table 15.1.2

CI = confidence interval

N = number of patients in specific group

n = number of patients with complete response

% = percentage based on N

These data from PALO-03-13 show that the percentage of patients with complete response in the 0 to 24 hour period was comparable in the three oral palonosetron treatment groups (less than 3% difference between the individual oral treatment groups), and slightly higher than the I.V. formulation. The highest percentage of patients with CR was seen in the 0.50 mg oral palonosetron group, and the lowest in the I.V. palonosetron group. No dose response relationship was observed.

The protocol stipulated that non-inferiority of oral palonosetron compared to the approved I.V. formulation would be demonstrated if the lower bound of the two-sided 98.3% confidence interval of the difference in the percentage of patients with complete response between each of the oral and the I.V. treatment groups was above the pre-set threshold of -15%. Based on these criteria the current study shows that all 3 oral palonosetron doses are non-inferior to 0.25 mg I.V., since the CI for the difference between each oral dose and I.V. exceeds -15%. The following table shows these results.

CR 0-24 HRS: CI FOR DIFFERENCES BETWEEN ORAL AND I.V.
Full analysis set, N=635

Oral Palonosetron 0.25 mg vs. I.V. Palonosetron 0.25 mg	Oral Palonosetron 0.50 mg vs. I.V. Palonosetron 0.25 mg	Oral Palonosetron 0.75 mg vs. I.V. Palonosetron 0.25 mg
98.3% CI(%) [-9.5%,15.8%]	98.3% CI(%) [-6.5%, 18.2%]	98.3% CI(%) [-8.9%,16.2%]

Prevention of Delayed CINV

The proportion of patients with CR in the 24 to 120 hour time period was analyzed as a key secondary efficacy variable. Results of this analysis show that during the 24 to 120 hour period the highest number of patients with CR was seen in the I.V. palonosetron group (65.4%) followed by the 0.50 mg oral palonosetron dose group (62.5%).

Table 7.1-8 shows data from the delayed phase of 24 to 120 hours.

Table 7.1-1: Patients with complete response during the 24-120 hour time period from start of chemotherapy (Full analysis set, N = 635)

Oral Palonosetron 0.25 mg (N = 155)			Oral Palonosetron 0.50 mg (N = 160)			Oral Palonosetron 0.75 mg (N = 158)			IV Palonosetron 0.25 mg (N = 162)		
n	%	95% CI (%)	n	%	95% CI (%)	n	%	95% CI (%)	n	%	95% CI (%)
92	59.4	[51.2, 67.1]	100	62.5	[54.5, 69.9]	95	60.1	[52.0, 67.7]	106	65.4	[57.5, 72.6]

Source: Appendix B-1.2.1, Table 15.1.1, Table 15.1.2

CI = confidence interval

N = number of patients in specific group

n = number of patients with complete response

% = percentage based on N

A further breakdown of the delayed phase into 24 hour intervals (as was done in the I.V. palonosetron review), is shown in sponsor Table 7.1-p.

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 Nancy Snow
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 Aloxi (Palonosetron)

Table 7.1-p: Patients with complete response after start of chemotherapy, per day (Full analysis set, N = 635)

Time period	Oral Palonosetron 0.25 mg (N = 155)			Oral Palonosetron 0.50 mg (N = 160)			Oral Palonosetron 0.75 mg (N = 158)			IV Palonosetron 0.25 mg (N = 162)		
	n	%	95% CI (%)	n	%	95% CI (%)	n	%	95% CI (%)	n	%	95% CI (%)
>24 – 48 h	107	69.0	[61.0, 76.1]	113	70.6	[62.8, 77.4]	117	74.1	[66.4, 80.5]	123	75.9	[68.5, 82.1]
>48 – 72 h	118	76.1	[68.5, 82.4]	118	73.8	[66.1, 80.2]	120	75.9	[68.4, 82.2]	130	80.2	[73.1, 85.9]
>72 – 96 h	126	81.3	[74.1, 86.9]	125	78.1	[70.8, 84.1]	121	76.6	[69.1, 82.8]	133	82.1	[75.1, 87.5]
>96 – 120 h	130	83.9	[76.9, 89.1]	140	87.5	[81.1, 92.0]	138	87.3	[80.9, 91.9]	141	87.0	[80.6, 91.6]

Source: Appendix B-1.2.1, Table 15.1.1, Table 15.1.2

CI = confidence interval

N = number of patients in specific group

n = number of patients with complete response

% = percentage based on N

These data show variability at each of the 24 hour time periods, and no clear cut advantage of one dose level over the other.

As with the acute phase, efficacy of palonosetron capsules in the delayed phase was based on showing that the proportion of complete responders to palonosetron was no more than 15% less than the proportion seen with the I.V. comparator. In other words, non-inferiority in the delayed phase was demonstrated if the lower bound of the two-sided 98.3% confidence interval of the difference in the percentage of patients with complete response between each of the oral treatment groups and the I.V. treatment group was above the pre-set threshold of -15%.

Sponsor's Table 7.1-m. shows that for the 24 to 120 hour time period (delayed phase), the lower limit of the CI for all the oral doses fell below the pre-set threshold of -15%.

Source: Appendix B-1.2.1, Table 15.1.3

(b) (4), the sponsor compiled an Historical Pooled Analysis, PALO-07-36, and Exploratory Analysis, PALO-07-35. As described earlier in this NDA review (under Study Design), the Historical Pooled Analysis combined data on the 0.25 mg I.V. dose from current and earlier CINV studies. When data are pooled from earlier studies the CI for the 0.50 mg dose was -13.3%, which falls within the -15% margin.

Medical Officer's Comment:

The Historical Pooled Analysis or the Exploratory Analysis were post-hoc analyses, not pre-specified in the SAP. A full analyses of these studies can be found in a separate Statistical Review of this NDA submission.

Although not primary or key secondary endpoints, additional analyses, including number of emetic episodes, and use of rescue medication were also done.

Number of Emetic Episodes

Complete response has two components: no emetic episodes, and no rescue medication. Sponsor's Table 7.1-t provides data on emetic episodes for oral palonosetron doses compared to the I.V. active control.

Table 7.1-t: Emetic episodes (patients with / without emesis) (Full analysis set, N = 635)

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Period	Emesis	Oral Palonosetron 0.25 mg (N = 155)		Oral Palonosetron 0.50 mg (N = 160)		Oral Palonosetron 0.75 mg (N = 158)		IV Palonosetron 0.25 mg (N = 162)	
		n	%	N	%	n	%	n	%
0 – 24 h	With	32	20.6	28	17.5	33	20.9	37	22.8
	Without	123	79.4	132	82.5	125	79.1	125	77.2
>24 – 48 h	With	33	21.3	34	21.3	34	21.5	30	18.5
	Without	122	78.7	126	78.8	124	78.5	132	81.5
>48 – 72 h	With	27	17.4	26	16.3	25	15.8	23	14.2
	Without	128	82.6	134	83.8	133	84.2	139	85.8
>72 – 96 h	With	19	12.3	17	10.6	26	16.5	18	11.1
	Without	136	87.7	143	89.4	132	83.5	144	88.9
>96 – 120 h	With	15	9.7	10	6.3	8	5.1	10	6.2
	Without	140	90.3	150	93.8	150	94.9	152	93.8
>24 – 120 h	With	49	31.6	42	26.3	52	32.9	41	25.3
	Without	106	68.4	118	73.8	106	67.1	121	74.7
0 – 120 h	With	60	38.7	47	29.4	61	38.6	53	32.7
	Without	95	61.3	113	70.6	97	61.4	109	67.3

Source: Appendix B-1.2.3, Table 17.2.1

N = number of patients in specific group

n = number of patients in the relevant category in the respective time period

% = percentage based on N

The table shows that in the 0 to 24 hour acute phase, the number of patients with emesis was lowest (or the number of patients without emesis was highest) in the proposed to-be-marketed oral dose of 0.50 mg. The highest number of emetic episodes was seen in the 0.25 mg I.V. dose.

In the 24 to 120 time period, the delayed phase of CINV, the 0.50 mg oral palonosetron group again had the lowest number of patients with emesis (and the highest without) among the three oral doses, and was close to the number seen with I.V. palonosetron (26.3% vs. 25.3%).

Use of Rescue Medication

The second component of CR is use of rescue medication. As sponsor Table 7.1-w shows, use of rescue medication was highest in the I.V. palonosetron group, and comparable in the oral dose groups during hours 0 to 24. In the delayed phase of CINV (24 to 120 hours), differences between PO and I.V. palonosetron were small, although less patients in the I.V. group used rescue medications compared to those receiving oral palonosetron. This was a change from the

acute phase, when more patients in the I.V. group used rescue compared to the oral group. Use of rescue medication in the 24 to 120 time period was similar among all oral doses tested.

Table 7.1-w: Need for rescue medication (patients with/without rescue medication)
(Full analysis set, N = 635)

Period	Rescue medication	Oral Palonosetron 0.25 mg (N = 155)		Oral Palonosetron 0.50 mg (N = 160)		Oral Palonosetron 0.75 mg (N = 158)		IV Palonosetron 0.25 mg (N = 162)	
		n	%	n	%	n	%	n	%
0 – 24 h	With	18	11.6	22	13.8	16	10.1	29	17.9
	Without	137	88.4	138	86.3	142	89.9	133	82.1
>24 – 48 h	With	33	21.3	31	19.4	26	16.5	21	13.0
	Without	122	78.7	129	80.6	132	83.5	141	87.0
>48 – 72 h	With	24	15.5	27	16.9	25	15.8	21	13.0
	Without	131	84.5	133	83.1	133	84.2	141	87.0
>72 – 96 h	With	20	12.9	27	16.9	22	13.9	19	11.7
	Without	135	87.1	133	83.1	136	86.1	143	88.3
>96 – 120 h	With	17	11.0	16	10.0	16	10.1	17	10.5
	Without	138	89.0	144	90.0	142	89.9	145	89.5
>24 – 120 h	With	42	27.1	42	26.3	41	25.9	37	22.8
	Without	113	72.9	118	73.8	117	74.1	125	77.2
0 – 120 h	With	47	30.3	47	29.4	49	31.0	47	29.0
	Without	108	69.7	113	70.6	109	69.0	115	71.0

Source: Appendix B-1.2.5, Table 19.1
N = number of patients in specific group
n = number of patients in the relevant category in the respective time period
% = percentage based on N

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The most commonly used rescue anti-emetic was metoclopramide, which was used more often by chemotherapy patients receiving oral palonosetron than I.V. These differences, which are not clinically meaningful, are shown in the following abbreviated sponsor Table 7.1-y.

Table 7.1-y: Anti-emetic rescue medication[†] (Full analysis set, N = 635)

ATC Level 4 Ingredient(s) (WHO-DRL 04/2004)	Oral Palonosetron 0.25 mg (N = 155)		Oral Palonosetron 0.50 mg (N = 160)		Oral Palonosetron 0.75 mg (N = 158)		IV Palonosetron 0.25 mg (N = 162)	
	n	%	n	%	n	%	n	%
No anti-emetic rescue medication	110	71.0	114	71.3	110	69.6	120	74.1
At least one anti-emetic rescue medication	45	29.0	46	28.8	48	30.4	42	25.9
Propulsives	20	12.9	22	13.8	18	11.4	12	7.4
Metoclopramide	20	12.9	22	13.8	18	11.4	11	6.8
Domperidone	0	0.0	0	0.0	0	0.0	1	0.6

The sponsor explains the slight differences in the two tables as the result of the “worst case principle”. In Table 7.1.-w data were obtained from the CRF and diary, whereas in Table 7.1-y data were obtained from the CRF alone. As such Table 7.1-w (diary and CRF) may be more prone to missing data.

Medical Officer's Comments:

The sponsor has not been able to demonstrate that, for any dose level of oral palonosetron capsules, there is a reasonable certainty that the proportion of complete responders in the 24 to 120 hour time period would be no more than 15% less than the comparator. Other analyses of efficacy, although helpful, do not negate this finding.

Further Efficacy Evaluations

In an April 24, 2008 Information Request to the sponsor (after submission of the current NDA), the FDA requested "additional information to explain clinical implications of the 2.9% worsening from the prespecified 15% margin for the secondary endpoint (delayed nausea and vomiting 24-72 hours)." In response to this information request the sponsor submitted a summary of clinical trials for the prevention of CINV to highlight the difference in CR between studied drug and active comparator. The following Table A1 provides a listing of some of these studies:

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Table A1. Summary of large published clinical trials which compare 5-HT₃ antagonists for the prevention of CINV

Reference, Title [Location]	Study Design (Patient Population)	Treatments (n = sample size)	Efficacy Endpoints	Efficacy Results	Authors Conclusions
Ref #1. Perez EA, Lembersky B, Kaywin P, et al, Cancer J Sci Am, 1998; 4: 52-58, Comparable Safety and Antiemetic Efficacy of a Bried (30-Secon Bolus) Intravenous Granisetron Infusion and a Standard (15-Minute) Intravenous Ondansetron Infusion in Breast Cancer Patients Receiving Moderately Emetogenic Chemotherapy [US – 64 sites]	Multicenter, randomized, double-blind, double-dummy, multicenter crossover study of 623 chemo-therapy-naïve patients (2 male, 621 female) receiving moderately emetogenic chemotherapy (cyclophosphamide plus doxorubicin, with or without 5FU) for breast cancer (Moderately emetogenic CINV patients)	Granisetron (GRAN), 10 µg/kg IV 30-second bolus within 5 minutes before start of chemotherapy (n=573) versus Ondansetron (OND) 32 mg IV 15 minute bolus beginning 30 minutes before start of chemotherapy (n=573)	Primary variables were (1) no emesis for 24 hours, and (2) no nausea for 24 hours Secondary efficacy variables included (1) no emesis for 48 hrs (2) no nausea for 48 hrs	<u>No emesis 0-24h (%pts):</u> GRAN: 58.6% OND: 62.7% Difference: 4.1% <u>No nausea 0-24h (%pts):</u> GRAN: 44.0% OND: 48.5% Difference: 4.5% <u>No emesis 0-48h (%pts):</u> GRAN: 42.2% OND: 45.0% Difference: 2.8% <u>No nausea 0-48h (%pts):</u> GRAN: 26.7% OND: 31.0% Difference: 4.3%	"These two intravenous 5-hydroxytryptamine ₃ -receptor antagonist antiemetics were <u>similarly effective</u> in controlling acute nausea and emesis during two cycles of moderately emetogenic chemotherapy." [underline added]
Ref #2. Gralla RJ, Navari RM, Hesketh PJ et al, J Clin Oncol, 1998; 16: 1568-1573. Single-Dose Oral Granisetron has Equivalent Antiemetic Efficacy to Intravenous Ondansetron for Highly Emetogenic Cisplatin [US – 103 sites]	Multicenter randomized, double-blind, double-dummy, parallel group study involving patients scheduled to receive cisplatin (≥60 mg/m ²) based chemotherapy (Highly emetogenic CINV patients)	Granisetron (GRAN) 2 mg (2, 1 mg tablets) one hour before chemotherapy (n=534) Versus Ondansetron (OND) 32 mg IV 30 minutes before chemotherapy (n=520)	Primary variable: Complete Control for 24 hours (no emesis, no nausea and no rescue med) Secondary efficacy variables included (1) incidence emesis (2) incidence and max severity of nausea (3) incidence of rescue medication	<u>Complete Control 0-24h, %pts:</u> GRAN: 54.7% OND: 58.3% Difference: 3.6% <u>No Nausea, %pts:</u> GRAN: 55.4% OND: 59.0% Difference: 3.6% <u>No Emesis, %pts:</u> GRAN: 61.2% OND: 67.1% Difference: 5.9%	"Oral granisetron, administered as a single 2-mg dose, provided <u>equivalent</u> total antiemetic control when compared with IV ondansetron (32 mg) in patients who received highly emetogenic, cisplatin-based chemotherapy." "This study shows that a single 2-mg oral dose of granisetron has <u>equivalent</u> efficacy to IV ondansetron (32 mg) in providing total antiemetic control." [underline added]

Table A1. Summary of large published clinical trials which compare 5-HT₃ antagonists for the prevention of CIN V
(continued)

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Reference, Title [Location]	Study Design (Patient Population)	Treatments (n = sample size)	Efficacy Endpoints	Efficacy Results	Authors Conclusions
Ref #3. Perez EA, Hesketh P, Sandbach J, et al, J Clin Oncol, 1998; 16: 754-760. Comparison of Single-Dose Oral Granisetron Versus Intravenous Ondansetron in the Prevention of nausea and vomiting induced by moderately emetogenic chemotherapy: a multicenter, double-blind, Randomized Parallel study [US, Canada and Puerto Rico – multiple sites]	Multicenter, randomized, double-blind, double dummy, parallel-group study involving patients scheduled to receive cyclophosphamide (500 to 1200 mg/m ²) or carboplatin (≥300 mg/m ²) based chemotherapy (Moderately emetogenic chemotherapy patients)	Granisetron (GRAN) 2 mg (2, 1 mg tablets) one hour before chemotherapy (n=542) Versus Ondansetron (OND) 32 mg IV infusion over 15 minutes 30 minutes before chemotherapy (n=543)	Primary variable was Total Control (no emesis, no nausea and no rescue meds) over 24h and 48h Secondary efficacy variables over 24h and 48h included (1) incidence emesis (2) incidence of max severity of nausea (3) incidence of rescue medication	<u>Total Control 0-24h, %pts:</u> GRAN: 59.4% OND: 58.0% Difference: 1.4% <u>Total Control 0-48h, %pts:</u> GRAN: 46.7% OND: 43.8% Difference: 2.9% <u>No Nausea 0-24h, %pts:</u> GRAN: 60.0% OND: 58.4% Difference: 1.6% <u>No Nausea 0-48h, %pts:</u> GRAN: 47.4% OND: 44.4% Difference: 3.0% <u>No Emesis 0-24h, %pts:</u> GRAN: 71.0% OND: 72.6% Difference: 1.6% <u>No Emesis 0-48h, %pts:</u> GRAN: 58.7% OND: 59.1% Difference: 0.4%	"A single oral dose of granisetron (2 mg) resulted in <u>equivalent</u> levels of antiemetic protection as IV ondansetron (32mg)" "Because the two anti-emetic regimens exhibited <u>equivalent efficacies</u> , additional factors such as convenience and cost of therapy should be considered." "This study has shown that single-dose oral granisetron (2 mg) is <u>equivalent</u> to IV ondansetron (32 mg) for the prophylaxis of emesis and nausea induced by moderately emetogenic chemotherapy." [underline added]

Differences between study drug and comparator in CR, and other parameters of efficacy, are similar to differences seen in CR in the current study. However the periods measured in these published trials do not distinguish acute from delayed.

PALO-03-14

Sponsor's Table 1 shows CR for the acute, delayed and overall 120 hour time period for cycles 1 through 4 for palonosetron alone, and palonosetron and dexamethasone.

Table 1: Complete response by cycle (Full analysis set, N = 654)

	Palonosetron 0.75 mg (N=171)			Palonosetron 0.75 mg + Dexamethasone (N=483)			Total (N=654)		
	CR _{0-24h}	CR _{24-120h}	CR _{0-120h}	CR _{0-24h}	CR _{24-120h}	CR _{0-120h}	CR _{0-24h}	CR _{24-120h}	CR _{0-120h}
Cycle 1	(N=53)			(N=164)			(N=217)		
	66.0	60.4	54.7	78.0	63.4	57.3	75.1	62.7	56.7
Cycle 2	(N=49)			(N=137)			(N=186)		
	57.1	59.2	46.9	75.2	63.5	62.0	70.4	62.4	58.1
Cycle 3	(N=40)			(N=103)			(N=143)		
	67.5	65.0	57.5	73.8	62.1	61.2	72.0	62.9	60.1
Cycle 4	(N=28)			(N=79)			(N=107)		
	50.0	50.0	46.4	63.3	63.3	58.2	59.8	59.8	55.1
N= Number of cycles in specific group, CR: percentage of cycles with complete response based on N									

In general, more patients receiving palonosetron and dexamethasone combined had CR than those receiving palonosetron alone. This is not a surprising finding since the standard of care calls for at a 5HT-3 receptor antagonist and dexamethasone. Considerably higher complete response rates were observed over the first 24 hours (acute phase) in cycle 1 than cycle 4, but over the 24 to 120 hour time period (delayed phase) there was negligible difference in CR between cycles.

Medical Officer's Comment:

Because patients receive chemotherapy at cycle 1, in subsequent cycles they are no longer naïve to chemotherapy. Any efficacy evaluations comparing efficacy at cycle 1 to later cycles would have to take this into account.

6.1.5 Efficacy Conclusions

Study PALO-03-13 demonstrated that palonosetron 0.25mg , 0.50 mg, and 0.75 mg were non-inferior to the active comparator, I.V. palonosetron 0.25 mg, for CR during the 0 to 24 hour time interval. For the 24 to 120 hour time interval the sponsor has not been able to demonstrate that, at any dose level of oral palonosetron capsules, there is a reasonable certainty that the proportion of complete responders would be no more than 15% less than the comparator. From a clinical perspective one may conclude that from 0 to 24 hours patients can be expected to receive the same protection from CINV with oral palonosetron as they currently derive from the marketed I.V. formulation. For later time periods oral palonosetron may be effective in preventing nausea or emesis in a percentage of patients, but may not perform at the same level as I.V. palonosetron.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety assessment of palonosetron is based primarily on 1061 patients enrolled in Phase 2 (Study 2332, PALO-04-03) and Phase 3 (PALO-03-13, and the first cycle of chemotherapy in PALO-03-14) studies. Eight-hundred ninety eight (84.%) patients were exposed to oral palonosetron and 163 (15.4%) received I.V. palonosetron.

A higher number of patients received the 0.75 mg dose because 0.75 mg was studied in both Phase 3 trials. The to-be-marketed dose of 0.50 mg was studied in only Phase 3 trial (PALO-03-13), and had the lowest exposure (182 patients/17.2%). Information on exposure is contained in Sponsor's Table 2.7.4:5.

Table 2.7.4:5 Exposure in the Integrated Oral Safety Database for Palonosetron by Dose

	Oral Palonosetron (mg)						IV Palo	Total
	< 0.25	0.25	0.50	0.75	> 0.75	Total		
Phase 2	31	46	21	39	68	205	-	205
Phase 3	-	157	161	375	-	693	163	856
Total All Phase 2/3	31	203	182	414	68	898	163	1061

Source: ISS End-of-Text Table A.1.

The four-month safety update for oral palonosetron NDA22-233 updates the NDA through July 29, 2008. The sponsor states that “there are no additional safety concerns and the safety profile of the drug has not changed.” The sponsor conducted a literature search and concluded that “the publications do not appear to identify any new safety data or safety concerns for palonosetron.”

7.1.1 Deaths

A total of 11 patients enrolled in Phase 2 and 3 oral palonosetron studies died. Three patients died in pivotal study PALO-03-13, one in supportive study PALO-03-14, and seven from Phase 2 study 2332, conducted by Syntex before the current sponsor acquired the drug. No deaths were judged related to the study drug, although data is missing on 5 subjects from the Syntex Phase 2 trial. It is important to note that Study 2332 enrolled patients set to receive highly emetogenic cancer chemotherapy.

Causes of death of the 11 patients are:

- 5 due to the cancer under treatment, 12 to 49 days post-treatment
- 2 from renal failure, 6 to 21 days post-treatment
- 2 from complications of disease/cancer chemotherapy, 11 to 28 days post-treatment
- 2 due to cardiac arrest, 15 to 25 days post-treatment

Sponsor Table 5:2 provides a listing of deaths in these trials.

Table 5:2 Listing of All Events with Outcome of Death in Subjects from All Oral Palonosetron Clinical Trials by Study Number

Subject ID	Gender Age (yrs)	Country	Cycle No.	Treatment [^]	Body System	Reported Term	Preferred Term	Relationship	Days Post Dose to Death
Palo-03-13 Study									
1147	Female (56)	United States	1	Oral Palo 0.75 mg	Cardiac Disorders	Cardiorespiratory Arrest	Cardio-Respiratory Arrest	Not related	(b) (6)
2146	Male (72)	Mexico	1	Oral Palo 0.75 mg	Blood and Lymphatic System Disorders	Febrile Neutropenia	Febrile Neutropenia	Not related	(b) (6)
2146	Male (72)	Mexico	1	Oral Palo 0.75 mg	Infections and Infestations	Septic Shock	Septic Shock	Not related	(b) (6)
3100	Male (53)	Romania	1	Oral Palo 0.50 mg	Gastrointestinal Disorders	Subocclusive Syndrome (Peritoneal Carcinomatosis)	Subileus	Not related	(b) (6)
Palo-03-14 Study									
4256	Male (50)	United States	2	Oral Palo 0.75 mg	Cardiac Disorders	Cardiac Arrest	Cardiac Arrest	Not related	(b) (6)
Study 2332									
1502	Male (71)	United States	1	Oral Palo 30 mcg/kg	Renal and Urinary Disorders	Renal Failure	Renal Failure	Unlikely	(b) (6)
2003	Male (43)	United States	1	Oral Palo 30 mcg/kg	Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	Neoplasm Malignant	Neoplasm Malignant	Missing/Unknown	(b) (6)

[^] 1 µg/kg is approximately equivalent to < 0.25 mg fixed dose, 10 µg/kg is approximately equivalent to 0.75 mg and 30-90 µg/kg is >0.75 mg
Source: ISS End-of-Text Table E.1

Table 5:2 Listing of All Events with Outcome of Death in Subjects from All Oral Palonosetron Clinical Trials by Study Number (continued)

Subject ID	Gender Age (yrs)	Country	Cycle No.	Treatment [^]	Body System	Reported Term	Preferred Term	Relationship	Days Post Dose to Death
Study 2332 (cont.)									
2104	Male (51)	United States	1	Oral Palo 90 mcg/kg	Metabolism and Nutrition Disorders	Metabolic Acidosis	Metabolic Acidosis	Missing/Unknown	(b) (6)
2604	Female (66)	United States	1	Oral Palo 10 mcg/kg	Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	Pulmonary Carcinoma	Lung Neoplasm Malignant	Missing/Unknown	(b) (6)
2710	Male (78)	United States	1	Oral Palo 30 mcg/kg	Renal and Urinary Disorders	Renal Failure	Renal Failure	Unlikely	(b) (6)
601	Male (54)	United States	1	Oral Palo 1 mcg/kg	Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	Pulmonary Carcinoma	Lung Neoplasm Malignant	Missing/Unknown	(b) (6)
706	Female (62)	United States	1	Oral Palo 30 mcg/kg	Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	Pulmonary Carcinoma	Lung Neoplasm Malignant	Missing/Unknown	(b) (6)

[^] 1 µg/kg is approximately equivalent to < 0.25 mg fixed dose, 10 µg/kg is approximately equivalent to 0.75 mg and 30-90 µg/kg is >0.75 mg
Source: ISS End-of-Text Table E.1

The following are narratives from the 3 deaths in PALO-03-13.

Patient 3100: A 53 year old male, chemotherapy non-naïve (oral palonosetron 0.50 mg treatment group; dexamethasone placebo group) diagnosed with adenocarcinoma of the colon with metastases to the liver. The patient received chemotherapy and palonosetron on July 13, 2006. The CRF indicates the patient required multiple doses of ondansetron and metoclopramide for vomiting, beginning on July 15, 2006, two days after chemotherapy. The patient continued to receive metoclopramide through July 27, 2006.

On (b) (6) the patient was diagnosed with peritoneal carcinomatosis, but the immediate cause of death (as per death certificate) was cardio-respiratory arrest due to multi-organ

insufficiency. The patient expired on (b) (6) days after chemotherapy and palonosetron. The investigator and the sponsor assessed the events of subocclusive syndrome (peritoneal carcinomatosis) and vomiting as unrelated to the study medication and likely related to the cancer disease.

Medical Officer's Comments:

The patient had multiple medical problems associated with his death. The continued need for ondansetron, and later metoclopramide, suggest a lack of therapeutic effect of palonosetron (and ondansetron) after 48 hours.

Patient no. 1147: A 56 year-old female, chemotherapy non-naïve, (oral palonosetron 0.75 mg treatment group; dexamethasone group), died of cardio-respiratory arrest (b) (6) days post study drug. The patient had a diagnosis of malignant melanoma, metastatic small cell lung cancer, with metastases to the brain and liver.

The patient had chemotherapy and palonosetron on Sept. 1, 2005. Starting on Sept. 4, 2005 the CRF reports nausea, and later vomiting, which resulted in multiple doses of ondansetron, and later dolasetron. The patient also reported intermittent abdominal pain around the time ondansetron and dolasetron were administered. The patient had a cardio-respiratory arrest (b) (6), but no autopsy was performed. The event of cardio-respiratory arrest was assessed by the Investigator as not related to study medication, but related to progression of the cancer. The sponsor agreed with the Investigator.

Medical Officer's Comment:

As with patient #3100, there may have an insufficient therapeutic effect of palonosetron 4 days after chemotherapy (delayed phase). However the cause of death was likely related to multiple medical problems and the patient's underlying malignancy.

Patient no. 2146: A 72 year-old male, chemotherapy naïve (oral palonosetron 0.75 mg treatment group; dexamethasone placebo group) was diagnosed with bronchial carcinoma November 2005 and enrolled in the study December 2005. On study Day 9, febrile neutropenia was documented, and septic shock reported on study Day 10. On study Day 11 the patient experienced irreversible cardiac arrest and died. The Investigator stated that the cause of death was the presence of secondary septic shock and post-chemotherapy febrile neutropenia. The Investigator assessed the events as having a relationship to the cancer chemotherapy and advanced status of the patient's tumor disease, but not the study medication. The sponsor agreed with the Investigator.

In supportive study **PALO-03-14** the following death occurred:

Patient 4256 –The patient was a 50 year old male diagnosed with stage IV colon cancer. He had multiple medical problems, and his baseline medical history included hypertension, coronary artery disease, and asthma. The patient underwent two cycles of chemotherapy, and received 0.75 mg palonosetron and dexamethasone in each. The first cycle was Sept. 7, 2005, and the second Sept. 21, 2005. The patient died on (b) (6) (b) (6) (b) (6)

Multiple ECGs were obtained throughout the study with variable interpretations. At baseline in cycle 2 the CRF notes the patient had a prolonged QT; 3 hours later in a repeat ECG the QT was not mentioned. The CSR indicates the QT interval was less than 500 msec, and read as normal by the Cardiologist. The patient had nausea, vomiting, diaphoresis and pallor during and after chemotherapy, but completed cycle 2. The patient had a cardiac arrest on (b) (6) (b) (6)

An autopsy performed on the day of death showed biventricular hypertrophy, cardiomegaly, and severe coronary atherosclerosis in the left anterior descending artery. The probable cause of death was determined to be coronary artery disease; the severe biventricular hypertrophy felt to have caused an associated dysrhythmia.

In Phase 2 **Study 2332** the following deaths occurred:

Patient 1502 – The patient was diagnosed with small cell lung cancer. The medical history includes asthma, black lung and COPD. Screening physical examination and ECG were abnormal, with the following noted: wheezing and decreased breath sounds, 2nd heart sound, ECG showing wandering pacemaker. Patient received high dose cisplatin and 30 µg/kg of palonosetron (≈0.75 mg). Twenty-four hours post-dose the patient had elevated blood pressure (154/79) and tachycardia (HR 111). On day 5, the patient was withdrawn from the study. ECG at the time of withdrawal showed sinus tachycardia and non-specific ST-T wave abnormalities. On physical exam the patient was comatose, not following commands, and diffusely tender on abdominal exam. No blood pressure readings are available beyond 24 hours, but laboratory values (presented below) show elevations in renal and liver tests. The patient expired 7 days post-dose. Cause of death was reported as renal failure.

Laboratory Values S2332/#1052		
	Baseline	24 hours post-dose
Total Bilirubin		(b) (4)
Alk Phos		
ALT		
AST		
LDH		
BUN		
Creatinine		
Neutrophil		
Urine Protein		

Medical Officer Comments:

Based on information from the CRF it is difficult to know if the cause of death was multi-organ failure due to ischemia (perhaps from decreased perfusion), or another cause. Certainly with the limited amount of information available, a relationship between the SAE leading to death and palonosetron cannot be ascertained.

Patient 2710 – The patient was enrolled in the study for treatment of bladder cancer. Co-existing conditions included urinary tract infection (UTI), and coronary artery disease (CAD). Screening ECG showed atrial fibrillation with rapid ventricular response. Patient received high dose

cisplatin and 30 µg/kg palonosetron. Patient developed multiple adverse events, including DVT, renal failure, stomatitis, tachycardia. The patient died approximately 20 days after receiving chemotherapy and palonosetron. Cause of death was listed as “symptoms of primary disease”.

Medical Officer’s Comments:

None of the deaths cast doubt on the safety of palonosetron. The cancer population for which this drug is intended has multiple co-morbidities and a high mortality. The two cases of cardiac arrest were related to sepsis, or underlying cardiac structural disease. One death in pivotal study PALO-03-13 occurred in the to-be-marketed 0.50 mg dose. This death, due to peritoneal carcinomatosis, does not raise a new safety concern about the 0.50 mg dose.

7.1.2 Other Serious Adverse Events

The following table shows serious adverse events (SAEs) whether or not related to study medication. There is a higher incidence of SAEs in the <0.25mg and >0.75 mg groups, possibly due to the small sample size at these dose levels. Across all doses evaluated in Phase 3 trials, the incidence of SAEs is similar.

Table 5:3 Number (Percentage) of Subjects Reporting Serious Adverse Events by SOC in All Integrated Phase 2 and 3 Oral Palonosetron Trials

SOC	Oral Palonosetron												IV Palonosetron	
	< 0.25 mg (N = 31)		0.25 mg (N= 203)		0.50 mg (N = 182)		0.75 mg (N = 414)		>0.75 mg (N = 68)		Total Oral (N = 898)		(N = 163)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
No SAE	23	74.2	192	94.6	172	94.5	399	96.4	57	83.8	843	93.9	162	99.4
Any SAE	8	25.8	11	5.4	10	5.5	15	3.6	11	16.2	55	6.1	1	0.6
General	2	6.5	3	1.5	3	1.6	4	1.0	3	4.4	15	1.6	1	0.6
Blood	1	3.2	2	1.0	3	1.6	8	1.9	0	0	14	1.6	1	0.6
Gastrointestinal	1	3.2	1	0.5	3	1.6	5	1.2	3	4.4	13	1.4	0	0
Metabolic	3	9.7	2	1.0	1	0.5	1	0.2	4	5.9	11	1.2	0	0
Respiratory	2	6.5	0	0	3	1.6	2	0.5	1	1.5	8	0.9	0	0
Infection	0	0	1	0.5	0	0	4	1.0	1	1.5	6	0.7	0	0
Neoplasm	1	3.2	0	0	2	1.1	1	0.2	2	2.9	6	0.7	0	0
Nervous	0	0	4	2.0	2	1.1	0	0	0	0	6	0.7	0	0
Investigational	1	3.2	0	0	1	0.5	0	0	2	2.9	4	0.4	0	0
Vascular	0	0	2	1.0	2	1.1	0	0	0	0	4	0.4	0	0
Cardiac	0	0	0	0	1	0.5	2	0.5	0	0	3	0.3	0	0
Renal	0	0	0	0	0	0	1	0.2	2	2.9	3	0.3	0	0
Skin	1	3.2	1	0.5	0	0	0	0	0	0	2	0.2	0	0
Musculoskeletal	0	0	1	0.5	1	0.5	0	0	0	0	2	0.2	0	0
Endocrine	0	0	0	0	1	0.5	0	0	0	0	1	0.1	0	0
Psychiatric	0	0	0	0	0	0	0	0	1	1.5	1	0.1	0	0

Source: ISS End-of-Text Table F.1

Of the 1061 patients receiving palonosetron (I.V. or oral) in Phase 2/ 3 trials, 56 patients experienced a total of 120 serious adverse events. For the most part SAEs were spread evenly across all oral palonosetron dosages. There were more SAEs seen with oral than I.V. palonosetron.

The following table shows patients with SAEs, by dose, from pivotal study PALO-03-13.

SAEs PALO-03-13					
Patient	Dose	SAE	Related	Study Day Onset	Outcome
1147	0.75 mg	cardio-respiratory arrest	No	(b) (6)	Death
2146	0.75 mg	febrile neutropenia, septic shock	No		Death
2426	0.75 mg	thrombocytopenia with hemorrhage	No	26	Recovered
3012	0.75 mg	right posterior thoracic pain	No	21	Recovered
1005	0. 50 mg	fever	No	21	Recovered
1007	0. 50 mg	anemia, CP, dyspnea	No	29	Recovered
1478	0. 50 mg	dyspnea	Unlikely	1	Recovered
1051	0. 50 mg	syncope, pancytopenia	No/Unlikely	11	Recovered
1294	0. 50 mg	chest pain	Possible*	1	Recovered
1765	0. 50 mg	anemia	Unlikely	16	Recovered
1578	0. 50 mg	Mobitz 2 heart block	Possible	2	Recovered
1959	0. 50 mg	Hyperventilation, circulatory collapse	No	6	Recovered
3100	0. 50 mg	vomiting, peritoneal carcinomatosis	No	(b) (6)	Death
1479	0.25 mg	hypotension, mental status change	Unlikely	7	Recovered
1778	0.25 mg	fever, headache	No	16	Recovered
1185	0.25 mg	angioedema	No	15	Recovered
2129	0.25 mg IV	anemia, mucositis	No	22	Recovered

More SAEs were seen in the 0.50 mg, to-be-marketed dose, than in the other dose levels. Half of the SAEs in the 0.50 mg group occurred beyond 2 weeks after receiving chemotherapy and study medication. Those that occurred < 2 week after treatment are discussed further.

- #1478 (0.5 mg PO) –The patient, with a baseline medical history of hypertension, colon cancer, and seasonal allergies, experienced shortness of breath (SOB), choking sensation and weakness on study day 1. The SOB and choking sensation were classified as unrelated to study medication. The CRF shows that the patient was given single doses of benadryl, solumedrol, and advil. The patient recovered from all but the weakness.

Information from the CRF is limited. It is possible the patient had an allergic reaction to the medication. This event does not represent a significant safety concern.

- #1294 (0.5 mg PO)-The patient, with multiple co-morbid conditions including chronic atrial fibrillation and diabetes mellitus, developed chest pain (CP) on study day 1. According to the CRF the CP continued for 3 days, and was described as a single episode, of severe intensity, that was possibly related to the study drug. The patient required hospitalization, but recovered. The etiology of the CP was never explained, but the patient was chronically taking nitroglycerin for atrial fibrillation, and famotidine and pepcid for indigestion. The SAE was re-classified as not related.

No mention was made of an ECG being obtained at the time of the CP. The patient's history of chronic atrial fibrillation, and chronic nitroglycerin and H2-antagonist (famotidine and pepcid) use suggest a history of angina and heartburn prior to receiving study drug.

- #1051(0.5mg PO)-The patient had numerous adverse reactions, including constipation, pancytopenia, dizziness, and near syncope. None of the AEs were attributed to palonosetron, and the patient recovered from all but the fatigue.
- #1479 (0.25 mg PO)-This 77 year old female was hospitalized for mental status changes, hypotension, and leukopenia. She recovered from all adverse reactions, and the relationship to study drug was unlikely.
- # 1578 (0.5 mg)-The patient was diagnosed with colon cancer in 2005 and metastases to hysterosalpinx 2006. Medical history included chronic left bundle branch block, mitral regurgitation, aortic stenosis, tobacco use, decreased cardiac output with an ejection fraction of 50%, ischemic heart disease, and vertebrogenic pain syndrome.

On (b) (6) the patient was admitted to the hospital and the study drug was administered as a single dose. Chemotherapy included cycle 1 of palliative chemotherapy consisting of Avastin (bevacizumab) and Folfiri (irinotecan, folinic acid, fluorouracil). Concomitant medications were nimesulide 100 mg orally daily for vertebrogenic pain syndrome, troxerutin 600 mg orally daily for varicose veins, and acetylsalicylic acid 100 mg orally daily for insufficiency of heart valve.

During screening an ECG was obtained as per the study protocol, and chronic left bundle branch block was diagnosed. The same abnormality was observed 3 hours after the study drug administration. On (b) (6) 24 hours after palonosetron and chemotherapy, an ECG was obtained that revealed Mobitz II AV block and QTc prolongation of 516 ms. The patient did not have cardiac symptoms. The hospitalization was prolonged and holter monitoring showed a bradycardic trend with 38 isolated ventricular extrasystoles without complex forms, 932 isolated supraventricular extrasystoles, and 50 supraventricular couplets during 23 hours and 31 minutes. On (b) (6) the patient underwent pacemaker placement and recovered with sequelae (pacemaker).

The patient had a cardiac history (i.e. prior to receiving study drug) of LBBB, ischemic heart disease, and decreased ejection fraction. In addition the patient received a chemotherapeutic regimen of Avastin (bevacizumab) and Folfiri (irinotecan, folinic acid, fluorouracil). These agents are used for the treatment of metastatic colon cancer, and have known anticholinergic side effects, including bradycardia. Therefore the combination of heart disease and cardiac conduction abnormalities, with drugs that have a vagotonic effect on the heart may have produced the Mobitz II heart block, QTc prolongation, and bradycardia. Causality for the increased QTc and 2nd degree heart block cannot be determined

In addition to the above SAEs, the following are narratives of SAEs judged as possibly related to study drug, taken from all studies included in the safety evaluation.

Study 2332, patient 1309 (1 µg/kg), Hypomagnesemia, anorexia, dehydration, hypokalemia, hyponatremia

The patient is a 56-year old female hospitalized with nausea and vomiting. She received a single dose of study medication and chemotherapy on (b) (6). On (b) (6) she presented

with 3 days of severe nausea and vomiting and was treated for dehydration, electrolyte abnormalities, and nausea and vomiting. The event resolved and the investigator reported there was a reasonable possibility that the events were study drug related, and due to lack of efficacy of study drug.

The reviewer agrees that dehydration and electrolyte abnormalities may have been due to a lack of efficacy of palonosetron in preventing chemotherapy-induced vomiting. It is worth noting that in Study 2332 patients received highly emetogenic cancer chemotherapy. The study assessed dose-response, safety, and PK of single oral doses administered over a range of doses.

Study 2332, patient 3602, Abdominal pain/constipation/fever

Patient #3602, with a history at baseline of diabetes and tobacco use, was diagnosed with transitional carcinoma of the bladder. On (b) (6) the patient received high dose cisplatin and 30 µg/kg palonosetron. Eighteen hours later he developed nausea and emesis, which was considered to be treatment failure. (b) (6) days after study drug administration the patient was hospitalized after 4-6 hours of severe abdominal pain, lack of bowel movements, and emesis. Abdominal x-rays revealed a large amount of stool in the ascending colon. Patient was treated with I.V. fluids, cathartics, and enemas. The CRF reported the adverse events of right flank/abdominal pain, and obstipation and constipation as possibly drug related.

The adverse event of fever was added to the CRF on 11/16/94, classified as not drug related. The CRF also indicates that the patient was terminated from the study, due to an unsatisfactory therapeutic effect on 11/17/94. The CSR notes that an intravenous pyelogram obtained (b) (6) revealed a moderate paralytic ileus, right hydronephrosis, and extravasation of contrast material along right psoas. On the following day the patient had exploratory surgery, and placement of a right ureteral stent for right hydronephrosis secondary to ureterovesical obstruction. The events improved. Neither the sponsor nor investigator considered the events related to study drug.

Although hydronephrosis may not have been related to study drug, fecal impaction may have been since constipation is one of the known adverse reactions of this drug class. It is also worth noting that the patient received 30 µg/kg of palonosetron, which is greater than the proposed to-be marketed formulation.

Study 2332, patient 601 (Syntex) (1 µg/kg), Granulocytopenia, fever, pulmonary carcinoma, rash

This 54-year old male patient was hospitalized for granulocytopenia approximately 7 days after administration of study drug and cisplatin based chemotherapy. He presented to the emergency room for evaluation of refractory nausea and vomiting. He developed a low grade fever and after evaluation was found to be granulocytopenic (WBC 0.4 x 10³/mL). The granulocytopenia improved after treatment with antibiotics and Neupogen. The investigator reported that there was no reasonable possibility that the nausea and vomiting and consequent granulocytopenia were study drug related.

The reviewer considers that the nausea and vomiting, though 7 days post chemotherapy, could have been an insufficient therapeutic effect of palonosetron. The granulocytopenia was likely due to the chemotherapeutic agent.

Study 2332, patient 802 (<0.25 mg), Renal failure

A 61 year old male (type of cancer unknown) patient developed progressively increasing serum creatinine levels immediately following administration of study drug and cisplatin-based chemotherapy. Over a period of 7 days post chemotherapy, his creatinine level rose from 1.2 mg/dL to 3.8 mg/dL with a concurrent rise of BUN to 83 mg/dL. Thereafter these values began to normalize. The investigator indicated that there was a reasonable possibility that the renal failure was study drug related. Though cisplatin is a known nephrotoxic agent, the investigator could not exclude the possibility that the study drug may have contributed to the development of renal dysfunction.

The reviewer agrees with the assessment that cisplatin is the likely cause of the renal failure, but a contribution by the study drug cannot be entirely ruled out. Renal failure is not a labeled adverse reaction of palonosetron.

PALO-03-14, patient #4351, Convulsion (Seizure)

The patient is a 39 year old female with a previous medical history of deafness, cardiac ablation for SVT, diabetes insipidus, anxiety, and multiple medication allergies, who was diagnosed with high grade ductal breast cancer, and treated with palonosetron 0.75 mg + dexamethasone. The patient experienced a serious adverse event classified as convulsion, on (b) (6)

According to the CSR approximately 5 minutes prior to completion of chemotherapy, the patient complained of headache and said she “felt funny” and asked for a doctor. She fell out from her chair and seized on the floor. Treatment with Ativan (lorazepam) 2 mg intravenous was given and seizure resolved within a minute, with postictal confusion and nausea. CT scan of the brain was negative for intracranial hemorrhage or other abnormality. The subject was withdrawn from the study. Relationship to study medication was assessed as possible by the investigator. The study report states that based on the pre-existing history of seizures and considering the patient's clinical condition a relationship between the study drug and the single transient seizure seems unlikely.

Medical Officer's Comments:

A review of the CRF by the medical reviewer does not find seizure in the patient history. Thus a relation with study drug cannot be ruled in or out. Seizure or convulsion is not listed as an adverse reaction in the current label for Aloxi® or any of the other approved drugs in the class.

When SAEs are compared between the 0.25 mg and 0.50 mg doses in Phase 3 studies, there are more SAEs in the 0.50 mg dose group. In the ISS the sponsor includes SAEs for these doses from Phase 2 and Phase 3 studies. Study S2332 (Phase 2) tested the 0.25 mg dose, and noted 7 patients with 11 SAEs. Study PALO-04-03 (Phase 2) produced 1 SAE that was included in the ISS. Thus the number of patients with SAEs is closer between these two dosages in the ISS, than they were in pivotal study PALO-03-13. And, as noted previously, Study S2332 administered highly emetogenic chemotherapy, and assessed patients for the first 24 hours only.

7.1.3 Dropouts and Other Significant Adverse Events

As seen in Sponsor's Table C.1, in Phase 2/3 studies 4 patients withdrew due to SAE/death, and 1 patient withdrew due to a non-serious SAE.

ISS Table C.1
Summary of Subject Withdrawal
Phase 2, and Phase 3 Studies in the Integrated Safety Database

		ORAL												IV	
		Palo <0.25 mg		Palo 0.25 mg		Palo 0.50 mg		Palo 0.75 mg		Palo >0.75 mg		Total Oral		Palo 0.25 mg	
		N=31		N=203		N=182		N=414		N=68		N=898		N=163	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Study Completion Status	Completed	14	45.2	176	86.7	179	98.4	396	95.7	33	48.5	798	88.9	161	98.8
	Unsatisfactory Therapeutic Effect	15	48.4	24	11.8	2	1.1	13	3.1	30	44.1	84	9.4		
	Early Discontinuation	2	6.5	3	1.5	1	0.5	5	1.2	5	7.4	16	1.8	2	1.2
	Total	31	100.0	203	100.0	182	100.0	414	100.0	68	100.0	898	100.0	163	100.0
Reason for Early Discontinuation	Serious Adverse Event / Death			1	33.3			1	20.0	2	40.0	4	25.0		
	Non-Serious Adverse Event			1	33.3							1	6.3		
	Protocol Violation	1	50.0			1	100.0	1	20.0	3	60.0	6	37.5		
	Lost to Follow-up	1	50.0	1	33.3			2	40.0			4	25.0	2	100.0
	Other Reason							1	20.0			1	6.3		
	Total	2	100.0	3	100.0	1	100.0	5	100.0	5	100.0	16	100.0	2	100.0

No patients withdrew for safety reasons in the 0.50 mg, to-be-marketed dose. Withdrawals due to SAEs occurred in the 0.25 mg dose (1), the 0.75 mg dose (1), and in the >0.75 mg dose (2) (>0.75 mg used only in Phase 2 study 2332). One patient withdrew due to a non-serious adverse event in the 0.25 mg dose. As previously noted, data from early Phase 2 studies conducted by Syntex are incomplete, and in those instances the sponsor used a conservative approach when generating tables.

7.1.3.1 Overall profile of dropouts

Most patient discontinuations occurred in the 0.75 mg (or greater) dose as discussed above. The main reasons for discontinuation were SAE/Death, protocol violation, and lost-to-follow up.

7.1.3.2 Adverse events associated with dropouts

Study 2332: Patient 6 (0.25 mg) A 74 year old female patient was hospitalized approximately 5 days after administration of study drug and cisplatin-based chemotherapy with right hemiparesis. The admission diagnosis was a transient-type cerebrovascular accident. A CT scan of her head (report not in the CRF) showed mild atrophy and no evidence of hemorrhage, hematoma, mass effect, or shift. The event improved, and the investigator reported that there was no reasonable possibility that the event was study drug related.

The medical reviewer agrees with this assessment.

Study 2332: Patient 706 (2.00 mg) This 62 -year-old female patient died of advanced lung cancer approximately 11 days after administration of study drug and cisplatin based chemotherapy. She had been hospitalized for her chemotherapy and then discharged with hospice support. Her condition was felt to be terminal, and her respiratory status was severely

compromised because of the cancer. The investigator reported that there was no reasonable possibility that the events were study drug related.

The medical reviewer agrees with this assessment.

Study 2332: Patient 1502 (2.00 mg) This 71 year old male patient was hospitalized with acute renal failure approximately 4 days following administration of study drug and cisplatin based chemotherapy. He died one day later. He arrived at the emergency room with low blood pressure and was admitted with acute renal failure, gastrointestinal bleeding, and chronic obstructive pulmonary disease. The patient was treated with I.V. fluids and a diuretic, and received a transfusion for the gastrointestinal bleeding. He expired the next day from acute renal failure. The investigator reported that there was no reasonable possibility that the event was study drug related and that it was the result of the administration of chemotherapy.

The medical reviewer agrees with this assessment.

PALO-03-13; Patient 1003 (0.25 mg) A 72 year old male had a history of metastatic malignant melanoma, atrial fibrillation, leukopenia and thrombocytopenia. He experienced the adverse events of nausea and thrombocytopenia on study Day 1. The patient was withdrawn from the study on Day 1, after the intake of the oral study medication dose but before receiving the I.V. study medication. The nausea was classified as unlikely and the thrombocytopenia not related.

The medical reviewer agrees with these assessments.

7.1.4 Common Adverse Events

The 5-HT₃ class of drugs is associated primarily with gastrointestinal (constipation), nervous system (headache), and general adverse events. In pivotal study PALO-03-13, examining the to-be-marketed 0.50 mg dose, 8 patients had AEs classified as possibly related, and 6 had AEs classified as probably related. At the 0.25 mg dose level 7 patients had possibly related AEs, and 4 had AEs considered probably related. These two categories are combined in the table below to compare the 0.25 and 0.50 mg doses.

**TEAE Classified as Possibly/Probably Related to Palonosetron
PALO-03-13**

Adverse Event	0.25 mg	0.50 mg
nausea		1
headache	6	6
increased bilirubin		1
constipation	1	1
insomnia		1
Mobitz Type 2 Heart Block		1
1 st degree Heart Block	1	1
dyspnea, edema		1
chills	1	
pruritis	1	
motion sickness	1	
myalgia, joint stiffness	1	2
TOTAL	12	15

Medical Officer's Comment:

Headache was the most commonly observed AE in this listing, consistent with adverse events known to be associated with the drug. With the exception of the Mobitz 2nd degree heart block, most TEAEs were minor, and do not suggest a difference between the two dose levels.

In the Integrated Safety Database, a total of 584 palonosetron-treated subjects (receiving either oral or I.V. palonosetron) who participated in Phase 2 and 3 clinical trials reported at least one AE. A review of AEs considered related to study medication and seen in $\geq 2\%$ of the study population shows that constipation and headache were the AEs seen most often in oral and I.V. treatment groups. These findings are shown in sponsor's Table 5:7. As the table shows, constipation was seen 3.2% with oral doses and 3.1% with I.V., but no clear cut correlation with dose was evident. Headache was seen 6.3% with oral formulations, and 8.6% with I.V.

7.1.4.1 Common adverse event tables

Table 5:7 Number (Percentage) of Subjects Reporting Related Adverse Events by SOC and MedDRA Preferred Term in Phase 2/3 Trials with an Incidence of Greater Than or Equal to 2%* after Single Exposure

SOC	Preferred Term	Oral Palonosetron Doses										IV Palonosetron			
		< 0.25 mg (N = 31)		0.25 mg (N = 203)		0.50 mg (N = 182)		0.75 mg (N = 414)		> 0.75 mg (N = 68)		Total Oral (N = 898)		(N = 163)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
	No AE	20	64.5	185	91.1	164	90.1	361	87.2	39	57.4	769	85.6	137	84.0
	Any AE	11	35.5	18	8.9	18	9.9	53	12.8	29	42.6	129	14.4	26	16.0
Gastrointestinal	Abdominal Pain	0	0	1	0.5	0	0	0	0	2	2.9	3	0.3	0	0
	Constipation	3	9.7	4	2.0	1	0.5	14	3.4	7	10.3	29	3.2	5	3.1
	Diarrhoea	1	3.2	1	0.5	1	0.5	3	0.7	5	7.4	11	1.2	0	0
	Dry Mouth	1	3.2	0	0	0	0	0	0	0	0	1	0.1	0	0
	Vomiting	1	3.2	1	0.5	0	0	2	0.5	1	1.5	5	0.6	0	0
General	Pyrexia	1	3.2	0	0	0	0	3	0.7	1	1.5	5	0.6	0	0
Investigations	Blood Creatinine Increased	1	3.2	0	0	0	0	0	0	0	0	1	0.1	0	0
	Blood Urea Increased	1	3.2	0	0	0	0	0	0	0	0	1	0.1	0	0

*Incidence $\geq 2\%$ in one or more treatment groups

Source: ISS End-of-Text Tables H.1

Table 5:7 Number (Percentage) of Subjects Reporting Related Adverse Events by SOC and MedDRA Preferred Term in Phase 2/3 Trials with an Incidence of Greater Than or Equal to 2%* after Single Exposure

SOC	Preferred Term	Oral Palonosetron Doses										IV Palonosetron			
		< 0.25 mg (N = 31)		0.25 mg (N = 203)		0.50 mg (N = 182)		0.75 mg (N = 414)		> 0.75 mg (N = 68)		Total Oral (N = 898)		(N = 163)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Metabolism	Anorexia	1	3.2	0	0	0	0	1	0.2	0	0	2	0.2	0	0
	Dehydration	1	3.2	0	0	0	0	0	0	0	0	1	0.1	0	0
	Hypokalaemia	1	3.2	0	0	0	0	0	0	0	0	1	0.1	0	0
	Hypomagnesaemia	1	3.2	0	0	0	0	0	0	0	0	1	0.1	0	0
	Hyponatraemia	1	3.2	0	0	0	0	0	0	0	0	1	0.1	0	0
Muscular	Muscular Weakness	1	3.2	0	0	0	0	0	0	0	0	1	0.1	0	0
Neoplasms	Lung Neoplasm Malignant	1	3.2	0	0	1	0.5	0	0	1	1.5	3	0.3	0	0
Nervous	Headache	2	6.5	10	4.9	8	4.4	25	6.0	12	17.6	57	6.3	14	8.6
Psychiatric	Insomnia	1	3.2	0	0	1	0.5	0	0	1	1.5	3	0.3	1	0.5
Skin	Rash	1	3.2	0	0	0	0	1	0.2	0	0	2	0.2	1	0.6
Vascular	Hypertension	0	0	0	0	0	0	1	0.2	2	2.9	3	0.3	0	0

*Incidence $\geq 2\%$ in one or more treatment groups
Source: ISS End-of-Text Tables H.1

Medical Officer's Comments:

The percentage of related adverse events was similar between the oral capsules and I.V. formulation. A comparison between the 0.25 mg and 0.50 mg oral dose levels showed little difference, and provided reassurance that both dosages were comparable to the approved I.V. formulation.

7.1.5 Laboratory Findings

Laboratory values were obtained for pivotal study PALO-03-13 at screening, day 2, and day 6-8. Laboratory values for supportive study PALO-03-14 were obtained at screening, 3 hours post-dose, 24 hours post dose, day 8-10 of cycle 1, and during consecutive cycles. In the ISS, laboratory AEs from PALO-03-13 are pooled with data from the first cycle of PALO-03-14, and Phase 2 studies PALO-04-03, and S2332. Given the one time administration of palonosetron in these analyses, a significant change in laboratory values due to the study medication is not expected.

Sponsor Table 7:3 reports SAEs related to hematology. These numbers are small, and would likely be caused by the cancer rather than palonosetron

Table 7:3 Number and Percentage of Subjects Reporting Serious Adverse Events Related to Clinical Laboratory Values by SOC and MedDRA Preferred Term (All Phase Phase 3 Oral Palonosetron Studies)

SOC/MedDRA Preferred Term	Oral Palonosetron						IV Palonosetron	
	0.25 mg (N = 157)		0.50 mg (N = 161)		0.75 mg (N = 375)		Total (N = 693)	
	n	%	n	%	n	%	n	%
Blood								
Anaemia	0	0	2	1.2	2	0.5	4	0.6
Leukopenia	1	0.6	0	0	0	0	1	0.1
Neutropenia	0	0	1	0.6	1	0.3	2	0.3
Febrile neutropenia	0	0	0	0	2	0.5	2	0.3
Thrombocytopenia	0	0	1	0.6	1	0.3	2	0.3
Investigational								
Band Neutrophil Percentage Increased	0	0	1	0.6	0	0	1	0.1

Source: ISS End-of-Text Table F.4

Table 7:2 summarizes patients with SAEs related to laboratory values for clinical chemistry, and Table 8.2-c (from PALO-03-13) summarizes patients with a change in lab values between visit 1 and visit 4 specifically related to the liver.

Table 7:2 Number and Percentage of Subjects Reporting Adverse Events Related to Clinical Chemistry by SOC and MedDRA Preferred Term (All Integrated Phase 3 Oral Palonosetron Studies)

SOC/MedDRA Preferred Term	Oral Palonosetron						IV Palonosetron	
	0.25 mg (N = 157)		0.50 mg (N = 161)		0.75 mg (N = 375)		Total (N = 693)	
	n	%	n	%	n	%	n	%
Investigational								
Blood Bilirubin Increased	0	0	1	0.6	0	0	1	0.1
Blood Calcium Increased	0	0	0	0	1	0.3	1	0.1
Blood Creatinine Increased	2	1.3	0	0	0	0	2	0.3
Blood Glucose Increased	0	0	0	0	1	0.3	1	0.1
Blood Urea Increased	1	0.6	0	0	0	0	1	0.1
Metabolic								
Hypocalcaemia	0	0	1	0.6	0	0	1	0.1
Hypoglycaemia	0	0	0	0	1	0.3	1	0.1
Hypokalaemia	0	0	0	0	2	0.5	2	0.3

Source: ISS End-of-Text Table G.2

Table 8.2-c continued: Blood chemistry values changing from normal to abnormal or from abnormal to normal between baseline (Visit 1) and Visit 4 (Safety set, N = 639)

Visit 4	Visit 1											
	Oral Palonosetron 0.25 mg (N = 157)			Oral Palonosetron 0.50 mg (N = 161)			Oral Palonosetron 0.75 mg (N = 158)			IV Palonosetron 0.25 mg (N = 163)		
	Low n	Normal %	High n	Low n	Normal %	High n	Low n	Normal %	High n	Low n	Normal %	High n
Alkaline phosphatase [U/L]												
Low	0	0.0	0	0	0.0	0	0	0.0	0	0	0.6	0
Normal	0	0.0	124	0	0.0	129	0	0.0	124	0	128	3
High	0	0.0	2	0	0.0	6	0	0.0	1	0	5	19
ALT/SGPT [U/L]												
Low	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Normal	0	0.0	129	0	0.0	128	0	0.0	121	0	128	7
High	0	0.0	5	0	0.0	4	0	0.0	5	0	9	9
AST/SGOT [U/L]												
Low	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Normal	0	0.0	126	0	0.0	128	0	0.0	124	0	125	9
High	0	0.0	3	0	0.0	7	0	0.0	4	0	8	10
Sodium [mmol/L]												
Low	2	1.3	5	5	3.1	6	1	0.6	3	4	13	0
Normal	3	1.9	146	1	0.6	146	3	1.9	146	1	140	0
High	0	0.0	0	0	0.0	0	0	0.0	1	0	0	0

These data show that a small percentage of patients had an increase from visit 1 to visit 4 in alkaline phosphatase, ALT, and AST. There were no major difference between the I.V. and the oral formulations with respect to these changes.

Medical Officer's Comments:

These findings are minor and not unexpected. The current Aloxi labeling notes a transient asymptomatic rise in AST, ALT and bilirubin associated with the drug in ≤1% of patients.

7.1.6 Vital Signs

Among the vital signs of interest were blood pressure and heart rate. The following table(s) shows the number of AEs classified as hypertension, or hypotension in studies included in the ISS.

AEs classified as Hypertension from ISS

	0.25 mg po	0.5 mg po	0.75 mg po	0.25 mg I.V.	2.0 mg po
PALO-03-13	1		3	3	
PALO-03-14			7		
S2332	1				4
Total	2	0	10	3	4

AEs classified as Hypotension from ISS

	0.25 mg po	0.5 mg po	0.75 mg po	0.25 mg I.V.	2.0 mg po
PALO-03-13	1	1	1		
PALO-03-14			2		
S2332					
Total	1	1	3		

As the tables show, there was a slightly higher incidence of hypertension in the 0.75 mg dosage. Overall, however, no trends are identified.

The following Table G.2 shows adverse events relating to cardiac disorders, including bradycardia and tachycardia.

ISS Table G.2
Number (%) of Patients Reporting Adverse Events by SOC and MedDRA Preferred Term
Phase 3 Studies in the Integrated Safety Database

		ORAL								IV	
		Palo 0.25 mg		Palo 0.50 mg		Palo 0.75 mg		Total Oral		Palo 0.25 mg	
		N	%	N	%	N	%	N	%	N	%
CARDIAC DISORDERS	-At least one-	5	3.2	3	1.9	7	1.9	15	2.2	3	1.8
	ARRHYTHMIA	1	0.6	0	0	2	0.5	3	0.4	0	0
	ATRIAL FIBRILLATION	0	0	0	0	0	0	0	0.0	2	1.2
	ATRIOVENTRICULAR BLOCK FIRST DEGREE	1	0.6	1	0.6	1	0.3	3	0.4	0	0
	ATRIOVENTRICULAR BLOCK SECOND DEGREE	0	0	1	0.6	0	0	1	0.1	0	0
	BUNDLE BRANCH BLOCK LEFT	1	0.6	0	0	0	0	1	0.1	0	0
	CARDIO-RESPIRATORY ARREST	0	0	0	0	1	0.3	1	0.1	0	0
	MYOCARDIAL ISCHAEMIA	0	0	0	0	1	0.3	1	0.1	0	0
	PALPITATIONS	0	0	0	0	1	0.3	1	0.1	0	0
	SINUS BRADYCARDIA	0	0	1	0.6	0	0	1	0.1	0	0
	SINUS TACHYCARDIA	2	1.3	0	0	1	0.3	3	0.4	0	0
	SUPRAVENTRICULAR EXTRASYSTOLES	1	0.6	0	0	1	0.3	2	0.3	0	0
	SUPRAVENTRICULAR TACHYCARDIA	1	0.6	0	0	0	0	1	0.1	0	0
	TACHYCARDIA	0	0	1	0.6	1	0.3	2	0.3	1	0.6

7.1.7 Electrocardiograms (ECGs)

7.1.7.1 Overview of ECG testing in the development program, including brief review of preclinical results

Since the original CINV NDA for the palonosetron I.V. formulation was approved, a thorough QT/QTc study (PALO-03-11, performed under IND 39,797) and a PONV Phase 3 program have been completed.

The tQT study was a randomized, double-blind, positive- and placebo-controlled parallel study in which 221 healthy subjects were administered single doses of palonosetron 0.25 mg,

palonosetron 0.75 mg, palonosetron 2.25 mg, moxifloxacin 400 mg, or placebo. At the supratherapeutic dose (2.25 mg), palonosetron plasma concentrations were 9-fold higher than concentrations following the therapeutic dose (0.25 mg). The plasma concentrations attained are sufficient to cover the increase in plasma concentrations expected due to known intrinsic factors.

A single dose of 400 mg moxifloxacin increased the QT interval by 11 ms (lower 95% confidence bound 8 ms) 2 hours after dosing indicating that the study was adequately designed and conducted to detect a mean increase in the QTc of about 5 ms. Results of the study showed that palonosetron had no significant effect on the QT interval.

ECGs collected in the PONV Phase 3 program provided ECG data in 915 subjects treated with palonosetron (at a lower dose), and 305 treated with placebo. Results were consistent across palonosetron doses and placebo, and no safety signal was observed.

Data from the current submission do not show an in vivo effect of palonosetron on ECG parameters, on outliers, or on new selected events either after a single dose or after multiple palonosetron doses administered once with each chemotherapy cycle up to 4 cycles.

7.1.7.2 Standard analyses and explorations of ECG data

The following sponsor Table 6:2 shows ECG data from single dose palonosetron study PALO-03-13, and cycle 1 PALO 03-14. In these studies patients received one dose of oral or I.V. palonosetron 60 minutes (oral), or 30 minutes (I.V.) before receiving chemotherapy. Although there was one case of QTc prolongation post-dose in the 0.75 mg oral, and 0.25 mg I.V. arms, overall QTc changes were minimal, and there were no significant differences across palonosetron doses.

Table 6:2 Number (Percentage) of Patients with Various ECG Abnormalities Post-Dose

Abnormality	Oral Palonosetron						IV Palonosetron	
	0.25 mg (N = 157)		0.50 mg (N = 161)		0.75 mg (N = 375)		(N = 163)	
	n	%	n	%	n	%	n	%
HR Abnormality	0	-	2	1.2	1	0.3	0	-
PR Abnormality	1	0.6	1	0.6	0	-	1	0.6
QRS Abnormality	0	-	1	0.6	2	0.5	1	0.6
QTc Abnormality	0	-	1	0.6	2	0.5	0	-
QTcF Increase from Baseline								
30 to 60 msec	16	10.2	16	9.9	52	13.9	16	9.8
> 60 msec	2	1.3	0	-	3	0.8	0	-
QTcF baseline ≤ 500 msec and post-dose >500 msec	0	-	0	-	1	0.3	1	0.6
QTcB Increase from Baseline								
30 to 60 msec	26	16.6	27	16.8	79	21.1	20	12.3
> 60 msec	3	1.9	1	0.6	7	1.9	1	0.6
QTcB baseline ≤ 500 msec and post-dose >500 msec	0	-	1	0.6	3	0.8	1	0.6

N= Number of patients in specific group.

n = Number of patients with changes.

Source: ISS End-of-Text Table I.1

Likewise in sponsor Table 6:3 there were no ST segment elevations, or episodes of complete heart block. There were few instances of prolonged QTc, the highest number being seen with the 0.75 mg dose level.

Table 6:3 Number (Percentage) of Patients with New Selected Abnormalities

	Oral Palonosetron						IV Palonosetron	
	0.25 mg (N = 157)		0.50 mg (N = 161)		0.75 mg (N = 375)		(N = 163)	
	n	%	n	%	n	%	n	%
U Waves	0	0	0	0	0	0	0	0
Any T Wave Abnormality	13	8.3	11	6.8	37	9.9	15	9.2
T Waves Inverted	5	3.2	3	1.9	9	2.4	5	3.1
ST Segment Depressed	2	1.3	4	2.5	1	0.3	3	1.8
ST Segment Elevated	0	0	0	0	0	0	0	0
Left Bundle Branch Block	0	0	0	0	1	0.3	1	0.6
Right Bundle Branch Block	0	0	0	0	1	0.3	1	0.6
Prolonged QTc	0	0	1	0.6	4	1.1	1	0.6
Left Anterior Hemiblock	1	0.6	0	0	0	0	0	0
Complete Heartblock	0	0	0	0	0	0	0	0
Atrial Fibrillation	1	0.6	0	0	1	0.3	2	1.2

PALO-03-14 examined the safety of palonosetron with multiple cycles of chemotherapy. In this study ECGs were obtained at baseline, 3 hours post-dose, and 24 hours post dose for cycles 1 to 4. As figure 6.2 shows, there was no signal of a cumulative effect of palonosetron on ECG parameters over the 4 cycles of drug administration.

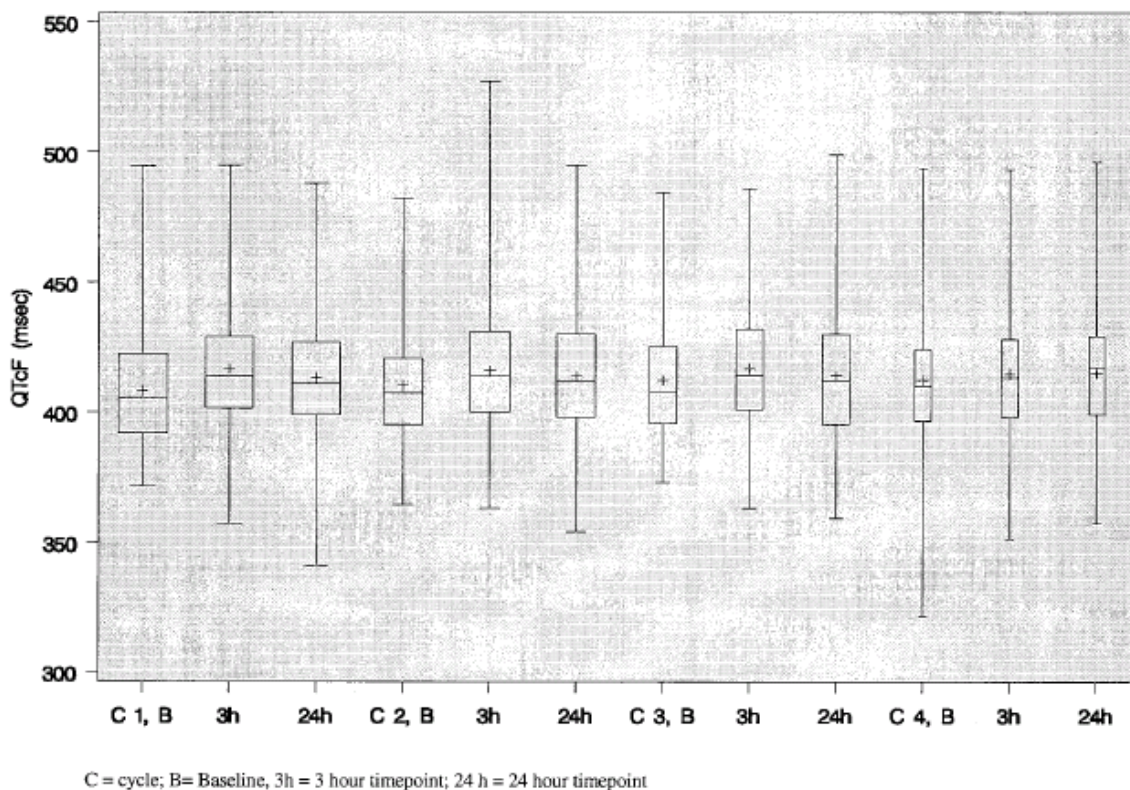


Figure 6:2 QTcF by Cycle and Time Points, Study PALO-03-14

Medical Officer's Comments:

These findings are particularly important since they show that palonosetron, when used for repeat chemotherapy cycles, does not significantly effect the QT interval.

7.1.8 Human Carcinogenicity

Rat and mouse carcinogenicity studies were submitted in the original NDA for I.V. palonosetron.

7.1.9 Special Safety Studies

No special safety studies were conducted for this submission.

7.1.10 Postmarketing Experience

Oral palonosetron has not been approved for marketing anywhere in the world. Intravenous palonosetron has been marketed in the United States since 2003, and is currently marketed worldwide in 53 countries. The sponsor has submitted annual reports and periodic safety update reports as required. An Annual Report, and the thirteenth Periodic Adverse Drug Experience report for NDA21-372 (I.V. palonosetron (Aloxi®)) covering the period July 25, 2006 to July 24, 2007, was received in September 2007.

7.2 Adequacy of Patient Exposure and Safety Assessments

Oral palonosetron has been developed for short term use for the prevention of acute (b) (4) CINV associated with moderately emetogenic agents. PALO-03-13 exposed patients to one dose of study medication, and PALO-03-14 examined the cumulative effects of palonosetron over four chemotherapy cycles. Pooling safety data from Phase 2 and 3 studies provides adequate exposure for a drug not intended for chronic use.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure)

Sponsor's Table 2.7.4:5 shows that 898 patients received oral palonosetron, and 163 patients received I.V. Taken together 1061 patients received palonosetron for oral CINV studies. Patients included in these studies had histologically or cytological confirmed malignant disease, were naïve or non-naïve to cancer chemotherapy, (if non-naïve had no more than mild nausea or vomiting following any previous chemotherapy cycle), and had a Karnofsky index¹ of $\geq 50\%$.

Table 2.7.4:5 Exposure in the Integrated Oral Safety Database for Palonosetron by Dose

	Oral Palonosetron (mg)						IV Palo	Total
	< 0.25	0.25	0.50	0.75	> 0.75	Total		
Phase 2	31	46	21	39	68	205	-	205
Phase 3	-	157	161	375	-	693	163	856
Total All Phase 2/3	31	203	182	414	68	898	163	1061

Source: ISS End-of-Text Table A.1.

Medical Officer's Comments:

Exposure was higher in the 0.75 mg dose since data was combined from PALO-03-13 and PALO-03-14. PALO-03-14 used only the 0.75 mg dose, and was open-label.

7.2.1.1 Study type and design/patient enumeration

A full discussion of study type and design/patient enumeration is contained in the Study Design section of the Efficacy review of this NDA.

7.2.1.2 Demographics

The following sponsor Table 2.7.3:5 shows baseline demographic data from pivotal study PALO-03-13, and compares these with subjects in I.V. palonosetron studies.

¹ Named for Dr. David A. Karnofsky, the Karnofsky Performance Scale Index classifies patients as to their functional impairment. The highest achievable score is 100, and corresponds to an individual with no complaints and no evidence of disease.

Table 2.7.3:5 Demographics and Baseline Characteristics for Phase 3 Oral Study PALO-03-13 (FAS), PALO-99-03 and PALO-99-04 Intravenous Palonosetron 0.25 mg Treatment Arms and for Pooled Analysis PALO-07-36							
	PALO-03-13				PALO-99-03	PALO-99-04	Pooled
	Palo PO 0.25 mg (N = 155)	Palo PO 0.50 mg (N = 160)	Palo PO 0.75 mg (N = 158)	Palo IV 0.25 mg (N = 162)	IV 0.25 mg (n=187)	IV 0.25 mg (n=189)	IV 0.25 mg (n=538)
Age							
Mean ± SD	57.1 ± 11.9	56.1 ± 12.3	55.8 ± 12.7	57.7 ± 12.7	56.1 ± 11.7	53.3 ± 13.1	55.6 ± 12.6
Gender, n (%)							
Male	40 (26)	42 (26)	44 (28)	45 (28)	54 (29)	34 (18)	133 (25)
Female	115 (74)	118 (74)	114 (72)	117 (72)	133 (71)	155 (82)	405 (75)
Height (cm)							
Mean ± SD	161.7 ± 11.3	162.2 ± 8.8	161.9 ± 9.4	163.2 ± 10.7	165.0 ± 7.2	159.7 ± 9.6	162.6 ± 9.5
Weight (kg)							
Mean ± SD	71.4 ± 15.6	69.6 ± 15.0	70.8 ± 14.8	72.3 ± 15.7	71.6 ± 13.3	71.3 ± 17.2	71.7 ± 15.5
Race, n (%)							
White	109 (70)	112 (70)	106 (67)	114 (70)	184 (98)	57 (30)	355 (66)
Black	2 (1)	1 (1)	2 (1)	0 (0)	0 (0)	12 (6)	12 (2)
Hispanic	43 (28)	44 (28)	49 (31)	45 (28)	1 (1)	115 (61)	161 (30)
Asian	1 (1)	1 (1)	0 (0)	2 (1)	2 (1)	3 (2)	7 (1)
Other	0 (0)	2 (1)	1 (1)	1 (1)	0 (0)	2 (1)	3 (1)
Chemotherapy history n (%)							
Naïve	95 (61)	91 (57)	93 (59)	96 (59)	75 (40)	124 (66)	295 (55)
Non-naïve	60 (39)	69 (43)	65 (41)	66 (41)	112 (60)	65 (34)	243 (45)
Use of dexamethasone n (%)							
Yes	78 (50)	79 (49)	80 (51)	82 (51)	0 (0)	11 (6)	93 (17)
No	77 (50)	81 (51)	78 (49)	80 (49)	187 (100)	178 (94)	445 (83)

There were approximately three times as many females as males in most studies, and in PALO-03-13 white and Hispanics outnumbered other races, and patients naïve to chemotherapy outnumbered non-naïve patients. There were over twice as many patients younger than 65 than older. Exposure by age ≥65 or <65 is shown in Sponsor Table 2:5.

Table 2:5 Exposure in Integrated Safety Database by Age

	Oral Palonosetron	IV Palonosetron
All Phase 2/3 PO Trials^a		
<65 years	624 (69.5%)	114 (69.9%)
≥65 years	274 (30.5%)	49 (30.1%)
Phase 3 PO Trials		
<65 years	503 (72.6%)	114 (69.9%)
≥ 65 years	190 (27.4%)	49 (30.1%)

^a Includes PALO-03-13, PALO-03-14, PALO-03-04 and 2332.

Source: ISS End-of-Text Tables D.1 and D.2

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

As noted previously in this review, thorough QT study (tQT) PALO-03-11 was submitted with NDA (b) (4) S008 (b) (4), S010 in 2007. The tQT study showed little effect of palonosetron on the QT interval and, as a result, removal of QTc prolongation warning information from the

Warnings and Precautions section of the product labeling was permitted. Results from tQT PALO-03-11 provided support for the safety evaluation of the current submission.

7.2.2.1 Postmarketing experience

No Postmarketing data are available for oral palonosetron, since an oral formulation has not yet been approved for any indication.

7.2.3 Adequacy of Special Animal and/or In Vitro Testing

Nonclinical studies of palonosetron were reviewed under NDA21-372. No nonclinical studies were submitted in the present application, as per agreement between the sponsor and the Division of Gastroenterology Products.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Constipation and headache were the only two drug-related adverse events with an incidence of $\geq 2\%$ after single exposure to palonosetron. Sponsor's Table 5:8 shows these data from oral palonosetron doses in Phase 3 studies.

Table 5:8 Number (Percentage) of Subjects Reporting Related Adverse Events by SOC and MedDRA Preferred Term in Phase 3 Oral Palonosetron Trials, Single Exposure, with an Incidence of Greater Than or Equal to 2%* after Single Exposure

SOC	Preferred Term	Oral Palonosetron Doses								IV Palonosetron	
		0.25 mg (N = 157)		0.50 mg (N = 161)		0.75 mg (N = 375)		Total (N = 693)		(N = 163)	
		n	%	n	%	n	%	n	%	n	%
	No AE	146	93.0	148	91.9	336	89.6	630	90.9	137	84.0
	Any AE	11	7.0	13	8.1	39	10.4	63	9.1	26	16.0
Gastrointestinal	Constipation	1	0.6	1	0.6	9	2.4	11	1.6	5	3.1
Nervous System	Headache	6	3.8	6	3.7	21	5.6	33	4.8	14	8.6

*Incidence $\geq 2\%$ in one or more treatment groups
Source: ISS End-of-Text Tables H.2

Medical Officer's Comments:

Constipation and headache are known adverse events associated with palonosetron. In Phase 3 studies constipation and headache were seen more at the 0.75 mg oral and 0.25 mg I.V. dose levels. The 0.25 mg and 0.5 mg oral dosages performed about the same in terms of these 2 AEs. Overall there were no new or unexpected drug-related AEs.

7.4 General Methodology

7.4.1.1 Pooled data vs. individual study data

Pooling of data from Phase 2 and 3 studies is used to improve the precision of adverse event incidence. However there are limitations to these pooled data.

- Study 2330 studied CR for only the first 24 hours in patients receiving highly emetogenic cancer chemotherapy
- PALO-03-14 studied CR for patients receiving 0.75 mg in single and repeated dosing in up to four cycles of chemotherapy

Therefore a review of adverse event data makes note of the study from which they are derived, and the limitations of these data.

7.4.2 Explorations for Predictive Factors

Among the factors that may affect the safety profile of palonosetron are age, gender, race, concomitant medication, and concomitant illnesses. There were fewer males, and subjects older than 65 than females or younger patients. Most subjects were Caucasian, followed by Hispanic.

Age

Sponsor's Table 11:1 shows that, at each dose studied, there were more patients younger than 65 than older.

Table 11:1 Age Disposition of All Phase 2/3 Trials

	Oral Palonosetron										IV Palo			
	< 0.25 mg (N = 31)		0.25 mg (N = 203)		0.50 mg (N = 182)		0.75 mg (N = 414)		> 0.75 mg (N = 68)		Total (N = 898)		(N = 163)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<65 years	20	65	140	69	129	71	296	72	39	57	624	70	114	70
≥65 years	11	36	63	31	53	29	118	29	29	43	274	31	49	30

Source: ISS End of Text Table D.1

Sponsor's Table 1 and 2 show complete response by age < 65 and ≥ 65. In the acute 0 to 24 hour time frame patients ≥65 had a higher percentage of CR in all doses except 0.5 mg, where they had a similar response. The confidence interval for the 0.5 mg (to-be-marketed) dose was well outside the NI margin, suggesting less efficacy in the elderly. The number of patients equal to or greater than 65 in each arm of the study was small, making it difficult to draw conclusions.

Table 1: Patients with complete response during 0-24 and 24-120 hour time period from start of chemotherapy (Full analysis set, subgroups: age, N = 635)

Time Period	Age	Oral Palonosetron 0.25 mg				Oral Palonosetron 0.50 mg				Oral Palonosetron 0.75 mg				IV Palonosetron 0.25 mg			
		N	n	CR%	95% CI (%)	N	n	CR%	95% CI (%)	N	n	CR%	95% CI (%)	N	n	CR%	95% CI (%)
0 – 24 Hr	< 65	112	74	66.1	(56.4, 74.6)	115	88	76.5	(67.5, 83.7)	114	77	67.5	(58.0, 75.8)	113	75	66.4	(56.8, 74.8)
	≥ 65	43	40	93.0	(79.9, 98.2)	45	34	75.6	(60.1, 86.6)	44	40	90.9	(77.4, 97.0)	49	39	79.6	(65.2, 89.3)
24 – 120 Hr	< 65	112	61	54.5	(44.8, 63.8)	115	69	60.0	(50.4, 68.9)	114	63	55.3	(45.7, 64.5)	113	72	63.7	(54.1, 72.4)
	≥ 65	43	31	72.1	(56.1, 84.2)	45	31	68.9	(53.2, 81.4)	44	32	72.7	(57.0, 84.5)	49	34	69.4	(54.4, 81.3)

Table 2: Complete response (0-24 and 24-120 hours): confidence intervals for differences between oral and IV treatment groups (Full analysis set, subgroups: age, N = 635)

Time Period	Age	Oral Palonosetron 0.25 mg – IV Palonosetron 0.25 mg	Oral Palonosetron 0.50 mg – IV Palonosetron 0.25 mg	Oral Palonosetron 0.75 mg – IV Palonosetron 0.25 mg
		98.3% Confidence Interval	98.3% Confidence Interval	98.3% Confidence Interval
0 – 24 Hr	< 65	(-16.2, 15.6)	(-4.9, 25.2)	(-14.6, 17.0)
	≥ 65	(-5.3, 32.2)	(-26.7, 18.7)	(-8.0, 30.7)
24 – 120 Hr	< 65	(-25.7, 7.2)	(-19.9, 12.5)	(-24.8, 7.9)
	≥ 65	(-22.1, 27.6)	(-25.4, 24.4)	(-21.3, 27.9)

Age-Safety

Adverse events were spread among older and younger patients in Phase 2 and 3 studies, as ISS Table G.5 shows. More AEs were seen in patients ≥65 at the 0.5 mg and 0.75 mg dose levels than the 0.25 mg dose level. However, the number of subjects with AEs in the proposed 0.5 mg oral capsule dose was similar to the number of subjects with AEs in the currently marketed 0.25 mg I.V. dose (57% vs., 60%).

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ISS Table G.5
Number (%) of Patients Reporting Adverse Events by SOC and MedDRA Preferred Term
Phase 2, and Phase 3 Studies in the Integrated Safety Database
By Age Category

			ORAL												IV	
			Palo <0.25 mg		Palo 0.25 mg		Palo 0.50 mg		Palo 0.75 mg		Palo >0.75 mg		Total Oral		Palo 0.25 mg	
			N	%	N	%	N	%	N	%	N	%	N	%	N	%
BODY SYSTEM	PREFERRED TERM	Age Category														
ALL	Total subjects	<65 years	20	100.0	140	100.0	129	100.0	296	100.0	39	100.0	624	100.0	114	100.0
		≥65 years	11	100.0	63	100.0	53	100.0	118	100.0	29	100.0	274	100.0	49	100.0
	Total subjects with AE	<65 years	15	75.0	77	55.0	62	48.1	149	50.3	35	89.7	338	54.2	50	43.9
		≥65 years	8	72.7	34	54.0	32	60.4	75	63.6	19	65.5	168	61.3	28	57.1

Older subjects tended to have more constipation, nausea and flatulence, while headache was more common in younger subjects. Sponsor's Table 11:2 shows that in the doses studied in Phase 3 trials (0.25 mg, 0.50 mg, 0.75 mg, 0.25 mg I.V.) there were more gastrointestinal AEs among patients older ≥65 than in those ≤65.

Table 11:2 Number (Percentage) of Subjects Reporting Adverse Events by SOC and Age Category in All Phase 2/3 Studies

SOC	Age Category ^a	Oral Palonosetron										IV Palo			
		< 0.25 mg (Yn = 20) (On = 11)		0.25 mg (Yn = 140) (On = 63)		0.50 mg (Yn = 129) (On = 53)		0.75 mg (Yn = 296) (On = 118)		> 0.75 mg (Yn = 39) (On = 29)		Total (Yn = 624) (On = 274)		0.25 mg (Yn = 114) (On = 49)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any AEs	<65 years	15	75.0	77	55.0	62	48.1	149	50.3	35	89.7	338	54.2	50	43.9
	≥65 years	8	72.7	34	54.0	32	60.4	75	63.6	19	65.5	168	61.3	28	57.1
No AEs	<65 years	5	25.0	63	45.0	67	51.9	147	49.7	4	10.3	286	45.8	64	56.1
	≥65 years	3	27.3	29	46.0	21	39.6	43	36.4	10	34.5	106	38.7	21	42.9
Blood	<65 years	2	10.0	7	5.0	4	3.1	27	9.1	4	10.3	44	7.1	5	4.4
	≥65 years	4	36.4	5	7.9	9	17.0	19	16.1	3	10.3	40	14.6	1	2.0
Cardiovascular	<65 years	0	0	6	4.3	4	3.1	5	1.7	1	2.6	16	2.6	1	0.9
	≥65 years	0	0	2	3.2	4	7.5	5	4.2	0	0	11	4.0	2	4.1
Ear	<65 years	2	10.0	5	3.6	3	2.3	5	1.7	3	7.7	18	2.9	0	0
	≥65 years	0	0	1	1.6	0	0	0	0	1	3.4	2	0.7	0	0
Endocrine	<65 years	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	≥65 years	0	0	0	0	1	1.9	0	0	0	0	1	0.4	0	0
Eye	<65 years	2	10.0	2	1.4	2	1.6	3	1.0	0	0	9	1.4	0	0
	≥65 years	1	9.1	0	0	0	0	0	0	0	0	1	0.4	0	0
Gastrointestinal	<65 years	10	50.0	28	20.0	34	26.4	64	21.6	21	53.8	157	25.2	21	18.4
	≥65 years	5	45.5	15	23.8	18	34	39	33.1	14	48.3	91	33.2	12	24.5
General	<65 years	7	35.0	24	17.1	15	11.6	43	14.5	18	46.2	107	17.1	13	11.4
	≥65 years	1	9.1	14	22.2	15	28.3	17	14.4	7	24.1	54	19.7	10	20.4
Hepatic	<65 years	0	0	0	0	2	1.6	1	0.3	0	0	3	0.5	0	0
	≥65 years	0	0	0	0	1	1.9	0	0	0	0	1	0.4	1	2.0

^a Yn = n of subjects aged <65 years, On = n of subjects aged ≥ 65 years.
Source: End-of-Text Table G.5

Gender

A subgroup analysis by gender was performed by the sponsor for primary and key secondary endpoints. As the following Tables 3 and 4 show, the percentage of patients with CR during the first 24, and 24 to 120 hours was higher in males than females. Non-inferiority to the I.V. comparator group was shown for the two highest oral palonosetron doses (0.50 mg and 0.75 mg) in male patients, while in female patients, non-inferiority of the oral palonosetron to the I.V. group was shown for all three oral palonosetron doses (the lower limit of the confidence interval was above the pre-set threshold of -15.0%).

Table 3: Patients with complete response during 0-24 and 24-120 hour time period from start of chemotherapy (Full analysis set, subgroups: gender, N = 635)

Time Period	Gender	Oral Palonosetron 0.25 mg				Oral Palonosetron 0.50 mg				Oral Palonosetron 0.75 mg				IV Palonosetron 0.25 mg			
		N	n	CR%	95% CI (%)	N	n	CR%	95% CI (%)	N	n	CR%	95% CI (%)	N	n	CR%	95% CI (%)
0 – 24 Hr	Male	40	35	87.5	(72.4, 95.3)	42	38	90.5	(76.5, 96.9)	44	41	93.2	(80.3, 98.2)	45	37	82.2	(67.4, 91.5)
	Female	115	79	68.7	(59.3, 76.8)	118	84	71.2	(62.0, 79.0)	114	76	66.7	(57.1, 75.0)	117	77	65.8	(56.4, 74.2)
24 – 120 Hr	Male	40	29	72.5	(55.9, 84.9)	42	36	85.7	(70.8, 94.1)	44	34	77.3	(61.8, 88.0)	45	34	75.6	(60.1, 86.6)
	Female	115	63	54.8	(45.3, 64.0)	118	64	54.2	(44.8, 63.4)	114	61	53.5	(44.0, 62.8)	117	72	61.5	(52.1, 70.2)

Table 4: Complete response (0-24 and 24-120 hours): confidence intervals for differences between oral and IV treatment groups (Full analysis set, subgroups: gender, N = 635)

Time Period	Gender	Oral Palonosetron 0.25 mg – IV Palonosetron 0.25 mg	Oral Palonosetron 0.50 mg – IV Palonosetron 0.25 mg	Oral Palonosetron 0.75 mg – IV Palonosetron 0.25 mg
		98.3% Confidence Interval	98.3% Confidence Interval	98.3% Confidence Interval
0 – 24 Hr	Male	(-15.5, 26.1)	(-11.4, 27.9)	(-7.6, 29.6)
	Female	(-12.7, 18.4)	(-9.9, 20.7)	(-14.9, 16.6)
24 – 120 Hr	Male	(-28.2, 22.1)	(-12.1, 32.5)	(-22.0, 25.4)
	Female	(-23.0, 9.5)	(-23.5, 8.9)	(-24.4, 8.3)

The number of male and female patients experiencing an AE after receiving 0.25 or 0.5 mg oral palonosetron, or 0.25 mg I.V. palonosetron, was similar. The to-be-marketed dose of 0.5 mg showed a lower percentage of GI and Nervous system AEs in males than females. The lower 0.25 mg dose showed similar percentages of GI AEs between men and women, but more headaches in females than males. The overall number of male patients was small overall, making conclusions difficult to draw.

Gastrointestinal and Nervous System Disorders by Gender, Phase 3 Trials

		0.25 mg m=64, f=139		0.50 mg m=55, f=127		0.75 mg m=130, f=284		0.25 mg I.V. m=45, f=118	
		n	%	n	%	n	%	n	%
Gastrointestinal	Male	15	23.4	11	20.0	37	28.5	11	24.4
	Female	28	20.1	41	32.3	66	23.2	22	18.6
Nervous system	Male	8	12.5	5	9.1	15	11.5	6	13.3
	Female	29	20.9	34	26.8	69	4.3	25	21.2

Based on experience in 640 Caucasians, 218 Hispanics, 27 Blacks, 7 Asian and 6 subjects of other races receiving oral palonosetron, no clinically relevant difference was apparent in the safety profile in Caucasians and non-Caucasians. Races including Blacks, Asians and other were not well-represented.

The sponsor notes that population PK analysis of data collected in 688 subjects during the pivotal Phase 3 CINV trials conducted during the I.V. development program showed no apparent gender, age or race effect on palonosetron disposition, although variability within groups was large. Body weight and race (20% higher in Caucasians relative to other races) were among several factors affecting the volume of distribution. While there were slight PK differences in C_{max} for elderly subjects, and in exposure of the parent drug in females compared to males, there is no clinical significance attributed to the PK differences of these demographic factors and the AE profile.

This finding supports the integrated analysis in the study subjects for this application. There was a lack of demographic effect on the incidence of AEs, with the possible exception of elderly subjects who had a slightly higher incidence of constipation. This finding is consistent in both I.V. and oral patient groups and is likely compounded by intrinsic and extrinsic factors in the older subjects, unassociated with palonosetron use.

7.4.2.1 Explorations for dose dependency for adverse findings

Sponsor's Table 5:1 summarizes the overall incidence of adverse events and discontinuation due to AEs, by treatment and dose.

Table 5:1 Number and Percentage of Subjects with Death, SAE, Discontinuations Due to an Adverse Event and Adverse Events in All Phase 2 and 3 Oral Palonosetron Clinical Trials in the Integrated Safety Database

Treatment	Deaths ^a		Serious AEs		Discontinuations due to AE		AEs ^b	
	n	%	n	%	n	%	n	%
Palonosetron all oral doses N = 898	11	1.2	55	6.1	5	<1	506	56.3
Palonosetron < 0.25 mg N = 31	1	3.2	8	25.8	0	0	23	74.2
Palonosetron 0.25 mg N = 203	0	0	11	5.4	2	<1	111	54.7
Palonosetron 0.50 mg N = 182	1	<1	10	5.5	0	0	94	51.6
Palonosetron 0.75 mg N = 414	4	<1	15	3.6	1	<1	224	54.1
Palonosetron >0.75 mg N = 68	5	7.3	11	16.2	2	2.9	54	79.4
Palonosetron 0.25 mg IV N = 163	0	0	1	<1	0	0	78	47.9

^a Events with an outcome of Death.

^b Includes all AEs from treatment through follow-up. Deaths are included in SAEs, and SAEs are included in AE counts.

Source: ISS End-of-Text Tables C.1, E.1, E. 2, F.1, G.1

There were fewer AEs, SAEs, and discontinuations due to AEs in the I.V. dose than in the oral doses. Sponsor's Table 5:1 shows a fairly even distribution of SAE between the 0.25 mg and 0.50 mg doses, due to the fact that Phase 2 studies are included in the analysis. When SAEs from Phase 3 study PALO-03-13 are examined separately, the 0.50 mg dose level showed more patients with SAEs (9), compared to the 0.25 mg dose (3).

Medical Officer's Comment:

Headache and constipation were the most commonly observed AE at both the 0.25 mg and 0.5 mg dose levels in PALO-03-13, consistent with adverse events known to be associated with the drug. With the exception of the Mobitz 2nd degree heart block, most TEAEs were minor, and do not suggest a difference between the two dose levels.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Doses studied in the oral development program were selected based on results of oral ADME (absorption, distribution, metabolism, elimination) study, phase 2 dose-response studies #2332 and #2330, and I.V. palonosetron phase 3 studies PALO-99-03 and PALO-99-04.

The 0.5 mg oral dose was chosen for marketing because it showed a more favorable efficacy profile than the other oral doses studied, and provided safety comparable to the 0.25 mg I.V. palonosetron formulation already on the market.

Medical Officer's Comments:

All three oral dosages had comparable efficacy in the acute phase, but none met the statistical threshold for efficacy in the delayed phase (0.50 mg coming closest). The approved I.V. dose is 0.25 mg, and the bioavailability of the oral formulations approach 97%.

From a safety perspective, there is a slight qualitative, but not statistically significant, imbalance in SAEs between the lower and mid-range doses. The relationship of adverse events to palonosetron with either dose is inconclusive and, overall, there are no safety findings that would definitely support the 0.25 mg over the 0.50 mg dose.

8.2 Drug-Drug Interactions

In-vitro studies conducted during the original development indicate that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5, nor does it induce the activity CYP1A2, CYP2D6 or CYP3A3/4. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low, as stated in current approved Aloxi® labeling.

The effect of concomitant administration of an antacid on PK of palonosetron (clinical trial formulation) was evaluated in healthy volunteers in a Phase 1 study. Antacid, Malox® 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.

As per the Clinical Pharmacology review:

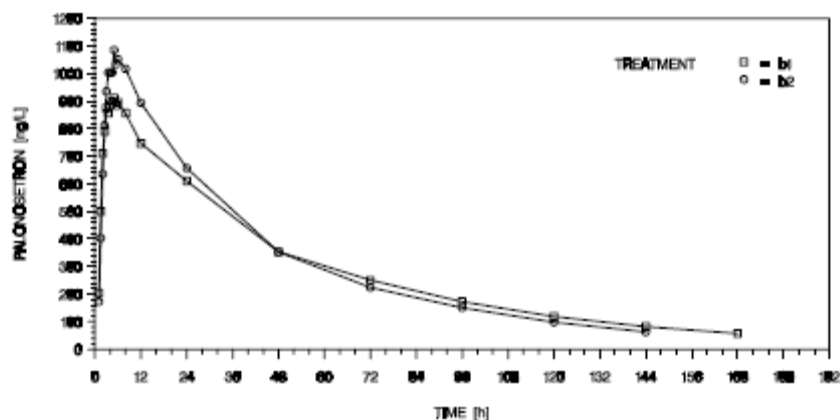
A mass balance study for oral administration indicated that metabolic profile of orally administered palonosetron is similar to that after intravenous administration and the contribution of pre-systemic intestinal metabolism is not significant based on the comparable recovery of unchanged palonosetron in the urine after oral and IV administration... the drug-drug interaction potential via intestinal metabolism appears to be low.

8.3 Special Populations

The only special population study performed during the oral development program was an evaluation of palonosetron PK in healthy elderly subjects (PALO-01-04). Other special population data such as pharmacokinetics in renal or hepatic impaired subjects, for support of the product label, is referenced from the original I.V. submission (NDA 21-372) and is reviewed briefly below.

The pharmacokinetics of palonosetron in elderly subjects are similar to younger subjects after oral administration of the softgel capsule.

Figure 2.5:2 Palonosetron plasma concentrations (arithmetic mean) (PALO-04-01)



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)

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 C_{max} was 13% lower than in the young.

More AEs were seen in patients ≥ 65 at the 0.5 mg and 0.75 mg dose levels than the 0.25 mg dose level. However the total number of subjects with AEs in the proposed 0.5 mg oral capsule dose was similar to the total number of subjects with AEs in the currently marketed 0.25 mg I.V. dose (57% vs., 60%). Older subjects tended to have more constipation, nausea and flatulence, while headache was more common in younger subjects. There is no need for dosage adjustment in the elderly.

The effect of varying degrees of renal or hepatic failure on the pharmacokinetics of palonosetron 0.75 mg administered as a single I.V. bolus was evaluated in two studies conducted in special populations, including subjects with mild to severe renal (PALO-99-35) or hepatic impairment (PALO-99-51). Both of these studies were submitted in the I.V. NDA submission. Severe renal impairment appears to reduce renal clearance of palonosetron; however, total body clearance in these patients was not different from healthy subjects.

No dosage adjustment is required for the elderly, or in patients with mild to moderate renal or hepatic impairment. However patients with end stage renal disease have not been studied, and a statement to this effect will be required in the oral Aloxi labeling.

8.4 Pediatrics

No pediatric studies have been conducted in children using the oral formulation. The sponsor has conducted studies in pediatric patients using the I.V. formulation, and has submitted a proposed pediatric study request (PPSR) to the FDA. Response to the PPSR was delayed awaiting the

results of an adult dose escalating study to evaluate the QT/QTc. That study was reviewed in 2007, and did not show cause for concern over QTc prolongation or Torsades de Pointes.

The following is the sponsor's pediatric development plan for moderately emetogenic CINV that includes both I.V. and oral pediatric studies.

A. I.V. Palonosetron Pediatric Study. Intravenous palonosetron pediatric study P ALO-99-07 was previously performed by the Sponsor. This study has undergone Pediatric Protocol Study Request (PPSR) evaluation by FDA under I.V. palonosetron IND 39,797 (Serial #285, February 14, 2007). A general description of study PALO-99-07 is as follows:

1. Type of Study/Design. A multicenter, randomized, balanced, double-blind, parallel, and stratified study to assess the safety, pharmacokinetics and efficacy of single I.V. doses of palonosetron, 3µg/kg or 10µg/kg, in pediatric cancer patients who were undergoing moderately or highly emetogenic chemotherapy.

2. Age Group and Patient Population. Pediatric cancer patients in the following three age groups were enrolled:

- 28 days to 23 months of age
- 2 to 11 years of age
- 12 to 17 years of age

3. Number of Patients Enrolled. 72 patients were enrolled in P ALO-99-07; 35 completed the study in the 3µg/kg dose group, and 37 patients completed in the 10µg/kg dose group.

4. Status of P ALO-99-07: This study is completed.

B. Oral Palonosetron Pediatric Study. One oral palonosetron pediatric study is planned, tentatively designated study PALO-09-PED. The following outlines characteristics of this planned trial.

1. Type of Study/Design. A multicenter, double-blind, randomized, parallel group, stratified (by age group) dose comparison study design involving two oral palonosetron doses, each given as a single oral dose approximately one hour prior to the start of moderately emetogenic chemotherapy. The aim is to assess the safety and efficacy of oral palonosetron for the prevention of moderately emetogenic CINV in pediatric patients.

Enrolled patients will be randomly allocated equally to two oral dose groups, receiving either approximately the weight-based equivalent of the proposed adult oral dose, 0.50 mg (low dose group), or a higher weight-based oral dose (high dose group). Since I.V. palonosetron pediatric study PALO-99-07 indicated that children have a somewhat greater clearance of palonosetron than adults, a high dose group is planned in this study. The two actual weight-based doses remain to be finalized by the Sponsor based on further consideration and evaluation.

2. Age Group and Patient Population. Pediatric cancer patients in the following two age groups who are scheduled to receive moderately emetogenic chemotherapy are planed to be enrolled:

- 4 to 11 years of age
- 12 to 16 years of age

3. Number of Patients to be Enrolled. Approximately 70 patients are planned to be enrolled in PALO-09-PED, about 35 patients in each of the two dose groups.

4. Planned Study Schedule for P ALO-09-PED:

- Planed Start Date: May 2009
- Planed Completion Date: May 2015
- Date Planed to Submit Final Study Report to FDA: May 2016

Medical Officer's Comment:

- *The sponsor's PPSR for the I.V. formulation has been previously reviewed, and found acceptable.*
- *The Pediatric Review Committee (PeRC) has agreed to a waiver of studies of neonates 0 to <28 days.*
- *All other age groups will receive a deferral.*
- *PeRC has agreed that Infants 28 days to 6 months can be studied using the I.V. formulation only.*
- *The sponsor plans to study the oral formulation in pediatric cancer patients 4 to 16 years. This is the same population studied with oral Ondansetron. Oral Dolasetron was studied in children with MEC age 2 to 16. Further internal discussion will be needed to finalize the pediatric age range needed for the oral formulation.*

8.5 Literature Review

A review of the literature was conducted in order to find placebo-controlled studies using a 5-HT³ receptor antagonist. Of particular interest were studies demonstrating a placebo response in the delayed, 24 to 120 hour period. Such studies have not been found. In the original delayed phase assessments with Ondansetron the studies consisted of dose-response evaluations, and did not include a placebo arm.

9 OVERALL ASSESSMENT

9.1 Conclusions

As discussed elsewhere in this review, the sponsor submitted one pivotal and one supportive Phase 3 study to support the use of palonosetron oral capsules for the prevention of acute (b) (4) nausea and vomiting following chemotherapy with agents of moderate emetogenic potential.

The pivotal study had a non-inferiority (NI) design, in which three oral doses of palonosetron were compared with the approved 0.25 mg I.V. dose, the active comparator. The primary efficacy endpoint was CR from 0 to 24 hours after administration of MEC. As per the non-inferiority design, the oral formulation would demonstrate efficacy by showing that it is not less effective than the control by a margin of -15%.

In the acute phase all three dosages of oral palonosetron fell within the prespecified margin, and a similar percentage of patients did not experience nausea, or require rescue medication (CR).

In the time period from 24 to 120 hours, considered the delayed phase, a clear-cut demonstration of non-inferiority was not obtained with any of the oral doses. However the percentage of patients with complete response was similar between oral and I.V. palonosetron.

(b) (4)



These data are analyzed in the Statistical Review for this NDA. The value of the a posteriori studies is limited due to the fact that they are post-hoc analysis, and utilized data from earlier studies that were not identical to the current study.

From a safety perspective AEs were similar across all treatment groups and do not favor one group over another.

9.2 Recommendation on Regulatory Action

The medical reviewer recommends approval of 0.50 mg palonosetron oral capsules for the prevention of chemotherapy induced nausea and vomiting during the acute, 0 to 24 hour, time period.

The sponsor is requesting the indication of prevention of acute (b) (4) nausea and vomiting associated with the administration of chemotherapeutic agents of moderate emetogenic potential, during initial and repeat administrations of chemotherapy for 0.50 mg palonosetron oral capsules. Acute CINV is defined as nausea and vomiting that occur within 24 hours of receiving chemotherapy, (b) (4)



Efficacy in the acute phase was demonstrated for all 3 oral palonosetron dosages, based on a demonstration of non-inferiority to the active control, I.V. palonosetron with respect to the efficacy parameter of complete response.^{(b) (4)}

The safety of palonosetron was demonstrated in trials supporting the I.V. formulation, and in post-marketing data. In the current submission adverse events are consistent with those already known to be associated with this drug. A dosage of 0.50 mg is recommended for marketing due to its favorable safety and efficacy profile.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

From a clinical perspective no risk management activity is recommended.

9.3.2 Required Phase 4 Commitments

From a clinical perspective no Phase 4 commitments are recommended.

9.4 Labeling Review

The labeling review will be contained in a separate document.

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