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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The results from the single pivotal study PALO-03-13 show that three oral doses of palonosetron are each non-inferior to the IV dose, as measured by complete response during the acute phase (0-24 hours) and a non-inferiority margin of 15%. However, none of the oral doses showed non-inferiority to the IV for the key secondary endpoint, complete response for the delayed phase (24-120 hours). Analysis results based on all secondary endpoints should be considered exploratory, since the sponsor's hierarchical testing procedure failed on the first secondary endpoint. From a statistical perspective, this study has demonstrated comparable efficacy between the oral and IV administrations of palonosetron for the acute phase (b) (4)

1.2 Brief Overview of Clinical Studies

PALO-03-13 was a multi-center, randomized, balanced, stratified, double-blind, double-dummy, parallel group, active control, non-inferiority phase 3 study which designed to assess the efficacy and the safety of single, oral doses of palonosetron, 0.25 mg, 0.50 mg or 0.75 mg, versus a single IV dose of palonosetron 0.25 mg in the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting (CINV). The study included 651 patients from 46 centers in five countries between the ages of 20 and 100, of whom 639 patients received the study treatment. The primary outcome was complete response (CR) for the 0-24 hour interval (acute phase) after the start of the administration of chemotherapy, where CR was defined as no emetic episodes and no rescue medication. The key secondary outcome was CR for the 24-120 hour interval (delayed phase). The study showed the three oral doses of palonosetron were non-inferior to the IV dose for the 0-24 hour time period only. The main focus of this review is on study PALO-03-13.

PALO-03-14 was a multi-center, open-label, uncontrolled phase 3 study to assess the safety and the efficacy of single oral doses of palonosetron 0.75 mg in the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting in repeated and consecutive moderately emetogenic chemotherapy cycles. The study included 217 patients in 22 study centers in four countries. All enrolled patients received a single oral dose of palonosetron 0.75 on Day 1 before each moderately emetogenic chemotherapy cycle, up to a maximum of four consecutive cycles. There were total of 654 cycles observed which consisted of 171 cycles with dexamethasone and 483 cycles without dexamethasone. Anti-emetic efficacy was not formally evaluated but was similar over the four application cycles for both acute and delayed phases.

1.3 Statistical Issues and Findings

The sponsor pre-specified a hierarchical testing procedure, starting with the key secondary endpoint (CR for 24-120 hours). Since this endpoint failed to show the pre-specified non-inferiority, formal statistical testing of the remaining secondary endpoints was stopped. Thus analysis results based on all secondary endpoints should be considered exploratory. From a statistical perspective, this study has demonstrated comparable efficacy between the oral and IV doses for the 0-24 hour time frame (b) (4)

The results from study PALO-03-13 support the effectiveness of the three oral doses as non-inferior to that of IV dose for the acute phase (0-24 hours), assessed by non-inferiority margin of 15%. However, for the delayed phase (24-120 hours), none of the oral doses showed non-inferiority to the IV dose. (b) (4)



The sponsor applied an adaptive randomization strategy to allocate treatment to subjects. The algorithm assigned additional probability to those treatments that were under-represented during the course of the randomization. The scheme used two stratification parameters based on gender and chemotherapy history (naïve, non-naïve). Within each stratum, patients were randomized to receive one of the four palonosetron doses with or without dexamethasone. Normally, for superiority studies, a re-randomization or permutation analysis is performed to assess the impact of the scheme on the validity of the primary endpoint comparisons; however, a re-randomization analysis was not possible for this non-inferiority design. Consequently, there is no rationale to deny the validity of the sponsor's adaptive randomization methods. Please refer to the supplemental review by Wen-Jen Chen, Ph.D., for technical details.

This reviewer conducted subgroup analyses by region, gender, race, age group, chemotherapy history, and dexamethasone use. Complete response rates (acute phase) were generally consistent over these subgroups. However, numerically higher rates were observed for males; for the non-U.S. regions; and for Dexamethasone treated subjects. The complete response rates varied widely among countries; however, due to the small number of patients enrolled in the U.S., no clear conclusions can be drawn regarding U.S. and non-U.S. differences. Complete response rates for chemotherapy naïve and non-naïve subjects were numerically similar.

2. INTRODUCTION

2.1 Overview

Palonosetron is a potent serotonin receptor subtype 3 (5-HT₃) antagonist that is structurally unrelated to other 5-HT₃ receptor antagonists. Intravenous palonosetron is approved in 53 countries around the world including the United States. It is indicated, at a dose of 0.25 mg IV, for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy. (Other commercially available 5-HT₃ receptor antagonists used as anti-emetic therapies include ondansetron, granisetron, and dolasetron).

The sponsor submitted two Phase 3 efficacy studies PALO-03-13 and PALO-03-14 and one Phase 2 dose-ranging study (2332) to support the clinical utility of Palonosetron (Aloxi®) Capsules in the treatment of prevention of acute (b) (4) nausea and vomiting associated with moderately emetogenic chemotherapy. Both phase 3 clinical studies were multinational, multicenter studies, however, only PALO-03-13 was a double blind evaluation whereas PALO-03-14 was an open label, uncontrolled study. The focus of this review is on the one Phase 3 study PALO-03-13. According to sponsor, the ability to use PALO-03-13 as the sole efficacy trial rests on the fact that the dose response relationships for the IV and oral formulations are similar.

In addition, to support their non-inferiority analyses, the sponsor submitted an historical pooled analysis (PALO-07-36) and an exploratory analysis (PALO-07-35). These analyses are addressed in the supplemental review by Wen-Jen Chen, Ph.D.

Table 1: Brief Summary of Phase III Clinical Studies for Oral Palonosetron (Aloxi®) Capsules

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population	Primary Endpoints	Treatments	Number Randomized (ITT)	Design ¹
PALO-03-13 (24 / EU & 7 / Mex & 15 / U S) Jun. 2005 to Aug. 2006	Patients: ≥ 18 years of age; with histologically or cytologically confirmed malignant disease; naïve or non-naïve to cancer chemotherapy; who had a Karnofsky index ≥ 50%.	The primary endpoint was proportion of patients considered to have achieved complete response (CR)* during the first 24 hours after the start of administration of chemotherapy	Palo Oral 0.25 mg Palo Oral 0.50 mg Palo Oral 0.75 mg Palo IV 0.25 mg Total	157 (155) 161 (160) 158 (158) 163 (162) 639 (635)	SD, R, DB, PG, MC, AC
PALO-03-14 (8 / EU & 5 / Mex & 9 / US) Jun 2005 to Apr 2006	CINV patients receiving moderately emetogenic chemotherapy	Proportion of patients considered to have achieved CR during the first 24 hours after the start of each administration of chemotherapy	Repeat Cycle of Palo Oral 0.75 mg	217 (217)	MC, OL, RC, U

¹ SD = Single Dose, R = Randomized, DB = Double-blind, PG = Parallel Group, MC = Multicenter, AC = Active Control, OL = Open-Label, RC = Repeated Cycle, U = Uncontrolled study

2.2 Data Sources

The study reports and additional information for this submission are available in paper format. The SAS data sets are complete and well documented. These items are located in the Electronic Document Room at [\\Fdswa150\nonectd\N22233\N_000](#).

3. STATISTICAL EVALUATION

3.1 Efficacy Evaluation of Study PALO-03-13

3.1.1 Objectives

To compare the effect of single doses of palonosetron 0.25 mg, 0.50 mg and 0.75 mg administered orally versus a single intravenous dose of palonosetron 0.25 mg on efficacy in preventing acute ^{(b) (4)} moderately emetogenic chemotherapy-induced nausea and vomiting (CINV) in patients with cancer.

To assess the safety and tolerability of single doses of palonosetron 0.25 mg, 0.50 mg and 0.75 mg administered orally and their relative safety in comparison with a single intravenous dose of palonosetron 0.25 mg in cancer patients receiving moderately emetogenic chemotherapy.

3.1.2 Study Design

PALO-03-13 was a multi-center, randomized, balanced, stratified, double-blind, double-dummy, parallel group, active control, phase 3 study to assess the efficacy and the safety of single oral doses of palonosetron, 0.25 mg, 0.50 mg or 0.75 mg, versus a single IV dose of palonosetron 0.25 mg in the prevention of moderately emetogenic CINV. The study was planned to be performed in about 40 sites in North America and Europe.

Patients scheduled to receive moderately emetogenic chemotherapy were enrolled in this study. Patients were randomly allocated to receive one of the four palonosetron doses with or without dexamethasone for prevention of CINV. A dynamic or adaptive randomization method was applied. This scheme was used to stratify patients into four strata: male or female, and previous chemotherapy (naïve or non-naïve). Within each stratum, patients were randomized to receive one of the four palonosetron doses with or without dexamethasone (two subgroups for each treatment group).

On Day 1 oral palonosetron (or placebo) was administered in the form of soft gel capsules 60 minutes before the administration of the first emetogenic chemotherapeutic agent; IV palonosetron (or placebo) was administered as a bolus over 30 seconds starting 30 minutes prior to administration of the first emetogenic chemotherapeutic agent. IV dexamethasone (or placebo) was administered after palonosetron IV (or placebo) injection 30 minutes before the start of the first emetogenic chemotherapy.

Demographic and baseline characteristics (including medical history, cancer treated in this study, concomitant illnesses, prior and concomitant medication, physical examination, vital signs, 12-lead ECG (in triplicate) and laboratory values) are documented at a screening visit. Efficacy and safety is assessed at three additional visits (Days 1, 2 and 6-8) and by one telephone contact or visit (Day 15). Patient diaries are used to record emetic episodes, use of rescue medication and severity of nausea as well as patients' satisfaction with anti-emetic therapy up to 120 hours after start of chemotherapy.

3.1.3 Data Sets for Analysis

The analysis data sets are summarized in Table 2. The safety set is defined as all patients treated and have at least one safety assessment after treatment. "Patients treated" is defined as any patient who received any study medication (palonosetron).

The full analysis set (FAS) is defined as all randomized patients who received the study medication and at least moderately emetogenic chemotherapy. The analysis based on the FAS is considered as primary analysis for all efficacy parameters.

The per-protocol (PP) set is defined as all patients who completed Day 1 (primary endpoint) and who were compliant with the study protocol. Patients who dropped out due to related adverse events are considered in the PP set. Minor violations not leading to exclusion from the PP set are defined during a blind review meeting after data cleaning.

Table 2: Analysis sets and number of patients

Analysis set	Oral	Oral	Oral	IV
	Palonosetron	Palonosetron	Palonosetron	Palonosetron
	0.25 mg	0.50 mg	0.75 mg	0.25 mg
	n	n	n	n
Safety (N = 639)	157	161	158	163
Full analysis (N = 635)	155	160	158	162
Sensitivity analysis for 0-24 h interval (N = 631)	154	159	158	160
Sensitivity analysis for 24-120 h interval (N = 631)	153	159	158	161
Per-protocol (N = 591)	143	152	149	147

(Source: Clinical Study Report: Study PALO-03-13; Table 6.3-a, page 93)

3.1.4 Efficacy Endpoints and Analyses

Primary and key secondary efficacy endpoints and analyses

The Primary efficacy endpoint was complete response (CR) (defined as no emetic episodes and no rescue medication) for the 0-24 hour interval after the start of the administration of the moderate emetogenic chemotherapeutic agent.

A key secondary endpoint was CR for the 24-120 hour interval.

The efficacy hypothesis was that at least one dose of oral palonosetron was non-inferior to the IV dose of palonosetron (0.25 mg) using a maximum delta of 15%, considering the complete response (CR) rate at 24 hours. The same applied to 24-120 hour interval.

To test the null hypothesis, the lower bound of the two-sided 98.3% confidence interval of the difference between the proportions of CR in each oral and IV dose of palonosetron was compared to the pre-set threshold of -15% . In addition, 95% confidence intervals were computed for the proportions. The analysis of the primary and key secondary efficacy parameter was done for the FAS and PP set. The formulas used, as specified in the statistical analysis plan, were as follow:

Confidence interval for rates:

$$P_L = \frac{\left(2np + c_{\alpha/2}^2 - 1\right) - c_{\alpha/2} \sqrt{c_{\alpha/2}^2 - \left(2 + \frac{1}{n}\right) + 4p(nq + 1)}}{2\left(n + c_{\alpha/2}^2\right)}$$

$$P_U = \frac{\left(2np + c_{\alpha/2}^2 + 1\right) + c_{\alpha/2} \sqrt{c_{\alpha/2}^2 + \left(2 - \frac{1}{n}\right) + 4p(nq - 1)}}{2\left(n + c_{\alpha/2}^2\right)}$$

$$q = 1 - p$$

n = number of observations

$c = \alpha$ - fractile of standard normal distribution

Confidence interval for difference between two rates:

$$(P_2 - P_1)_L = (p_2 - p_1) - c_{\alpha/2} \sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2} - \frac{1}{2} \left(\frac{1}{n_1} + \frac{1}{n_2} \right)}$$

$$(P_2 - P_1)_U = (p_2 - p_1) + c_{\alpha/2} \sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2} + \frac{1}{2} \left(\frac{1}{n_1} + \frac{1}{n_2} \right)}$$

$$q_1 = 1 - p_1, q_2 = 1 - p_2$$

n_1 = number of observations in group 1

n_2 = number of observations in group 2

$c = \alpha$ - fractile of standard normal distribution

In addition, to identify factors potentially influencing CR rates, logistic regression analysis was performed, adjusted by confounders, e.g. gender, age, chemotherapeutic history, use of dexamethasone, chemotherapeutic treatment, country/region and study treatment.

The sponsor performed a sensitivity analysis for the primary and key secondary endpoint. This analysis excluded patients that had incomplete or discrepant information in their diary card records. Patients with partly or completely missing data for the primary and key secondary efficacy variable were classified as not having a complete response following the worst case principle.

Additional secondary efficacy endpoints and analyses

- CR daily for the 24-120 hour interval, for cumulative time intervals (0-48 hours, 0-72 hours and 0-96 hours) and for the overall 0-120 hour interval (Days 1-5)

- Complete control (CC) (defined as complete response 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
- Number of emetic episodes daily for the 0-120 hour interval and for the overall 0-120 hour interval (Days 1-5)
- Time to first emetic episode
- Time to first administration of rescue therapy
- Time to treatment failure (time to first emetic episode or to administration of rescue therapy, whichever will occur first)
- Severity of nausea (4-point Likert scale) daily for the 0-120 hour interval
- 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
- 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
- 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
- Patient global satisfaction with anti-emetic therapy (VAS) daily for the 0-120 hour interval

In clinical study results of POLO-03-13, the sponsor stated that “Although not fully detailed in the study protocol and in the SAP, the meaning of ‘key secondary efficacy variable’ implied an order of importance for the interpretation of the data: first the primary efficacy variable, then the key secondary efficacy variable and thereafter all the other secondary efficacy variables.” For all secondary efficacy variables except CR, the differences between the three oral doses of palonosetron were tested using a two-sided test with $\alpha = 0.05$ following a closed testing procedures. First, an overall comparison (between the three oral doses of palonosetron) was performed. In case of significance, pairwise comparisons were done without the need for further adjustment of α .

CR on a daily basis (24-48, 48-72, 72-96 and 96-120 hour time periods), during the cumulative 0-48, 0-72, 0-96, and overall 0-120 hour time periods) were examined using the same statistical methods as for the primary efficacy variable. A sensitivity analysis similar to the primary endpoint was done for the key secondary efficacy variable only.

The proportion of patients who did / did not experience emesis, the proportion of patients who did / did not experience nausea and the proportion of patients who needed/did not need rescue medication was calculated daily for the 0-120 hour interval, the overall 0-120 hour interval and for the 24-120 hour interval. The comparison between treatment groups was done using Chi-square test.

Additional subgroup analyses

Subgroup analyses for the FAS were conducted by country, by gender (male/female), by age (<65 years, ≥ 65 years), by chemotherapy history (naïve/non-naïve), by use of dexamethasone (yes/no) and by most frequently used chemotherapeutic agents / combinations.

Determination of sample size

The total sample size of 640 patients, or 160 patients per treatment group, was based on the assumption of a responder rate during the first 24 hours of 80% in the palonosetron IV dose (with half of the population taking dexamethasone) and a delta of no more than 15% in the complete response rate. For a one-sided test of equivalence, using $\alpha = 0.008$ (obtained as type I error / number of comparisons = $0.025 / 3$), a sample size of 151 evaluable patients per group will be needed to ensure 80% power for each comparison. The number is rounded up to 160 patients per group.

Handling of missing data

Missing or incomplete data for efficacy variables on Day 1 were replaced according to worst case assumptions using the worst value observed in the FAS for the same variable. Missing or incomplete data on Days 2-5 were replaced by the last value available using the LOCF method. This imputation method was used for nausea, intake of rescue medication, patient global satisfaction and number of emetic episodes. Complete response and complete control were then calculated from the completed data.

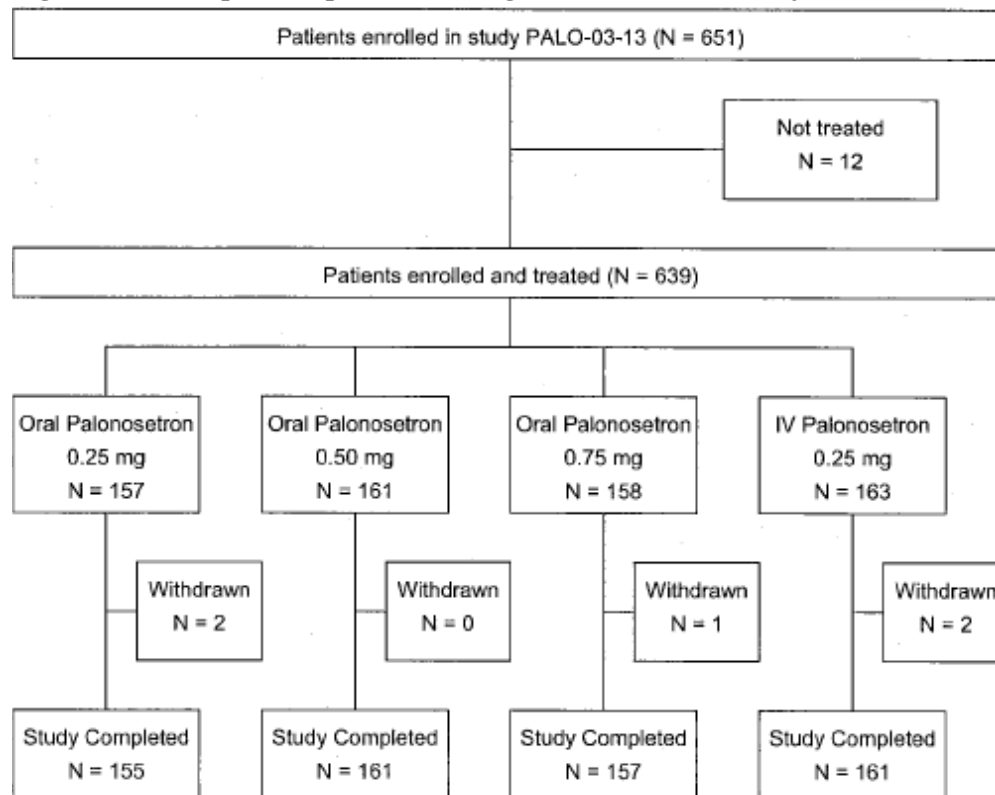
3.1.5 Efficacy Results

3.1.5.1 Study Population

The patient disposition is summarized in Figure 1 and Table 3. A total of 46 centers enrolled 651 patients of whom 639 patients received the study treatment. Twelve patients (patient no. 0001 at site 127, patient no. 0001 at site 902, and patient nos. 0002, 1876, 1943, 2003, 2068, 2074, 2200, 3067, 3148, and 3157) did not receive any study medication. One patient (patient no. 1003) received only the oral study medication because she experienced an adverse event afterwards. This patient did not receive the IV study medication and chemotherapy, but was eligible for the safety set as she was randomized to and treated in the oral palonosetron 0.25 mg study group.

This review also conducted the patient enrollment study by country. As seen in Table 4, the study enrollment duration for Romania was only 21 days which was much less than any other country. Additional information was request. According to the response from the Sponsor, Romania was added toward the end of the study due to enrollment being behind schedule.

Figure 1: Description of patients during the course of the study



(Source: Clinical Study Report: Study PALO-03-13; Figure 6.1-a, page 87)

Table 3: Summary of patient disposition (All patients)

Number of patients	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)		Not treated (N = 12)	
	n	%	n	%	n	%	n	%	n	%
Who never received any study drug	0	0.0	0	0.0	0	0.0	0	0.0	12	100.0
Treated	157	100.0	161	100.0	158	100.0	163	100.0	0	0.0
Who completed study	155	98.7	161	100.0	157	99.4	161	98.8	0	0.0
Withdrawn during study	2	1.3	0	0.0	1	0.6	2	1.2	12	100.0
Due to										
Serious adverse event/death	0	0.0	0	0.0	1	0.6	0	0.0	0	0.0
Non-serious adverse event	1	0.6	0	0.0	0	0.0	0	0.0	1	8.3
Violation of in-/exclusion criteria	0	0.0	0	0.0	0	0.0	0	0.0	4	33.3
Patient lost to follow-up	1	0.6	0	0.0	0	0.0	2	1.2	0	0.0
Patient's decision	0	0.0	0	0.0	0	0.0	0	0.0	2	16.7
Investigator's decision	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other reason	0	0.0	0	0.0	0	0.0	0	0.0	5	41.7

(Source: Clinical Study Report: Study PALO-03-13; Table 6.1-b, page 88)

Table 4: Enrollment by Country (All Patients)

COUNTRY	# of Patient	% of Total	# of Sites	Starting Enrollment Date	Ending Enrollment Date	Study Enrollment Duration (Days)
Czech Republic	109	17%	11	6-Dec-05	19-Jul-06	226
Mexico	174	27%	7	1-Aug-05	19-May-06	292
Poland	119	18%	7	14-Nov-05	19-Jul-06	248
Romania	121	19%	6	29-Jun-06	19-Jul-06	21
US	128	20%	15	21-Jun-05	18-Jul-06	393
Total	651	100%	46	21-Jun-05	19-Jul-06	394

Baseline demographic and disease characteristics of the safety population are summarized in Appendix, Table 36. In general, demographic and anamnestic data were comparable for the four treatment groups. More than 70% of patients in all treatment groups were female. The ages of patients were from 18 to 87 with average of 56 to 58 in four treatment groups. The majorities of patients were White, chemotherapy naïve before the study, non-smokers, consumed no alcohol and were not of childbearing potential. In the oral 0.50 mg palonosetron group, a slightly higher frequency of smokers was seen compared to the other treatment groups.

The sponsor also conducted baseline study by cancer history. Breast cancer was the most frequently reported cancer treated in this study and was treated in more than 50% of patients in all four treatment groups.

3.1.5.2 Efficacy Results for Primary and Key Secondary Endpoint

The primary efficacy variable was the proportion of patients considered to have achieved complete response (CR) during the first 24 hours (acute phase) after the first administration of the emetogenic chemotherapeutic agent, whereas complete response during the 24-120 hour period (delayed phase) after administration of chemotherapy was the key secondary efficacy variable.

The 95% confidence intervals for primary and a key secondary endpoint are presented in Table 5 and Table 6 for FAS and PP set, respectively. The confidence intervals for differences between the oral and IV treatment groups are shown in Table 7 and Table 8 for FAS and PP set, respectively.

Table 5: Proportion of patients achieving CR during first 24 and 24 -120 hours from start of chemotherapy (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	CR%	95% CI (%)	n	CR%	95% CI (%)	n	CR%	95% CI (%)	n	CR%	95% CI (%)
0 – 24 Hr	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)
24 – 120 Hr	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)

Table 6: Proportion of patients achieving CR during first 24 and 24 -120 hours from start of chemotherapy (Per-protocol set, N = 591)

Time Period	Oral Palonosetron 0.25 mg (N = 143)			Oral Palonosetron 0.50 mg (N = 152)			Oral Palonosetron 0.75 mg (N = 149)			IV Palonosetron 0.25 mg (N = 147)		
	n	CR%	95% CI (%)	n	CR%	95% CI (%)	n	CR%	95% CI (%)	n	CR%	95% CI (%)
0 – 24 Hr	111	77.6	(69.7, 84.0)	122	80.3	(72.9, 86.1)	114	76.5	(68.7, 82.9)	111	75.5	(67.6, 82.1)
24 – 120 Hr	85	59.4	(50.9, 67.5)	98	64.5	(56.3, 71.9)	91	61.1	(52.7, 68.8)	102	69.4	(61.2, 76.6)

Table 7: Complete response during the first 24 and 24-120 hours: confidence intervals for differences between oral and IV treatment groups (Full analysis set, N = 635)

Time Period	Oral Palonosetron 0.25 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.50 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.75 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval
0 – 24 Hr	(-9.5, 15.8)	(-6.5, 18.2)	(-8.9, 16.3)
24 – 120 Hr	(-19.7, 7.5)	(-16.3, 10.5)	(-18.8, 8.2)

Table 8: Complete response during the first 24 and 24-120 hours: confidence intervals for differences between oral and IV treatment groups (Per-protocol set, N = 591)

Time Period	Oral Palonosetron 0.25 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.50 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.75 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval
0 – 24 Hr	(-10.5, 14.7)	(-7.4, 16.9)	(-11.5, 13.5)
24 – 120 Hr	(-24.0, 4.1)	(-18.6, 8.7)	(-22.2, 5.5)

According to the statistical hypothesis, non-inferiority of the oral palonosetron doses to the IV palonosetron dose 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 IV treatment group was above the pre-set threshold of -15%. As shown in Table 7 and Table 8, the non-inferiority of the three oral doses to IV dose are achieved when assessed by the primary endpoint for both FAS and PP set. However, for the delayed phase (24-120 hours), none of the lower bounds for the three oral doses on the complete response rate differences is above -15% of the non-inferiority margin. It indicates that none of the three oral doses is non-inferior to IV dose when assessed by the key secondary endpoint. Since the complete response rate of 0.75 mg is not larger than that of 0.50 mg, dose response is not supported.

3.1.5.3 Efficacy Results for Other Secondary Endpoints

This section presents results for two secondary efficacy endpoints, which the clinical reviewer deemed clinically useful. These results are descriptive only, as the statistical significance of the comparisons was not prospectively adjusted for the multiple comparisons. Additional secondary efficacy endpoint results are presented in the Appendix.

Complete response at further time periods

In addition to the analyses for the primary and the key secondary efficacy variables, complete response was analyzed for the cumulative time intervals 0-48 hours, 0-72 hours, 0-96 hours, for the overall 0-120 hour time interval and daily for the 24-120 hour time interval.

Complete response for the cumulative time periods is shown in Table 9, while Table 10 provides 98.3% confidence intervals for the differences between the oral and IV treatment groups with respect to complete response rates for the cumulative time periods. Results of the analysis of complete response daily for the 24-120 hour interval are provided in Table 11. The Table 12 provides the confidence intervals for the differences between oral and IV treatment groups with regard to the complete response per day.

Table 9: Patients with complete response after start of chemotherapy, cumulative time periods (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	CR%	95% CI (%)	n	CR%	95% CI (%)	n	CR%	95% CI (%)	n	CR%	95% CI (%)
0 – 48 Hr	97	62.6	(54.4, 70.1)	103	64.4	(56.4, 71.7)	102	64.6	(56.5, 71.9)	104	64.2	(56.2, 71.5)
0 – 72 Hr	92	59.4	(51.2, 67.1)	98	61.3	(53.2, 68.7)	94	59.5	(51.4, 67.1)	101	62.3	(54.4, 69.7)
0 – 96 Hr	85	54.8	(46.7, 62.8)	94	58.8	(50.7, 66.4)	86	54.4	(46.3, 62.3)	98	60.5	(52.5, 68.0)
0 – 120 Hr	83	53.5	(45.4, 61.5)	94	58.8	(50.7, 66.4)	84	53.2	(45.1, 61.1)	96	59.3	(51.3, 66.8)

Table 10: Complete response (cumulative time periods): confidence intervals for differences between oral and IV treatment groups (Full analysis set, N = 635)

Time Period	Oral Palonosetron 0.25 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.50 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.75 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval
0 – 48 Hr	(-15.17%, 11.93%)	(-13.19%, 13.54%)	(-13.05%, 13.76%)
0 – 72 Hr	(-16.71%, 10.73%)	(-14.64%, 12.45%)	(-16.49%, 10.79%)
0 – 96 Hr	(-19.52%, 8.21%)	(-15.42%, 11.93%)	(-19.86%, 7.73%)
0 – 120 Hr	(-19.62%, 8.20%)	(-14.21%, 13.20%)	(-19.94%, 7.75%)

Table 11: Patients with complete response after start of chemotherapy (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	CR%	95% CI (%)	n	CR%	95% CI (%)	n	CR%	95% CI (%)	n	CR%	95% CI (%)
24 – 48 Hr	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 Hr	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 Hr	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 Hr	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)

Table 12: Complete response (per day): confidence intervals for differences between oral and IV treatment groups (Full analysis set, N = 635)

Time Period	Oral Palonosetron 0.25 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.50 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.75 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval
24 – 48 Hr	(-19.48%, 5.69%)	(-17.68%, 7.07%)	(-14.06%, 10.31%)
48 – 72 Hr	(-15.82%, 7.58%)	(-18.28%, 5.29%)	(-15.95%, 7.35%)
72 – 96 Hr	(-11.81%, 10.19%)	(-15.20%, 7.25%)	(-16.93%, 5.89%)
96 – 120 Hr	(-13.25%, 6.92%)	(-9.02%, 9.95%)	(-9.24%, 9.85%)

Complete control

The proportion of patients who were considered to have achieved complete control (defined as complete response and no more than mild nausea) daily for the 0-120 hour interval, for cumulative time intervals (0-48 hours, 0-72 hours, 0-96 hours and 24-120 hours) and for the overall 0-120 hour interval (Days 1-5) was used to further investigate the efficacy of palonosetron in this study. As shown in Table 13 and Table 14, similar trends are seen as for complete response.

Table 13: Patients with complete control after start of chemotherapy (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	CC%	95% CI (%)	n	CC%	95% CI (%)	n	CC%	95% CI (%)	n	CC%	95% CI (%)
0 – 24 Hr	106	68.4	(60.4, 75.5)	119	74.4	(66.8, 80.8)	115	72.8	(65.0, 79.4)	111	68.5	(60.7, 75.5)
24 – 120 Hr	80	51.6	(43.5, 59.7)	90	56.3	(48.2, 64.0)	93	58.9	(50.7, 66.5)	101	62.3	(54.4, 69.7)
0 – 48 Hr	89	57.4	(49.2, 65.2)	97	60.6	(52.6, 68.2)	100	63.3	(55.2, 70.7)	99	61.1	(53.1, 68.6)
0 – 72 Hr	82	52.9	(44.8, 60.9)	91	56.9	(48.8, 64.6)	91	57.6	(49.5, 65.3)	95	58.6	(50.6, 66.2)
0 – 96 Hr	73	47.1	(39.1, 55.2)	84	52.5	(44.5, 60.4)	84	53.2	(45.1, 61.1)	93	57.4	(49.4, 65.1)
0 – 120 Hr	70	45.2	(37.2, 53.3)	84	52.5	(44.5, 60.4)	82	51.9	(43.8, 59.9)	91	56.2	(48.2, 63.9)
24 – 48 Hr	99	63.9	(55.7, 71.3)	106	66.3	(58.3, 73.4)	114	72.2	(64.4, 78.8)	118	72.8	(65.2, 79.4)
48 – 72 Hr	111	71.6	(63.7, 78.4)	110	68.8	(60.9, 75.7)	116	73.4	(65.7, 80.0)	123	75.9	(68.5, 82.1)
72 – 96 Hr	117	75.5	(67.8, 81.9)	118	73.8	(66.1, 80.2)	121	76.6	(69.1, 82.8)	127	78.4	(71.1, 84.3)
96 – 120 Hr	125	80.6	(73.4, 86.4)	135	84.4	(77.6, 89.4)	136	86.1	(79.5, 90.9)	137	84.6	(77.9, 89.6)

Table 14: Complete control: confidence intervals for differences between oral and IV treatment groups (Full analysis set, N = 635)

Time Period	Oral Palonosetron 0.25 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.50 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.75 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval
0 – 24 Hr	(-13.2, 13.0)	(-6.8, 18.5)	(-8.5, 17.0)
24 – 120 Hr	(-24.6, 3.1)	(-19.8, 7.6)	(-17.1, 10.2)
0 – 48 Hr	(-17.49, 10.11)	(-14.09, 13.12)	(-11.38, 15.74)
0 – 72 Hr	(-19.67, 8.19)	(-15.53, 11.99)	(-14.84, 12.74)
0 – 96 Hr	(-24.27, 3.65)	(-18.75, 8.93)	(-18.12, 9.64)
0 – 120 Hr	(-24.97, 2.95)	(-17.54, 10.19)	(-18.19, 9.64)
24 – 48 Hr	(-22.02, 4.09)	(-19.42, 6.25)	(-13.23, 11.85)
48 – 72 Hr	(-16.73, 8.11)	(-19.66, 5.31)	(-14.74, 9.72)
72 – 96 Hr	(-14.84, 9.01)	(-16.60, 7.31)	(-13.58, 9.96)
96 – 120 Hr	(-14.72, 6.87)	(-10.45, 10.06)	(-8.56, 11.57)

Severity of nausea:

Severity of nausea was evaluated by patients using a 4-point Likert scale and recorded in their diaries on a daily basis throughout the 0-120 hour interval (Days 1 to 5). As presented in Table 38, in general, no clear differences between the four treatment groups were evident on a daily basis for the percentage of patients without nausea and for the different severity grades of nausea except for day 2.

Table 15: Severity of nausea (patients with / without nausea) (Full analysis set, N = 635)

Period	Nausea	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	63	40.6	66	41.3	59	37.3	69	42.6
	Without	92	59.4	94	58.8	99	62.7	93	57.4
>24 – 48 h	With	72	46.5	72	45.0	64	40.5	64	39.5
	Without	83	53.5	88	55.0	94	59.5	98	60.5
>48 – 72 h	With	65	41.9	63	39.4	60	38.0	60	37.0
	Without	90	58.1	97	60.6	98	62.0	102	63.0
>72 – 96 h	With	52	33.5	52	32.5	45	28.5	56	34.6
	Without	103	66.5	108	67.5	113	71.5	106	65.4
>96 – 120 h	With	42	27.1	40	25.0	31	19.6	47	29.0
	Without	113	72.9	120	75.0	127	80.4	115	71.0
>24 – 120 h	With	90	58.1	81	50.6	85	53.8	85	52.5
	Without	65	41.9	79	49.4	73	46.2	77	47.5
0 – 120 h	With	96	61.9	87	54.4	92	58.2	93	57.4
	Without	59	38.1	73	45.6	66	41.8	69	42.6

(Source: Clinical Study Report: Study PALO-03-13; Table 7.1-v, page 145)

During the labeling review phase, the sponsor pointed out that the proportion of the patients without nausea was clinically important. This reviewer performed additional analysis, similar to that used for the primary endpoint. As shown in Table 16 and Table 17, non-inferiority of oral Palonosetron 0.50 mg to IV dose was indicated for all three periods, assessed by a non-inferiority margin of 15%. Because the sponsor used the closed test principle and failed to reject the null non-inferiority hypothesis for the key secondary endpoint, analyses for all secondary endpoints should be considered exploratory and not appropriate for labeling.

Table 16: Without Nausea after start of chemotherapy (Full analysis set, N = 635) (Reviewer's Results)

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	CR%	95% CI (%)	n	CR%	95% CI (%)	n	CR%	95% CI (%)	n	CR%	95% CI (%)
0 – 24 Hr	92	59.4	(51.2, 67.1)	94	58.8	(50.7, 66.4)	99	62.7	(54.6, 70.1)	93	57.4	(49.4, 65.1)
24 – 48 Hr	65	41.9	(34.1, 50.1)	79	49.4	(41.4, 57.4)	73	46.2	(38.3, 54.3)	77	47.5	(39.7, 55.5)
0 – 120 Hr	59	38.1	(30.5, 46.2)	73	45.6	(37.8, 53.7)	66	41.8	(34.1, 49.9)	69	42.6	(34.9, 50.6)

Table 17: Without Nausea: confidence intervals for differences between oral and IV treatment groups (Full analysis set, N = 635) Reviewer's Results

Time Period	Oral Palonosetron 0.25 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.50 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.75 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval
0 – 24 Hr	(-11.9, 15.8)	(-12.4, 15.1)	(-8.4, 18.9)
24 – 120 Hr	(-19.5, 8.4)	(-12.1, 15.8)	(-15.3, 12.6)
0 – 120 Hr	(-18.3, 9.2)	(-10.8, 16.9)	(-14.6, 13.0)

Time to treatment failure

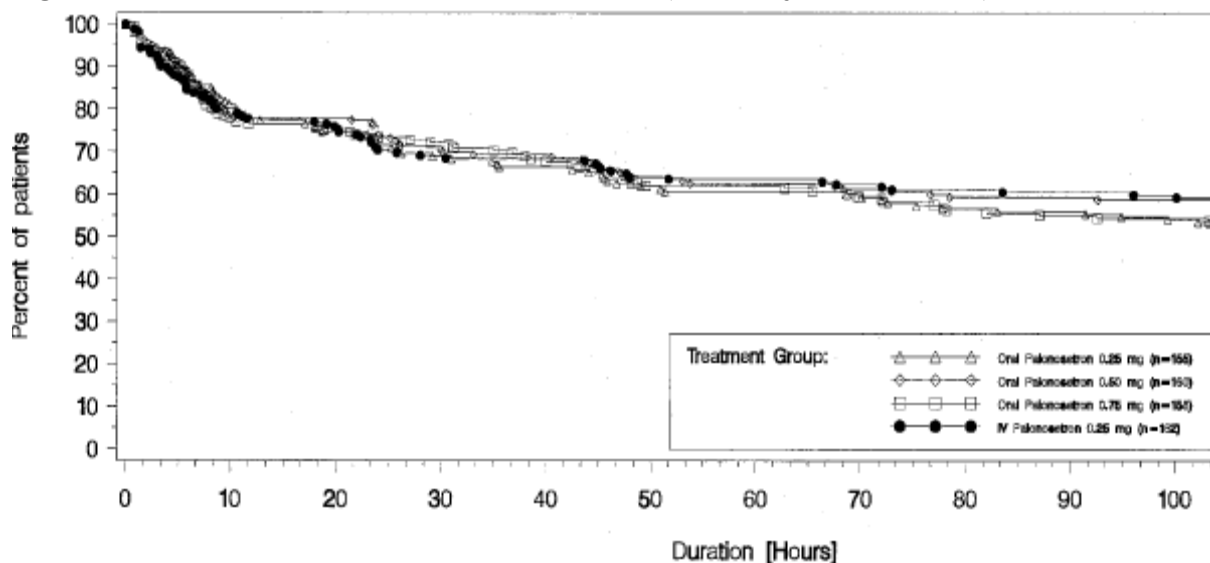
The time to treatment failure (time to first emetic episode or to administration of rescue medication, whichever occurred first) was evaluated as a further efficacy variable. Table 18 displays the median time to treatment failure. Since more than 50% of patients were considered censored at the end of 120 hour, only 25% quantiles were presented. The survival curve for time to treatment failure is shown in Figure 2.

Table 18: Median time (h) to treatment failure (Full analysis set, N = 635)

Time period [hours]	Oral Palonosetron 0.25 mg (N = 155) 25% Quantile Median*	Oral Palonosetron 0.50 mg (N = 160) 25% Quantile Median*	Oral Palonosetron 0.75 mg (N = 158) 25% Quantile Median*	IV Palonosetron 0.25 mg (N = 162) 25% Quantile Median*
0-120	18.7 >120	24.0 >120	21.4 >120	20.3 >120

(Source: Clinical Study Report: Study PALO-03-13; Table 7.1-z, page 153)

Figure 2: Time to treatment failure: survival curve (Full analysis set, N = 635)



(Source: Clinical Study Report: Study PALO-03-13; Table 7.1-z, page 154)

3.1.5.4 Sponsor's Sensitivity Efficacy Analyses

A sensitivity analysis was done for primary and key secondary endpoint. This analysis excluded patients that had incomplete or discrepant information in their diary card records. As shown in Table 19 and Table 20, the results of the sensitivity analysis were similar to the results obtained for the primary and key secondary endpoint based on the FAS.

Table 19: Sensitivity Analysis: Patients with complete response after start of chemotherapy (Full analysis sensitivity set)

Time Period	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	154	114	74.0	(66.2, 80.6)	159	122	76.7	(69.2, 82.9)	158	117	74.1	(66.4, 80.5)	160	114	71.3	(63.5, 78.0)
24 – 120 Hr	153	92	60.1	(51.9, 67.9)	159	100	62.9	(54.8, 70.3)	158	95	60.1	(52.0, 67.7)	161	106	65.8	(57.9, 73.0)

Table 20: Sensitivity Analysis of Complete response: confidence intervals for differences between oral and IV treatment groups (Full analysis sensitivity set)

Time Period	Oral Palonosetron 0.25 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.50 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.75 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval
0 – 24 Hr	(-9.9, 15.4)	(-6.9, 17.8)	(-9.8, 15.4)
24 – 120 Hr	(-19.3, 7.9)	(-16.3, 10.5)	(-19.2, 7.8)

3.1.5.5 Statistical Reviewer's Results and Comments

This reviewer confirmed the sponsor's findings for the primary and key secondary endpoints. The findings for secondary endpoints should be considered exploratory since type I error was not controlled for the multiple doses and multiple endpoints.

The sponsor's sensitivity analyses showed that efficacy conclusions are not affected by different analyze populations. Patients with partly or completely missing data for the primary efficacy variable were classified as not having complete response. The missing or incomplete data on Days 2-5 were replaces using LOCF method. There is no review issue regarding missing data.

For the acute phase (0-24 hours), efficacy for the three oral doses is non-inferior to that of the IV dose, as assessed by a non-inferiority margin of 15%. However, for the delayed phase (24-120 hours), none of the three oral doses is non-inferior to IV dose. The results from secondary endpoints provide supportive but exploratory evidence for non-inferiority of oral doses in acute phase; for the delayed phase, the secondary results indicate that the oral dose may be less efficacious as the IV.

3.2 Brief Efficacy Evaluation of Study PALO-03-14

PALO-03-14 was a multi-center, open-label, repeated cycle, and uncontrolled phase3 study to assess the safety and the efficacy of single oral doses of palonosetron 0.75 mg in the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting in repeated and consecutive moderately emetogenic chemotherapy cycles. All enrolled patients received a single oral dose of palonosetron 0.75 mg on Day 1 before each moderately emetogenic chemotherapy

cycle, up to a maximum of four consecutive cycles. The minimal time interval between two consecutive study medications was 7 days.

The efficacy of oral palonosetron 0.75 mg was evaluated in each cycle. The efficacy variables of main interests in this study were complete response for the 0-24 hour interval and for the 24-120 hour interval after the start of administration of chemotherapy. All analyses variables were performed for the FAS only which was defined as all patients with at least one cycle of moderately emetogenic chemotherapy and with administration of oral palonosetron 0.75 mg.

The study enrolled 223 patients in 22 study centers in four countries. Of the 223 patients, 217 were treated with at least one cycle of study medication. There were total of 654 cycles observed which consisted of 171 cycles with dexamethasone and 483 cycles without dexamethasone.

The percentage of cycles with complete response for the 0-24, 24-120 and 0-120 hour intervals is shown by cycle in Table 21. The percentage of cycles in which patients showed a complete response was higher for both the 0-24 and the >24-120 hours periods when palonosetron was given together with dexamethasone (73.9% and 63.1 %, respectively) than when palonosetron was given alone (61.4% and 59.6 %, respectively). In general, the anti-emetic efficacy for 0-24 hour and 24-120 hour interval was similar throughout the 4 repeated and consecutive study cycles.

Table 21: 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

(Source: Clinical Study Report: Study PALO-03-14; Table 1, page 12)

3.3 Evaluation of Safety

The evaluation of safety can be found in the clinical reviewer's report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Gender

A subgroup analysis by gender was performed by sponsor for primary and key secondary endpoints. As shown in Table 22, the percentage of patients with complete response during the first 24 hours and from 24 to 120 hours was higher in male than in female patients. Non-inferiority to the IV comparator group was indicated 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 administration to the IV group was indicated for all three oral palonosetron doses.

Table 22: 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 23: 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)

4.1.2 Race

A subgroup analysis by race was conducted by this reviewer but not by the sponsor. As shown in Table 36, about 70% subjects were white and 28% Hispanic. We combined the race into white and others and the results are presented in Table 24 and Table 25. In general, there were higher complete response rates in White patients than in non-white. Non-inferiority of all three oral palonosetron doses to IV palonosetron was indicated in White patients. In non-white patients, only oral palonosetron 0.50 mg appears to be non-inferior to IV palonosetron 0.25 mg.

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

Time Period	Race	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	White	109	84	77.1	(67.8, 84.3)	112	87	77.7	(68.6, 84.8)	106	83	78.3	(69.0, 85.5)	114	87	76.3	(67.3, 83.6)
	Others	46	30	65.2	(49.7, 78.2)	48	35	72.9	(57.9, 84.3)	52	34	65.4	(50.8, 77.7)	48	27	56.3	(41.3, 70.2)
24 – 120 Hr	White	109	66	60.6	(50.7, 69.6)	112	76	67.9	(58.3, 76.2)	106	67	63.2	(53.2, 72.2)	114	83	72.8	(63.5, 80.5)
	Others	46	26	56.5	(41.2, 70.8)	48	24	50.0	(35.4, 64.6)	52	28	53.8	(39.6, 67.5)	48	23	47.9	(33.5, 62.6)

Table 25: Complete response (0-24 and 24-120 hours): confidence intervals for differences between oral and IV treatment groups (Full analysis set, subgroups: race, N = 635)

Time Period	Race	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	White	(-13.7, 15.2)	(-12.9, 15.6)	(-12.4, 16.4)
	Others	(-17.1, 35.0)	(-8.4, 41.7)	(-16.1, 34.4)
24 – 120 Hr	White	(-28.1, 3.6)	(-20.3, 10.4)	(-25.5, 6.3)
	Others	(-18.0, 35.2)	(-24.4, 28.5)	(-19.9, 31.8)

4.1.3 Age

The results by age group (< 65 and ≥ 65) are presented in Table 26 and Table 27. In general, the percentages of patients with complete response in all treatment groups were higher in patients with age ≥ 65 except for the 0.50 mg group. The complete response rates in the acute phase were not consistent across the two age groups since the highest complete response rate achieved in the oral palonosetron 0.50 mg group was for age < 65 while the highest response rate achieved in the 0.25 mg group was for age ≥ 65 .

Table 26: 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 27: 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)

4.2 Other Special/Subgroup Populations

4.2.1 Region

We conducted analysis for primary and key secondary endpoints by U.S. vs. non-U.S., in addition to analyses by country, which was also submitted by the sponsor. The results are presented in Table 28 and Table 29. In general, the highest percentages of patients with complete response in all treatment groups were in Romania, whereas the percentages of patients with complete response were lowest for U.S. Non-inferiority is indicated for Non-U.S. and for the oral palonosetron 0.50 mg versus the IV palonosetron group in Mexico, while in all the other countries all three oral doses do not indicate a trend toward non-inferiority. Since the numbers of patients per country are small, one should not draw conclusions of regional differences.

Table 28: Patients with complete response during 0-24 and 24-120 hour time period from start of chemotherapy (Full analysis set, subgroups: region, N = 635)

Time Period	Region	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	US	32	19	59.4	(40.8, 75.8)	30	17	56.7	(37.7, 74.0)	26	18	69.2	(48.1, 84.9)	37	20	54.1	(37.1, 70.2)
	Non-US	123	95	77.2	(68.6, 84.1)	130	105	80.8	(72.7, 86.9)	132	99	75.0	(66.6, 81.9)	125	94	75.2	(66.5, 82.3)
	Czech Republic	25	18	72.0	(50.4, 87.1)	29	19	65.5	(45.7, 81.4)	25	17	68.0	(46.4, 84.3)	28	19	67.9	(47.6, 83.4)
	Poland	29	21	72.4	(52.5, 86.6)	27	23	85.2	(65.4, 95.1)	33	23	69.7	(51.1, 83.8)	30	25	83.3	(64.5, 93.7)
	Romania	27	26	96.3	(79.1, 99.8)	32	30	93.8	(77.8, 98.9)	29	28	96.6	(80.4, 99.8)	27	26	96.3	(79.1, 99.8)
	Mexico	42	30	71.4	(55.2, 83.8)	42	33	78.6	(62.8, 89.2)	45	31	68.9	(53.2, 81.4)	40	24	60.0	(43.4, 74.7)
24 – 120 Hr	US	32	16	50.0	(32.2, 67.8)	30	15	50.0	(31.7, 68.3)	26	14	53.8	(33.7, 72.9)	37	18	48.6	(32.2, 65.3)
	Non-US	123	76	61.8	(52.6, 70.3)	130	85	65.4	(56.5, 73.4)	132	81	61.4	(52.5, 69.6)	125	88	70.4	(61.5, 78.1)
	Czech Republic	25	14	56.0	(35.3, 75.0)	29	19	65.5	(45.7, 81.4)	25	14	56.0	(35.3, 75.0)	28	21	75.0	(54.8, 88.6)
	Poland	29	16	55.2	(36.0, 73.0)	27	22	81.5	(61.3, 93.0)	33	21	63.6	(45.1, 79.0)	30	23	76.7	(57.3, 89.4)
	Romania	27	21	77.8	(57.3, 90.6)	32	24	75.0	(56.2, 87.9)	29	22	75.9	(56.1, 89.0)	27	25	92.6	(74.2, 98.7)
	Mexico	42	25	59.5	(43.3, 74.0)	42	20	47.6	(32.3, 63.4)	45	24	53.3	(38.0, 68.1)	40	19	47.5	(31.8, 63.7)

Table 29: Complete response (0-24 and 24-120 hours): confidence intervals for differences between oral and IV treatment groups (Full analysis set, subgroups: region, N = 635)

Time Period	Region	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	US	(-26.1, 36.7)	(-29.5, 34.8)	(-17.2, 47.6)
	Non-US	(-11.7, 15.7)	(-7.6, 18.7)	(-13.9, 13.5)
	Czech Republic	(-29.7, 38.0)	(-35.6, 31.0)	(-34.3, 34.6)
	Poland	(-39.9, 18.1)	(-24.7, 28.4)	(-41.9, 14.6)
	Romania	(-16.0, 16.0)	(-19.4, 14.3)	(-15.2, 15.7)
	Mexico	(-15.9, 38.7)	(-7.7, 44.9)	(-18.2, 36.0)
24 – 120 Hr	US	(-30.4, 33.1)	(-31.0, 33.7)	(-28.6, 39.0)
	Non-US	(-23.7, 6.5)	(-19.7, 9.7)	(-23.9, 5.8)
	Czech Republic	(-53.5, 15.5)	(-41.7, 22.8)	(-53.5, 15.5)
	Poland	(-53.6, 10.6)	(-24.4, 34.0)	(-43.4, 17.3)
	Romania	(-41.1, 11.5)	(-42.9, 7.7)	(-42.8, 9.3)
	Mexico	(-16.5, 40.6)	(-28.7, 28.9)	(-22.4, 34.1)

4.2.2 Chemotherapy History

The complete response during the 0-24 and 24-120 hour time periods are summarized by chemotherapy history. Non-inferiority of all three oral palonosetron doses to IV palonosetron is indicated in naïve patients since the lower limit of the confidence interval for the differences between oral and IV treatment groups was above the -15% threshold. In non-naïve patients, only oral palonosetron 0.50 mg indicates possible non-inferiority to IV palonosetron.

Table 30: Patients with complete response during 0-24 and 24-120 hour time period from start of chemotherapy (Full analysis set, subgroups: chemotherapy history, N = 635)

Time Period	Chemo History	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	Naïve	95	67	70.5	(60.2, 79.2)	91	66	72.5	(62.0, 81.1)	93	66	71.0	(60.5, 79.7)	96	64	66.7	(56.2, 75.8)
	Non-Naïve	60	47	78.3	(65.5, 87.5)	69	56	81.2	(69.6, 89.2)	65	51	78.5	(66.2, 87.3)	66	50	75.8	(63.4, 85.1)
24 – 120 Hr	Naïve	95	50	52.6	(42.2, 62.9)	91	51	56.0	(45.3, 66.3)	93	48	51.6	(41.1, 62.0)	96	59	61.5	(50.9, 71.1)
	Non-Naïve	60	42	70.0	(56.6, 80.8)	69	49	71.0	(58.7, 81.0)	65	47	72.3	(59.6, 82.3)	66	47	71.2	(58.6, 81.4)

Table 31: Complete response (0-24 and 24-120 hours): confidence intervals for differences between oral and IV treatment groups (Full analysis set, subgroups: chemotherapy history, N = 635)

Time Period	Chemo History	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	Naïve	(-13.2, 20.9)	(-11.2, 23.0)	(-12.8, 21.4)
	Non-Naïve	(-16.9, 22.1)	(-13.0, 23.8)	(-16.3, 21.7)
24 – 120 Hr	Naïve	(-26.9, 9.3)	(-23.7, 12.8)	(-28.0, 8.4)
	Non-Naïve	(-22.2, 19.8)	(-20.3, 19.9)	(-19.2, 21.4)

4.2.3 Use of Dexamethasone

The complete response during the 0-24 and 24-120 hour time period are summarized by use of dexamethasone in Table 32 and Table 33. For complete response in the 0-24 hour time period, non-inferiority of the respective oral palonosetron doses to the IV palonosetron dose was indicated for all oral palonosetron doses in both dexamethasone and no dexamethasone subgroups, except for oral palonosetron 0.25 mg in the subgroup using dexamethasone.

Table 32: Patients with complete response during 0-24 and 24-120 hour time period from start of chemotherapy (Full analysis set, subgroups: use of dexamethasone, N = 635)

Time Period	Dex	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	Dex	78	60	76.9	(65.8, 85.4)	79	68	86.1	(76.0, 92.5)	80	68	85.0	(74.9, 91.7)	82	68	82.9	(72.7, 90.0)
	Non-Dex	77	54	70.1	(58.5, 79.8)	81	54	66.7	(55.2, 76.5)	78	49	62.8	(51.1, 73.3)	80	46	57.5	(46.0, 68.3)
24 – 120 Hr	Dex	78	45	57.7	(46.0, 68.6)	79	50	63.3	(51.6, 73.6)	80	51	63.8	(52.2, 74.0)	82	56	68.3	(57.0, 77.9)
	Non-Dex	77	47	61.0	(49.2, 71.7)	81	50	61.7	(50.2, 72.1)	78	44	56.4	(44.7, 67.4)	80	50	62.5	(50.9, 72.9)

Table 33: Complete response (0-24 and 24-120 hours): confidence intervals for differences between oral and IV treatment groups (Full analysis set, subgroups: use of dexamethasone, N = 635)

Time Period	Dex	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	Dex	(-22.4, 10.4)	(-11.7, 18.0)	(-12.9, 17.1)
	Non-Dex	(-6.8, 32.0)	(-10.3, 28.6)	(-14.5, 25.2)
24 – 120 Hr	Dex	(-30.0, 8.8)	(-24.1, 14.1)	(-23.5, 14.4)
	Non-Dex	(-21.3, 18.3)	(-20.3, 18.7)	(-26.0, 13.8)

4.2.4 Most frequently used chemotherapeutic agents / combinations

Table 34 and Table 35 summarize the complete response during the 0-24 and 24-120 hour time period by most frequently used chemotherapeutic regimens. Non-inferiority to IV palonosetron is indicated for the intermediate (0.50 mg) and high (0.75 mg) oral palonosetron doses in the AC/EC subgroup and for all three oral doses in the platinum based subgroup.

Table 34: Patients with complete response during 0-24 and 24-120 hour time period from start of chemotherapy (Full analysis set, subgroups: most frequently used chemotherapeutic regimen)

Time Period	Chemo Agents	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	AC/EC regimen	82	52	63.4	(52.0, 73.6)	84	56	66.7	(55.4, 76.3)	87	58	66.7	(55.7, 76.2)	81	49	60.5	(49.0, 71.0)
	Platinum based regimen	55	50	90.9	(79.3, 96.6)	49	45	91.8	(79.5, 97.4)	47	43	91.5	(78.7, 97.2)	58	45	77.6	(64.4, 87.1)
	Other regimen	18	12	66.7	(41.2, 85.6)	27	21	77.8	(57.3, 90.6)	24	16	66.7	(44.7, 83.6)	23	20	87.0	(65.3, 96.6)
24 – 120 Hr	AC/EC regimen	82	36	43.9	(33.1, 55.3)	84	42	50.0	(39.0, 61.0)	87	45	51.7	(40.8, 62.5)	81	46	56.8	(45.3, 67.6)
	Platinum based regimen	55	44	80.0	(66.6, 89.1)	49	38	77.6	(63.0, 87.8)	47	32	68.1	(52.7, 80.5)	58	43	74.1	(60.7, 84.4)
	Other regimen	18	12	66.7	(41.2, 85.6)	27	20	74.1	(53.4, 88.1)	24	18	75.0	(52.9, 89.4)	23	17	73.9	(51.3, 88.9)

Table 35: Complete response (0-24 and 24-120 hours): confidence intervals for differences between oral and IV treatment groups (Full analysis set, subgroups: most frequently used chemotherapeutic regimen, N = 635)

Time Period	Chemo Regimen	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	AC/EC regimen	(-16.5, 22.3)	(-12.9, 25.2)	(-12.7, 25.1)
	Platinum based regimen	(-4.5, 31.1)	(-3.7, 32.2)	(-4.3, 32.1)
	Other regimen	(-56.6, 16.0)	(-38.6, 20.3)	(-53.0, 12.4)
24 – 120 Hr	AC/EC regimen	(-32.7, 6.9)	(-26.5, 12.9)	(-24.6, 14.5)
	Platinum based regimen	(-14.7, 26.5)	(-18.2, 25.1)	(-29.2, 17.1)
	Other regimen	(-46.6, 32.1)	(-33.6, 33.9)	(-33.5, 35.7)

5.1 Statistical Issues and Collective Evidence

The results from study PALO-03-13 support the effectiveness of the three oral doses as non-inferior to that of IV dose for the acute phase (0-24 hours), assessed by non-inferiority margin of 15%. However, for the delayed phase (24-120 hours), none of the oral doses showed non-inferiority to the IV dose. (b) (4)

This reviewer conducted subgroup analyses by region, gender, race, age group, chemotherapy history, and dexamethasone use. Complete response rates (acute phase) were generally consistent over these subgroups. However, numerically higher rates were observed for males; for the non-U.S. regions; and for Dexamethasone treated subjects. The complete response rates varied widely among countries; however, due to the small number of patients enrolled in the U.S., no clear conclusions can be drawn regarding U.S. and non-U.S. differences. Complete response rates for chemotherapy naïve and non-naïve subjects were numerically similar.

5.2 Conclusions and Recommendations

The results from the single pivotal study PALO-03-13 show that three oral doses of palonosetron are each non-inferior to the IV dose, as measured by complete response during the acute phase (0-24 hours) and a non-inferiority margin of 15%. However, none of the oral doses showed non-inferiority to the IV for the key secondary endpoint, complete response for the delayed phase (24-120 hours). Analysis results based on all secondary endpoints should be considered exploratory, since the sponsor's hierarchical testing procedure failed on the first secondary endpoint. From a statistical perspective, this study has demonstrated comparable efficacy between the oral and IV administrations of palonosetron for the acute phase (b) (4)

APPENDIX

Table 36: Demographic and anamnestic data (Safety set, N = 639)

	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)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age [years]	57.2	11.9	56.0	12.3	55.9	12.8	57.7	12.6
Height [cm]	161.7	11.2	162.2	8.8	162.0	9.4	163.2	10.7
Weight [kg]	71.5	15.7	69.5	15.0	70.9	15.0	72.4	15.7
Karnofsky index [%]	92.0	7.9	92.6	8.4	93.1	7.5	92.8	8.2
	Median	Range	Median	Range	Median	Range	Median	Range
	90.0	70-100	90.0	60-100	90.0	70-100	90.0	60-100
	n	%	n	%	n	%	n	%
Gender								
Male	40	25.5	43	26.7	45	28.5	45	27.6
Female	117	74.5	118	73.3	113	71.5	118	72.4
Ethnic group								
White	111	70.7	112	69.6	106	67.1	115	70.6
Black	2	1.3	1	0.6	2	1.3	0	0.0
Hispanic	43	27.4	45	28.0	49	31.0	45	27.6
Asian	1	0.6	1	0.6	0	0.0	2	1.2
Other	0	0.0	2	1.2	1	0.6	1	0.6
Chemotherapy history								
Naïve	95	60.5	92	57.1	92	58.2	97	59.5
Non-naïve	62	39.5	69	42.9	66	41.8	66	40.5
Use of dexamethasone								
Yes	79	50.3	79	49.1	81	51.3	82	50.3
No	78	49.7	82	50.9	77	48.7	81	49.7
Tobacco consumption								
Non-smoker	107	68.2	105	65.2	102	64.6	110	67.5
Ex-smoker	31	19.7	29	18.0	41	25.9	36	22.1
Smoker	19	12.1	27	16.8	15	9.5	17	10.4

(Source: Clinical Study Report: Study PALO-03-13; Table 6.4-a, page 88)

Additional Secondary Efficacy Endpoint Results

Emetic episodes

Patients were asked to document details about their emetic episodes (episodes of retching or vomiting) until Day 5 (daily, for every 24 hour period) in a patient diary. The results are presented in Table 37. There was no clear trend in favor of one particular treatment group in acute phase 0 – 24h, however, the percent of patients with emetic episodes are higher in oral palonosetron groups than that of IV palonosetron in delay phase 24 – 120 h.

Table 37: Emetic episodes (patients with / without emesis) (Full analysis set, N = 635)

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: Clinical Study Report: Study PALO-03-13; Table 7.1-t, page 139)

Rescue medication

Patients were asked to document daily (Day 1 to 5) in their diary whether they had taken any medication for the treatment of nausea and vomiting during the last 24 hours. As shown in Table 38, the percentage of patients using rescue medication was slightly higher in the IV palonosetron group than in the oral treatment groups in acute phase 0 – 24 h, and the percent of patients using rescue medication are higher in oral palonosetron groups than that of IV palonosetron in delay phase 24 – 120 h.

Table 38: 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: Clinical Study Report: Study PALO-03-13; Table 7.1-w, page 146)

Patient global satisfaction with anti-emetic therapy

Global satisfaction with the anti-emetic therapy was assessed daily by the patients and recorded in their patient diaries. The patient was asked the following question: 'Overall, how satisfied have you been with the control of nausea and vomiting during the last 24 hours?'. The assessment was made on a 100 mm Visual Analogue Scale (VAS) with the left end (= 0) being equivalent to 'not at all satisfied' and the right end (= 100) referring to 'totally satisfied'. The patient was asked to evaluate his/her satisfaction by marking the VAS with a vertical line daily for the 0-120 hour interval (Days 1 to 5) in the patient diary.

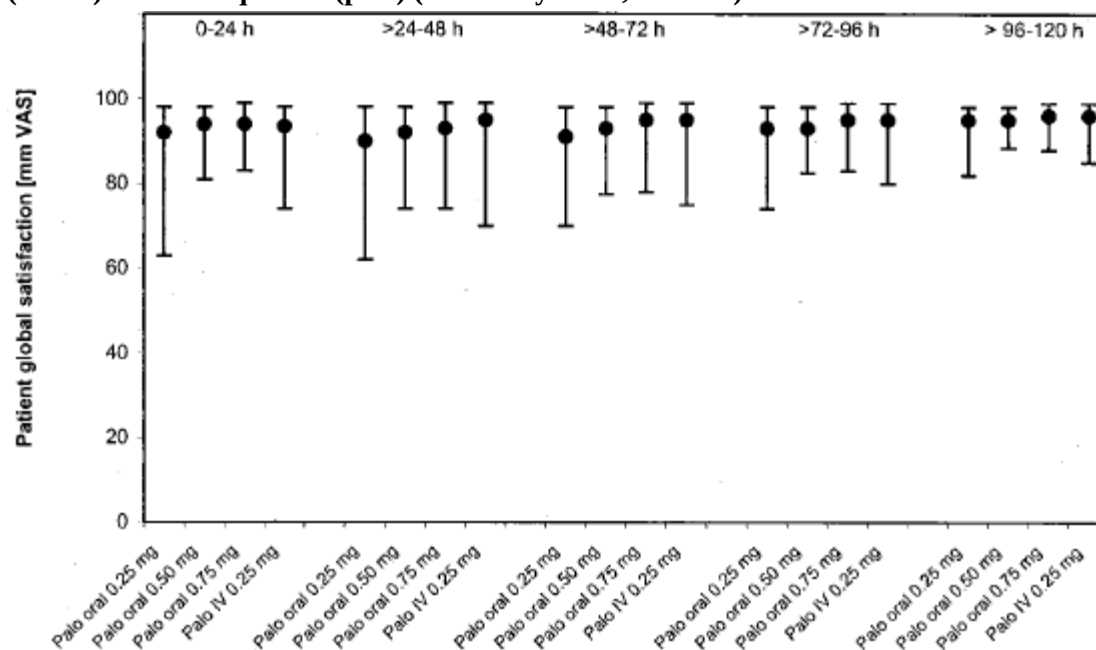
The global satisfaction of the patients with anti-emetic therapy is shown in Table 39 and Figure 3. There was a trend for the median patient global satisfaction to be slightly lower in the oral palonosetron 0.25 mg and 0.50 mg dose group than in the oral palonosetron 0.75 mg and IV treatment group. This tendency was best seen on Days 2 and 3. The 25% quantile was lower in the 0.25 mg palonosetron group than in the other study treatment groups for all days, showing a slightly worse patient's global satisfaction with anti-emetic therapy in the lower oral dose group. Additionally, the 25% quantile was highest in the oral 0.50 mg and 0.75 mg palonosetron groups during all daily time periods.

Table 39: Patient global satisfaction with anti-emetic therapy (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	25% Q	Median	75% Q	n	25% Q	Median	75% Q	n	25% Q	Median	75% Q	n	25% Q	Median	75% Q
0 – 24 h	155	63.0	92.0	98.0	160	81.0	94.0	98.0	158	83.0	94.0	99.0	162	74.0	93.5	98.0
>24 – 48 h	155	62.0	90.0	98.0	160	74.0	92.0	98.0	158	74.0	93.0	99.0	162	70.0	95.0	99.0
>48 – 72 h	155	70.0	91.0	98.0	160	77.5	93.0	98.0	158	78.0	95.0	99.0	162	75.0	95.0	99.0
>72 – 96 h	155	74.0	93.0	98.0	160	82.5	93.0	98.0	158	83.0	95.0	99.0	162	80.0	95.0	99.0
>96 – 120 h	155	82.0	95.0	98.0	160	88.5	95.0	98.0	158	88.0	96.0	99.0	162	85.0	96.0	99.0

(Source: Clinical Study Report: Study PALO-03-13; Table 7.1-aa, page 156)

Figure 3: Patient global satisfaction with anti-emetic therapy per day, median, 25% quantile (minus) and 75% quintile (plus) (Full analysis set, N = 635)



(Source: Clinical Study Report: Study PALO-03-13; Figure 7.1-g, page 157)

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Mike Welch
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Concur with review.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION
 CENTER FOR DRUG EVALUATION AND RESEARCH
 OFFICE OF BIostatISTICS

STATISTICAL REVIEW AND EVALUATION

SUPPLEMENTAL REVIEW—CLINICAL STUDIES

NDA/Ser Nr: 22-233
 DATE RECEIVED: October 24, 2007
 PDUFA DATE: August 22, 2008
 DRUG NAME: Aloxi (palonosetron hydrochloride)
 INDICATION: Prevention of Chemotherapy-Induced Nausea
 and Vomiting

APPLICANT: Helsinn Healthcare SA
 REVIEW PRIORITY: Standard
 DOCUMENT REVIEWED: Volumes for Study PAL-03-13 & Documents
 submitted on May 13 and June 6, 2008.

BIOMETRICS DIVISION: Division of Biometrics 3 (HFD-725)
 PRIMARY STATISTICAL REVIEWER: Kate Dwyer, Ph.D.
 SUPPLEMENTAL REVIEWER: Wen-Jen Chen, Ph.D.
 CONCURRING REVIEWER: Mike Welch, PhD, Dep. Dir., DB3

MEDICAL DIVISION: Gastroenterology Products (HFD-180)
 CLINICAL REVIEWER: Nancy Snow, MD
 PROJECT MANAGER: Jagjit Grewal, MPH

Supplemental Review of NDA 22-233

This is an addendum to the primary statistical review by Kate Dwyer, Ph.D.. In this addendum, I comment on the following two issues regarding the pivotal Study PALO-03-13: 1) Baseline adaptive randomization, and 2) Post-hoc analysis for the key secondary endpoint.

1) Baseline adaptive randomization

It is noted that the applicant applied baseline adaptive randomization (BAR) to allocate patients into the four different treatment groups (oral palonosetron 0.25 mg, 0.50 mg, and 0.75 mg, and IV palonosetron 0.25 mg). In order to assess the impact of the applicant's BAR scheme on the validity of the primary endpoint comparisons, this reviewer had requested the applicant performs the following re-randomization analysis using the algorithm below (items a. to d.).

- a. Re-randomize the original order of the patient enrollment to generate 30,000 lists of re-randomized patients.
- b. For each of these re-randomized patient lists, apply your dynamic randomization treatment assignment algorithm to re-allocate patients to the four treatment groups (three studied oral palonosetron groups and one active controlled IV palonosetron group).
- c. For each of these re-allocated patient lists, compute a Z statistic based on your primary endpoint formulas for each of the three study arm comparisons to the IV palonosetron:

$$Z = ((p_{PO} - p_{PI} + 0.15) - \frac{1}{2} (1/n_1 + 1/n_2)) / (\text{std}(p_{PO} - p_{PI})) ,$$

where p_{PO} and p_{PI} are the estimated proportions (complete response in the acute phase) for one of the three oral palonosetron groups and IV palonosetron group, respectively; 0.15 is the non-inferiority margin; n_1 and n_2 are the numbers of patients for the oral and IV groups; and std is the standard deviation formula you applied in your primary endpoint analysis.

- d. For each of the three study arm comparisons to the IV palonosetron, based on the distribution of the 30,000 simulated Z scores, please calculate the 0.0083th and 0.9917th quantiles.

Here, the Z-statistic stated in item c. is used to test the non-inferiority null hypothesis:

$H_0: \pi_{PO} - \pi_{PI} \leq -0.15$; where π_{PO} and π_{PI} are the population proportions (complete response in the acute phase) for one of the three oral palonosetron groups and IV palonosetron group, respectively; 0.15 is the selected non-inferiority margin.

It should be noted that the re-allocation of patients to the three oral palonosetron arms and active control IV palonosetron based upon the re-randomization scheme listed in items a. and b. will generate equal proportions of complete response (binary data: success or failure) rates for the four treatment groups. However, for non-inferiority hypothesis testing, the equal proportions generated by the re-randomization technique for the test drug (oral palonosetron) and the control drug (IV palonosetron) are not the proportions restricted by the non-inferiority null hypothesis H_0 but in the range of the non-inferiority alternative hypothesis. Accordingly, the numerator of the Z-statistic stated in item c. is not zero and the re-randomization algorithm stated from above items a. to d. can not be used to simulate the distribution of Z-statistic under the non-inferiority null hypothesis $H_0: \pi_{PO} - \pi_{PI} \leq -0.15$.

In addition, the applicant's cover letter dated July 16, 2008 indicated that in order to generate the test statistic under the non-inferiority null hypothesis H_0 , all possible responses need to be available. However, in the PALO-03-13 non-inferiority trial, for all four treatment arms, the complete response rates for the acute phase were between 70% and 76%. Therefore, no matter how the data are re-sampled, under the null hypothesis ($H_0: \pi_{PO} - \pi_{PI} \leq -0.15$) the distribution of $p_{PO} - p_{PI}$ would have a mean of zero rather than -15%. Actually, a mean of zero rather than -15% as stated in the sponsor's cover letter reflected that using the re-randomization scheme, it was not possible to correctly generate/simulate the distribution of the Z-statistic under the non-inferiority null hypothesis $H_0: \pi_{PO} - \pi_{PI} + 0.15 \leq 0$.

As a consequence, based upon this reviewer's comments and the applicant's simulation results, one may conclude that the re-sampling analysis method stated in items a. to d. above can not assess the impact of the applicant's baseline adaptive randomization scheme on the validity of the non-inferiority claimed by the applicant for oral palonosetrons versus IV palonosetron in the acute phase using the complete response of binary data.

Finally, in order to correctly apply a simulation analysis to assess the impact of BAR on the non-inferior analysis pre-specified for the primary endpoint of binary data, at the design stage of the phase III protocol, prior to study enrollment, the Agency should emphasize that if an applicant plans to use BAR to allocate patients into different treatment groups, then, before conducting the trial, the applicant should be requested to conduct a simulation to assess the impact of BAR on the non-inferior analysis pre-specified in the protocol.

2) Post-hoc analysis for the key secondary endpoint

For the key secondary endpoint (defined as proportion of patients without emesis and rescue therapy during the 24-120 hour time period after chemotherapy), the applicant's pre-specified non-inferiority analysis has shown that all of the three oral palonosetron groups (0.25 mg, 0.50 mg, and 0.75 mg) failed to show non-inferiority to the IV treatment group for the 24-120 hour interval after chemotherapy [for detail, refer to the applicant's sub-section 7.1.2.1 relating to the key secondary efficacy variable]. However, the applicant also reported the results from

two, post-hoc analyses: historical pooled analysis presented by as PALO-07-36 and exploratory analysis presented as PALO-07-35. (b) (4)



In order to validate the applicant's non-inferiority claim made for the key secondary endpoint, this reviewer would like to comment on these two post-hoc analysis methods from the perspective of sound statistical principles.

i. Issue on the historical pooled analysis

First, it is well known that the Phase 3 study is a confirmatory trial. Traditionally, the applicant needs to conduct two studies to demonstrate the test drug palonosetron 0.50 mg is non-inferior to IV palonosetron 0.25 mg in the sense that one study shows a non-inferior efficacy result and the other study confirms the non-inferior result. As a consequence, for proper efficacy assessment, even two concurrent phase 3 studies following the same protocol should not be pooled, but analyzed separately.

It is noted that for this NDA submission, the non-inferiority of palonosetron 0.50 mg to IV palonosetron 0.25 mg was not shown when assessed by the key secondary endpoint based upon one single phase 3 Study PALO-03-13. However, in order to change the result of the comparison of oral palonosetron 0.50 mg to IV palonosetron 0.25 mg shown by the non-inferiority analysis pre-specified by the single phase 3 study to non-inferiority, the applicant performed a post-hoc analysis using pooled data from two historical studies for IV palonosetron 0.25 mg with data from the single pivotal study PALO-03-13. Then the sponsor compared the pooled data to the oral palonosetron 0.50 mg. Based upon the efficacy assessment criteria required for the confirmatory phase 3 trials, as stated in the previous paragraph, even if data from two concurrent phase 3 studies are not allowed to be pooled, the pooled historical analysis for the key secondary endpoint is not acceptable.

Second, since the applicant applied baseline adaptive randomization to allocate patients into treatment groups, patients for the four treatment groups including IV palonosetron patients from two historical studies do not follow the principle of baseline adaptive randomization. In addition, the pooled patients can not be randomized following the same randomization scheme designed for the original single study PALO-03-13. Accordingly, the pooled patients can not represent a sample from the population specified by the protocol. Strictly speaking, no valid/sound statistical analysis method can be applied to the pooled patient data.

Finally, the complete response proportions for the key secondary endpoint for palonosetron 0.50 mg and IV palonosetron 0.25 mg were derived from a logistic regression with selected covariates. It follows that the variance of the derived proportions are not the same as that of sample proportions. Therefore, it is invalid to apply the protocol specified formula to calculate

the lower bound of two-sided 98.3% confidence interval for the model-based estimated proportions.

Accordingly, based upon the above three comments on the pooled historical analysis method, the result from the pooled data analysis is not valid and is not acceptable.

ii. Comments on the exploratory analysis

The Hauck-Anderson method the applicant applied (reported in the Appendices of Volume 1.65) for the exploratory analysis to calculate the lower bound of two-sided confidence interval is more liberal than the one pre-specified in the protocol.

The lower bound of the two-sided 98.3% confidence for the difference of the proportion of oral palonosetron 0.5 mg minus that of IV palonosetron 0.25 mg calculated by this reviewer using Hauck-Anderson method is -16.05%, still less than -15%, the negative value of the non-inferiority margin. The result still shows that oral palonosetron 0.5 mg does not demonstrate non-inferiority to IV palonosetron 0.25 mg assessed by key secondary endpoint.

In addition, the lower bound of the two-sided 96.4% confidence interval for the two proportion difference calculated by this reviewer using Hauck-Anderson method is -14.66%, very close to that (-14.65%) reported by the applicant in Volume 1.65. However, instead of using a 98.3% level to correctly adjust for multiplicity, the applicant's reported lower bound (-14.65%) appears to be the lower bound for the two-sided 96.4% interval. Since the confidence level associated with the lower bound for the difference in proportions reported by the applicant is not correctly adjusted for multiplicity, the result reported by the applicant is not acceptable.

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Wen-Jen Chen
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Mike Welch
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Concur with review.

Screening of New NDA for Statistical Filing Division of Biometrics III

NDA #: 22-233 (Serial 000)

Applicant: Helsinn Healthcare SA

Trade/Generic Name: Aloxi®/ Palonosetron HCl

Indication: Prevention of moderately emetogenic chemotherapy-induced nausea and vomiting

Date of Submission: October 22, 2007

Filing Meeting Date: November 30, 2007

User Fee Goal Date: August 22, 2008

Project Manager: Jagjit Grewal

Medical Reviewer: Nancy Snow, M.D.

Statistical Reviewer: Kate Dwyer, Ph.D.

Background

The sponsor submitted one pivotal Phase III efficacy study in support of Aloxi®/ Palonosetron HCl administered orally for prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. Brief summary of the study is shown below. The primary efficacy objective of this single study is to show non-inferiority of all three oral palonosetron doses to IV palonosetron.

Brief Summary of Phase III Clinical Study for Aloxi®/ Palonosetron HCl

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population	Primary Endpoints	Treatments	Number Randomized (ITT)	Design ¹
PALO-03-13 (24 / EU & 7 / Mex & 15 / U S) Jun. 2005 to Aug. 2006	Patients: ≥ 18 years of age; with histologically or cytologically confirmed malignant disease; naïve or non-naïve to cancer chemotherapy; who had a Karnofsky index ≥ 50%.	The primary endpoint was proportion of patients considered to have achieved complete response (CR) during the first 24 hours after the start of administration of chemotherapy	Palo Oral 0.25 mg Palo Oral 0.50 mg Palo Oral 0.75 mg Palo IV 0.25 mg Total	157 (155) 161 (160) 158 (158) 163 (162) 639 (635)	SD, R, DB, PG, MC, AC

¹ SD = Single Dose, R = Randomized, DB = Double-blind, PG = Parallel Group, MC = Multicenter, AC = Active Control

Checklist for Fileability	Remarks (NA if not applicable)
Index sufficient to locate study reports, analyses, protocols, ISE, ISS, etc.	OK
Original protocols & subsequent amendments submitted	OK
Study designs utilized appropriate for the indications requested	OK
Endpoints and methods of analysis spelled out in the protocols	OK
ISS and ISE submitted	OK
Appropriate references included for novel statistical methodology (if present)	NA
Data and reports from primary studies submitted to EDR according to Guidances	EDR data present
Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups investigated	NA

Conclusion

After the preliminary review of the submission, we have not identified any deficiencies that would be a reason for refuse-to-file. All data sets submitted are accessible. In conclusion, this NDA is fileable from a statistical perspective.

Team Leader: Mike Welch

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/s/

Kate L Dwyer
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Mike Welch
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