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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-372

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21- 372 / N000
Drug Name:	Palonosetron HCl 0.25mg/5ml
Indication(s):	Prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy
Applicant:	Helsinn Healthcare S.A.
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Review Priority:	Standard (10-month)
Biometrics Division:	Division of Biometrics 2 (HFD-715)
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Keywords: minimization, active control trials, non-inferiority, meta-analysis.

1. Executive Summary

1.1 Conclusions and Recommendations

There is sufficient evidence and reasonable certainty that palonosetron 0.25 mg is efficacious in the prevention of acute nausea and vomiting following moderately and highly emetogenic cancer chemotherapy. There is also sufficient evidence that it is efficacious in the prevention of delayed emesis following moderately (but not highly) emetogenic chemotherapy. While the efficacy analyses are based on comparisons to approved anti-emetics (ondansetron and dolasetron), the efficacy conclusions and claims are relative to placebo; the label should reflect this distinction.

1.2 Brief Overview of Clinical Studies

The applicant proposes a single, intravenous injection of palonosetron 0.25 mg, given 30 minutes prior to moderately or highly emetogenic chemotherapy. Eighteen clinical trials were conducted to study the safety and efficacy of palonosetron. Of these, four are presented in support of the applicant's claim of efficacy of palonosetron 0.25 mg IV to prevent chemotherapy-induced nausea and vomiting (CINV) and are reviewed here. Two are for the prevention of CINV following moderately emetogenic chemotherapy (PALO-99-03 and PALO-99-04) and two are for the prevention of CINV following highly emetogenic chemotherapy (2330/PALO-00-01 and PALO-99-03).

Studies PALO-99-03, 99-04, and 99-05 were double-blind, multicenter, active-controlled studies enrolling 570, 592 and 680 patients respectively. They were conducted in Europe, including Russia, (99-03 and 99–05), and North America (99-04 and 99–05). Each study had three arms: 0.25 mg IV palonosetron, 0.75 mg IV palonosetron, and an active comparator (ondansetron 32 mg IV in 99-03 and 99-05, dolasetron 100 mg IV in 99-04). Allocation to treatment was a mixture of algorithms primarily relying on minimization rather than randomization. That is, the assignment of a new patient to a group was made to minimize differences among the treatment groups. Balance among the groups was in terms of the number of patients assigned to each stratum defined by prognostic criteria of gender, chemotherapy history (naïve or not naïve) and use of corticosteroids. This scheme does not correspond to what is usually thought of as randomization in a clinical trial. It most closely resembles a deterministic dynamic allocation procedure.

Study 2330 was designed as a phase 2 study using the IV formulation of palonosetron. It was a randomized, double-blind, multicenter, dose-ranging trial of palonosetron given to chemotherapy-naïve patients 30 minutes before the administration of highly emetogenic chemotherapy. The enrolled population consisted of 161 subjects. Palonosetron was administered at weight-based doses of 0.3, 1, 3, 10 or 30 μg/kg. Helsinn considers study 2330 supportive. It was a dose-ranging study conducted by the drug innovator Syntex. It used a weight-based dosing regimen, which was roughly translated into the eventual (fixed) dosing regimen.

1.3 Statistical Issues and Findings

A primary concern from a statistical point of view is the minimization allocation procedure used in studies PALO-99-03, PALO-99-04 and PALO-99-05. It is not randomization, but rather a deterministic allocation with the occasional random assignment. Several drawbacks of using minimization have been cited in the literature (Scott et al., 2002). The concern in this application is that standard statistical tests, or, equivalently, confidence interval calculations, make the assumption of random allocation: more generally, "the correct statistical analysis is complex and not yet clearly worked out." (Scott et al., 2002) Permutation methods can be used to check the results of standard analyses. The two approaches are likely but not guaranteed to yield similar conclusions; there are situations where the standard methods are very misleading. These situations have not been completely characterized and a permutation test is a good way to know whether the trials in this application fall into the problematic case. Apparently they do not: The results of the permutation analysis are in accordance with the primary, standard analysis.

None of the efficacy trials done as part of this application included a placebo control. To assess trial validity and justify the value of delta used to declare non-inferiority of palonosetron to ondansetron or dolasetron, an examination and meta-analysis of results from the anti-emetic literature was carried out. In the few studies where ondansetron or dolasetron was directly compared to placebo, the active treatment reliably out-performed placebo to a greater extent than seen between treatments in the trials in this application. A less direct comparison of the effects of setron treatments and placebo, achieved through logistic regression modeling by the applicant, yielded similar results and similar confidence in the assay sensitivity of the NDA studies. The magnitudes of the differences found or modeled in the meta-analysis also were large enough to justify a conclusion of non-inferiority of palonosetron in the current trials.

In studies PALO-99-03, 99-04, and 99-05, a higher proportion of the patients responded to palonosetron than to the comparator anti-emetics. Response rates ranged from a low of 57%, for ondansetron 32 mg following the administration of highly emetogenic chemotherapy, to a high of 81% for palonosetron 0.25 mg following moderately emetogenic chemotherapy

The applicant calculated the two-sided 97.5% confidence interval of the difference between the proportions of complete response in each dose of palonosetron and comparator (calculated as palonosetron minus comparator) to demonstrate non-inferiority of palonosetron to the comparators. In all cases, the lower boundary of the interval was above -10%, implying a reasonable certainty that the proportion of complete responders to palonosetron was no less than 10% less than the proportion among the comparators. Results of the permutation test confirmed these conclusions.

The applicant wishes to include a secondary outcome as part of the labeled indication, namely that palonosetron is effective for prevention of delayed nausea and vomiting. Following highly emetogenic chemotherapy (PALO-99-05), the rates of complete

response are consistently numerically higher for palonosetron 0.25 mg; however, there is no time period for which palonosetron is statistically significantly higher than the comparator ondansetron (as judged by the lower limit of the confidence interval of the difference). Following moderately emetogenic chemotherapy, the rates of complete response again are consistently numerically higher for palonosetron 0.25. It is statistically significantly higher than ondansetron at all time periods other than the final 96-120 hours, when there are high response rates in all three treatment arms; its performance against dolasetron is mixed, but is statistically significantly higher than for the overall time period 24-120 hours.

The results for the primary efficacy outcome for study PALO-00-01 (essentially the same as study 2330) support the choice of 0.25 mg as a threshold efficacy dose and confirm the results of 99-05 for highly emetogenic chemotherapy.

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2. Introduction

2.1 Overview

Palonosetron is a 5-HT_3 (serotonin) receptor antagonist, described by the applicant as structurally unrelated to other currently available 5-HT_3 receptor antagonists. This application was filed in support of palonosetron for "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-HT_3 receptor antagonists used as anti-emetic therapies include ondansetron, granisetron, and dolasetron).

The applicant proposes a single, intravenous (IV) injection of palonosetron 0.25 mg, given 30 minutes prior to moderately or highly emetogenic chemotherapy. (Moderately emetogenic chemotherapy includes carboplatin, cisplatin $\leq$ 50 mg/m^2, cyclophosphamide < 1500 mg/m^2, doxorubicin > 25 mg/m^2, epirubicin, irinotecan, methotrexate > 250 mg/m^2; highly emetogenic includes cisplatin > 50 mg/m^2, cyclophosphamide >1500 mg/m^2, and dacarbazine.) Eighteen clinical trials, including healthy volunteer, pharmacokinetic, dose-ranging, controlled or open label studies, were conducted to study the safety and efficacy of palonosetron. Of these, four controlled studies are presented in support of the applicant's claim of efficacy of palonosetron 0.25 mg IV to prevent chemotherapy-induced nausea and vomiting (CINV) and are reviewed here. Two are for the prevention of CINV following moderately emetogenic chemotherapy (PALO-99-03 and PALO-99-04) and two are for the prevention of CINV following highly emetogenic chemotherapy (2330/PALO-00-01 and PALO-99-03). Helsinn considers study 2330 supportive. It was a dose-ranging study conducted by the drug innovator Syntex, and used a weight-based dosing regimen, which was roughly translated into the eventual (fixed) dosing regimen.

2.2 Data Sources

Materials reviewed included NDA paper volumes 1, 273-371, amendment #006 dated 24 April 2003, amendment #009 dated 16 June 2003, and data sets in CDER's electronic document room

3. Statistical Evaluation

3.1 Evaluation of Efficacy

Because studies PALO-99-03, -04, -05 were very similar in purpose, design and analysis, these studies will be discussed together. Study 2330/PALO 00-01 is discussed separately

3.1.1 Studies PALO-99-03, PALO-99-04, PALO-99-05

Design

Studies PALO-99-03, 99-04, and 99-05 were double-blind, multicenter, active-controlled studies enrolling 570, 592 and 680 patients respectively. They were conducted in Europe, including Russia, (99-03 and 99–05), and North America (99-04 and 99–05). Each study had three arms: 0.25 mg IV palonosetron, 0.75 mg IV palonosetron, and an active comparator (ondansetron 32 mg IV in 99-03 and 99-05, dolasetron 100 mg IV in 99-04). In 99-03 and 99-04, these treatments were administered following moderately emetogenic chemotherapy and in 99-05 following highly emetogenic chemotherapy.

Dexamethasone 20 mg IV administered once prior to chemotherapy was allowed as a concomitant medication. However, due to late implementation of this practice as a protocol change, none of the patients in 99-03 and only 6% in 99-04 received concomitant steroids, while about 60% in 99-05 did. Other corticosteroids – 20 mg oral dexamethasone and 125 mg IV methylprednisolone – were also allowed due to a dexamethasone shortage in the United States.

Allocation to treatment was a mixture of algorithms primarily relying on minimization rather than randomization. That is, the assignment of a new patient to a group was made to minimize differences among the treatment groups. Balance among the groups was in terms of the number of patients assigned to each stratum defined by prognostic criteria of gender, chemotherapy history (naïve or not naïve) and use of corticosteroids. The initial allocation and final allocation schemes differ in their calculations of imbalance, with the first following the method outlined by Taves and the final that of Pocock and Simon. Scott et al., 2002; minutes of 22 May 2003 telecon with applicant).

If a new patient could equally well be assigned to either of two treatment arms, or in the case of on-site shortage of assigned treatment, an assignment was made at random. All assignments took into account the stratification criteria of gender, chemotherapy history (naïve or not naïve) and use of corticosteroids.

This scheme does not correspond to what is usually thought of as randomization in a clinical trial. It most closely resembles a deterministic dynamic allocation procedure, described in ICH E9 as an approach that "should be avoided." (ICH E9, p.10)

The applicant's description of the allocation procedure can be found in the Appendix of this review.

The evaluable, intent-to-treat (ITT) population was defined as all randomized subjects who received chemotherapy and study medication, and consisted of 563 patients in PALO-99-03, 569 in PALO-99-03, and 667 in PALO-99-05. The numbers in each of the prognostic strata are given in Table 1. The applicant attributes the high proportion of female patients to the type of cancer for which moderately emetogenic chemotherapy is most frequently given, namely breast cancer (v. 273, p 237)

Table 1. Numbers of patients in prognostic subgroups

Study and treatment arm		Gender		Chemotherapy		Corticosteroid use	
		Female	Male	Naïve	Non-naïve	Yes	No
	N_{tot}	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PALO-99-03							
Palonosetron 0.25	189	135 (71)	54 (29)	76 (40)	113 (60)	0	189
Palonosetron 0.75	189	138 (73)	51 (27)	80 (42)	109 (58)	0	189
Ondansetron 32	185	133 (72)	52 (28)	78 (42)	107 (58)	0	185
PALO-99-04							
Palonosetron 0.25	189	155 (82)	34 (18)	124 (66)	65 (34)	11 (6)	178 (94)
Palonosetron 0.75	189	156 (83)	33 (17)	131 (69)	58 (31)	12 (6)	177 (94)
Dolasetron 100	191	156 (82)	35 (18)	125 (65)	66 (35)	8 (4)	183 (96)
PALO-99-05							
Palonosetron 0.25	223	115 (52)	108 (48)	133 (60	90 (40)	150 (67)	73 (33)
Palonosetron 0.75	223	113 (51)	110 (49)	129 (58)	94 (42)	150 (67)	73 (33)
Ondansetron 32	221	113 (51)	108 (49)	131 (59)	90 (41)	147 (67)	74 (33)

Analysis

Primary efficacy outcome

The primary efficacy outcome in all three studies was the proportion of subjects considered to have achieved a complete response (CR), defined as no emetic episode and no rescue medication, during the first 24 hours after administration of chemotherapy. Subjects with partially or completely missing data for the primary outcome were classified as not having a complete response.

The primary efficacy hypothesis was that at least one dose of palonosetron was non-inferior to the comparator dose, using a maximum delta of 15%. To demonstrate this non-inferiority, the lower bound of the two-sided 97.5% confidence interval of the difference between the proportions of complete response at 24 hours in each dose of palonosetron and comparator (calculated as palonosetron minus comparator) was compared to the pre-set threshold of -15%.

In addition, the applicant calculated 95% confidence intervals for the proportion of responders in each treatment group and compared these intervals between the two doses of palonosetron.

The applicant assessed assay sensitivity and "confirm[ed] the value of delta" (v. 297, p.61) using the results of study PALO-01-23, a meta-analysis of historical data. This meta-analysis is described separately, in section 3.1.2 below.

The applicant "check[ed] if the treatment allocation procedure described [above]...worked correctly " by performing permutation tests on the primary outcome.

Specifically, in the original NDA submission the applicant performed the following procedure: (v. 297, p.61)

> ...the proportion of complete responders in the observed trial was compared between treatment groups by a one-sided Fisher's exact test taking delta into account. For Fisher's permutation test a random sample (n=30,000) of all possible permutations was used for construction of the permutation distribution. The probability attached to the null hypothesis (i.e., p-value) was calculated as follows: (number of the same or more extreme outcomes as that observed)/30,000. This probability was compared to the p-value of Fisher's exact test.

In review, the nature of the allocation procedure was identified as a crucial element of the validity of the efficacy analysis in these trials (see discussion of this issue in section 5.1 below). Moreover, the permutation test as originally performed by the applicant did not adequately address this issue. The appropriate permutation test should take into account the actual allocation scheme used; the set of potential permutations of outcome values should be restricted to those that result from simulations of the trial as it actually occurred. That is, potential permutations are those that result from the observed enrollment sequence of patients, with their fixed values of prognostic factors. A potential permutation would correspond to an allocation sequence based on a random assignment of the first enrollee, deterministic assignment of subsequent enrollees based on prognostic factors and the calculation of imbalance between treatment arms, until a tie occurs, then a random assignment of the patient who creates that tie, then deterministic assignment with imbalance scores recalculated until a tie occurs, etc. This revision of the confirmatory permutation test was agreed upon in a teleconference with the applicant on 22 May 2003.

Secondary efficacy outcomes

Secondary outcomes in these studies included

- The proportion of subjects with a complete response evaluated on a daily basis and during the overall 0 to 48, 0 to72, 0 to 96, 0 to 120, and 24 to 120-hour time periods; these were analyzed using the same statistical methods as for the primary efficacy parameter.
- The proportion of subjects with complete control (complete response and no more than mild nausea) evaluated daily and for the overall 0 to 120-hour interval; analyzed with a Pearson chi-squared test.
- number of emetic episodes daily for the 0 to 120-hour interval and for the overall 0 to 120-hour interval; analyzed with a Wilcoxon or Kruskal-Wallis test.
- time to first emetic episode; Kaplan-Meier estimates were calculated and a log-rank test used to compare treatments.
- severity of nausea measured on a Likert scale daily for the 0 to 120-hour interval; analyzed with a Wilcoxon or Kruskal-Wallis test.
- need and time of administration of rescue medication; proportion receiving rescue medication analyzed using a chi-squared test, and time to administration was analyzed with Kaplan-Meier estimates and a log-rank test.
- time to treatment failure (emetic episode or rescue medication); Kaplan-Meier estimates were calculated and a log-rank test used to compare treatments.

- subject VAS of global satisfaction with anti-emetic therapy daily for the 0 to 120-hour interval; and quality of life measured (twice) by the Functional Living Index-Emesis (FLIE) questionnaire; analyzed with a Wilcoxon or Kruskal-Wallis test.

Results

All results presented below are from analyses done by the applicant, unless otherwise indicated.

Primary efficacy outcome

The proportion of patients achieving a complete response during the first 24 hours after chemotherapy is shown below in tables 2a-c. Following that, in table 3, are the 97.5% confidence intervals for the difference between the palonosetron doses and the comparators in complete response rates during the first 24 hours after chemotherapy.

Table 2a. Proportion of patients achieving a complete response (CR) during the first 24 hours after chemotherapy, study PALO-99-03

Palonosetron 0.25		Palonosetron 0.75		Ondansetron 32	
Proportion	CI	Proportion	CI	Proportion	CI
153/189 (81%)	75, 86	139/189 (74%)	67, 80	127/185 (69%)	61, 75

Table 2b. Proportion of patients achieving a complete response (CR) during the first 24 hours after chemotherapy, study PALO-99-04

Palonosetron 0.25		Palonosetron 0.75		Dolasetron 100	
Proportion	CI	Proportion	CI	Proportion	CI
119/189 (63%)	56, 70	108/189 (57%)	50, 64	101/191 (53%)	46, 60

Table 2c. Proportion of patients achieving a complete response (CR) during the first 24 hours after chemotherapy, study PALO-99-05

Palonosetron 0.25 mg		Palonosetron 0.75 mg		Ondansetron 32 mg	
Proportion	CI	Proportion	CI	Proportion	CI
132/223 (59%)	52, 66	146/223 (66%)	59, 72	126/221 (57%)	50, 64

A higher proportion of the patients responded to palonosetron than to the comparator anti-emetics. The response rates in 99-04 were higher in all treatment arms than in 99-03, although both sets of patients received moderately emetogenic chemotherapy. The two studies differed primarily in the geographic location of the centers; response rates were higher in Europe. Also, in both of 99-03 and 99-04, response rates at the lower dose of palonosetron were higher than at the higher one. I was not able to find an explanation for this.

Table 3a. Confidence intervals for the difference between the palonosetron doses and the comparators in complete response rates during the first 24 hours after chemotherapy, standard analysis

Study	Palonosetron 0.25 vs. Ondansetron	Palonosetron 0.75 vs. Ondansetron	Palonosetron 0.25 vs. Dolasetron	Palonosetron 0.75 vs. Dolasetron
99-03	2, 23	-6, 16		
99-04			-2, 22	-8, 16
99-05	-9, 13	-2, 19		

In all cases, the lower boundary of the 97.5 % CI was above -10% , implying a reasonable certainty that the proportion of complete responders to palonosetron was no more than 10% less than the proportion among the comparators. The lower boundary of the confidence interval for the difference between palonosetron 0.25 and ondansetron in 99-03 is above zero, which the applicant takes as evidence of the superiority of palonosetron 0.25 to ondansetron in the treatment of acute nausea and vomiting following moderately emetogenic chemotherapy.

Confirmatory permutation analysis

For each of studies PALO-99-03, -04 and –05, the applicant computed a permutation distribution of the difference in response rates between each dose of palonosetron and the comparator. This distribution was based on 30,000 simulations of the trial; each simulation represented treatment assignments possible under the allocation scheme used and patient arrival sequence observed. The 2.5^{th} and 97.5^{th} percentiles of this distribution, added to the point estimate (the observed difference), represent the ends of the 95% confidence interval around the observed difference. I calculated these intervals, given in table 3b. The results are in accordance with the primary, standard analysis.

Table 3b. Confidence intervals for the difference between the palonosetron doses and the comparators in complete response rates during the first 24 hours after chemotherapy, permutation analysis

Study	Palonosetron 0.25 vs. Ondansetron	Palonosetron 0.75 vs. Ondansetron	Palonosetron 0.25 vs. Dolasetron	Palonosetron 0.75 vs. Dolasetron
99-03	3, 20	-4, 3		
99-04			0, 20	-6, 14
99-05	-7, 11	0, 18		

Secondary efficacy outcomes

A large number of secondary outcomes were recorded and analyzed. In general, palonosetron, particularly the 0.25 dose, compared favorably to the comparators. Complete response after 24 h is discussed below separately from the other secondary outcomes, since it is closely related to the primary efficacy outcome as well as a part of the basis for the proposed indication.

Delayed complete response

The applicant carried out an analysis for complete response rates for the time periods 24-48, 48-72, 72-96, and 96-120 hrs identical to the primary analysis. The results are shown below in tables 4 and 5.

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Table 4. Complete response rates, 24-120 hours. The N for a time period refers to the number of patients with complete response.

Study and time period	Palonosetron 0.25		Palonosetron 0.75		Ondansetron 32		Dolasetron 100	
	N	%	N	%	N	%	N	%
99-03	189		189		185			
24-120	140	74	122	65	102	55		
24-48	154	82	132	70	122	66		
48-72	161	85	147	78	124	67		
72-96	168	89	161	85	145	78		
96-120	175	93	169	89	161	87		
99-04	189		189				191	
24-120	102	54	107	57			74	39
24-48	118	62	118	62			85	45
48-72	128	68	138	73			107	56
72-96	149	79	155	82			137	72
96-120	167	88	162	86			156	82
99-05	223		223		221			
24-120	101	45	107	48	86	39		
24-48	127	57	129	58	109	49		
48-72	137	61	139	62	118	53		
72-96	149	67	164	74	142	64		
96-120	165	74	170	76	156	71		

Table 5. Confidence intervals for the difference between the palonosetron doses and the comparators in complete response rates during 24 –120 hours after chemotherapy

Study	Palonosetron 0.25 vs. ondansetron	Palonosetron 0.75 vs. ondansetron	Palonosetron 0.25 vs. dolasetron	Palonosetron 0.75 vs. dolasetron
99-03				
24-120	8, 30	-2, 21		
24-48	5, 26	-8, 15		
48-72	8, 28	-0.1, 22		
72-96	2, 20	-3, 16		
96-120	-2, 13	-6, 10		
99-04				
24-120			3, 27	6, 30
24-48			6, 30	6, 30
48-72			0.1, 23	6, 28
72-96			-3, 18	0.1, 20
96-120			-2, 15	-5, 13
99-05				
24-120	-5, 17	-2, 20		
24-48	-3, 20	-3, 20		
48-72	-3, 19	-2, 20		
72-96	-8, 13	-1, 20		
96-120	-7, 13	-4, 16		

On the basis of this analysis, the applicant claims that palonosetron is effective for prevention of delayed nausea and vomiting. There are two issues with including this as part of the indication for palonosetron. The first is that neither ondansetron nor dolasetron are approved for prevention of delayed emetogenesis, and thus may not be valid comparators in this situation. However, there is no reason to think that they would be less efficacious than placebo over a 5-day period, given their efficacy in prevention of emesis in the first 24 hours following chemotherapy. Thus a finding of greater efficacy of palonosetron relative to ondansetron and dolasetron could be taken as evidence of the general efficacy of palonosetron over the extended time period. Following highly emetogenic chemotherapy (PALO-99-05), the rates of complete response are consistently numerically higher for palonosetron 0.25 mg; however, there is no time period for which palonosetron is statistically significantly higher than the comparator ondansetron (as judged by the lower limit of the confidence interval of the difference). Following moderately emetogenic chemotherapy, the rates of complete response again are consistently higher for palonosetron 0.25 mg. It is statistically significantly higher than ondansetron at all time periods other than the final 96-120 hours, when there are high

response rates in all three treatment arms. Its performance against dolasetron is mixed, but is statistically significantly higher for the overall time period 24-120 hours as well as for each of the first two days in the extended time period.

The second issue is that 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. The lower limit of the confidence interval for the difference between palonosetron 0.25 mg and the comparator is well above zero for this time period in both 99-03 and 99-04.

Other secondary outcomes

The treatment groups were generally comparable on secondary outcomes. Differences that were found tended to be in favor of palonosetron relative to the comparators.

Prognostic subgroups

Gender, chemotherapy history (naïve or non-naïve) and corticosteroid use were prognostic factors taken into consideration in the allocation algorithm to balance the treatment groups. Complete response rates for 0-24 hours for each prognostic subgroup are shown below in table 6.

A greater proportion of the men than of the women responded to anti-emetic treatment. The differences between the genders were mostly on the order of 15-20%. Men responded markedly better than women to palonosetron 0.25 mg in study 99-04, and women to palonosetron 0.75 mg relative to the other treatments in 99-05, but there were no consistent differences between men and women among the treatments (i.e., no interaction between treatment group and gender). Both male and female subjects responded better to palonosetron than to the comparators.

There were no consistent or significant differences in complete response rates based on chemotherapeutic history or corticosteroid use.

Table 6. Complete response rates, 0-24 hours, for prognostic subgroups. N_{cr} is the number of patients with complete response

Study and subgroup	Palonosetron 0.25			Palonosetron 0.75			Ondansetron 32			Dolasetron 100		
	N	N_{cr}	%	N	N_{cr}	%	N	N_{cr}	%	N	N_{cr}	%
99-03	189			189			185					
Gender												
Male	54	49	91	51	46	90	52	41	79	--	--	--
Female	135	104	77	138	93	67	133	86	65			
Chemotherapy												
Naïve	76	67	88	80	55	69	78	58	74	--	--	--
Non-naïve	113	86	76	109	84	77	107	69	65			
99-04	189			189						191		
Gender												
Male	34	30	88	33	21	64	--	--	--	35	22	63
Female	155	89	57	156	87	56				156	79	51
Chemotherapy												
Naïve	124	75	61	131	73	56	--	--	--	125	58	46
Non-naïve	65	44	68	58	35	60				66	43	65
Corticosteroid use												
Yes	11	8	73	12	6	50				8	5	63
No	178	111	62	177	102	58				183	96	53
99-05	223			223			221					
Gender												
Male	108	72	67	110	75	68	108	73	68			
Female	115	60	52	113	71	63	113	53	47			
Chemotherapy												
Naïve	133	75	56	129	87	67	131	72	55			
Non-naïve	90	57	63	94	59	63	90	54	60			
Corticosteroid use												
Yes	150	97	65	150	94	63	147	82	56			
No	73	35	48	73	52	71	74	44	60			

3.1.2 Study PALO 99-01-23: Meta-analysis of historical data

The applicant says (v.368, p.5)

> Effective antiemetics are currently available for use by patients undergoing emetogenic chemotherapy. For this reason it is considered unethical to include a placebo control arm in trials investigating treatments for the prevention of chemotherapy-induced nausea and vomiting.

The efficacy trials done as part of this application did not include a placebo control. To assess trial validity and justify the value of delta used to declare non-inferiority of palonosetron to ondansetron or dolasetron, a meta-analysis of results from the anti-emetic literature was carried out, to estimate both historical placebo response and the corresponding historical rates for active comparators. These rates were then adjusted for covariates, in an attempt to make the historical populations comparable to the patients under study in PALO-99-03, -04 and –05. Covariates included features of the study, such as endpoint and emetogenicity of the administered chemotherapy, as well as of the patient population, such as the percentage of males in the study.

The applicant included information from 46 studies, with a total of 78 treatment arms. These studies were selected from the results of a literature search of Medline, along with studies suggested by Dr. Robert Prizont, FDA medical officer, or included in the FDA Summary Bases of Approval of ondansetron, dolasetron and granisetron. Study inclusion criteria are summarized in the Appendix.

I present some descriptive summaries gleaned from the database of study findings analyzed by the applicant (v. 371, appendix 5). Of the included studies, only four compared either ondansetron or dolasetron to placebo, with the results shown below. (The remaining studies either had no placebo control or compared placebo to other anti-emetogenics.) The response in all four was defined as no emetic episodes in 24 hours.

Table 7. Response rates in comparative trials

Study	Active treatment	Response in placebo	Response in active	Difference in rates	Emeto-genicity
Beck et al, 1993	Ondansetron	15/81 (19%)	52/79 (66%)	47%	Moderate
Cubeddu et al, 1990	Ondansetron	0/10 (0%)	7/10 (70%)	70%	Moderate
Cubeddu et al, 1990	Ondansetron	0/14 (0%)	2/14 (14%)	14%	High
Cubeddu et al, 1994	Ondansetron	9/73 (12%)	47/71 (66%)	54%	Moderate

The differences in response rates range from 14 to 70% overall, and from 47 to 70% for moderately emetogenic chemotherapy. In studies PALO-99-03, -04, -05, the observed lower limits of the confidence intervals for the difference between palonosetron and

dolasetron or ondansetron (table 3) fall well within this range. The lowest lower limit of a confidence interval is –9, above the smallest historical difference of 14.

The placebo response rates in these studies ranged from 0 to 50%, with a mean of 17 and a standard deviation of 16. The response rates for dolasetron or ondansetron ranged from 14 to 94%, with a mean of 59% and a standard deviation of 16. When these were broken down by emetogenicity of the administered chemotherapy, the placebo mean (SD) for highly emetogenic was 7 (10) and for moderately emetogenic was 20 (16), while for dolasetron or ondansetron the mean (SD) were 49 (12) and 70 (11), respectively.

Taking into account other differences among the studies leads naturally to the more formal analysis that the applicant performed (v 368, p15):

> ...Each observation was a treatment arm of a study identified and abstracted from the literature database....the dependent (response) variable was the fraction of CRs, as defined in each study. Independent variables in [the initial] model...were: percentage male; non-setron anti-emetics (pooled together); ondansetron; granisetron; dolasetron (placebo was used as a reference so it was not specifically identified in the model as a variable); endpoint timeframe (2 df= 24 [hrs] vs. 48 vs. all others); endpoint types (4 df = the four meta-analysis protocol specified types: a, b, c, d plus e (nausea only)); co-administration of corticosteroids (percentage of patients receiving steroids); emetogenicity potential (highly, moderate, and intermediate); location (US vs. Europe vs. South America); multi-center vs. single center; route (IV vs. PO); naïvety (Yes vs. No); analysis type (ITT vs. Per-Protocol); age; and gender.

This model was progressively simplified, testing for significance of the covariates. The final model did not distinguish among the setrons; combined US and South American locations into a single value; and did not include an adjustment for age. It also included interaction terms for setrons with fraction of patients with co-administration of corticosteroids and for setrons with fraction of males.

The applicant used this model to calculate hypothetical "historical" placebo and comparator results for each efficacy study PALO-99-03, -04 and -05 based on the relevant features of each of these studies as covariate values. The calculated confidence intervals are based on the standard errors of the estimates.

Table 8a. Complete response rates, meta-analysis modeling applied in study PALO-99-03

	CR	95% CI	Lower limit 95% CI minus upper limit 95% CI
Modeled historical placebo	17	13, 22	
Modeled historical ondansetron	63	55, 71	
Observed ondansetron	69	61, 75	
Historical ondansetron minus historical placebo			33
Observed ondansetron minus historical placebo			35

Table 8b. Complete response rates, meta-analysis modeling applied in study PALO-99-04

	CR	95% CI	Lower limit 95% CI minus upper limit 95% CI
Modeled historical placebo	15	11, 20	
Modeled historical dolasetron	60	51, 68	
Observed dolasetron	53	46, 60	
Historical dolasetron minus historical placebo			31
Observed dolasetron minus historical placebo			26

Table 8c. Complete response rates, meta-analysis modeling applied in study PALO-99-05

	CR	95% CI	Lower limit 95% CI minus upper limit 95% CI
Modeled historical placebo	12	9, 16	
Modeled historical ondansetron	52	43, 60	
Observed ondansetron	57	50, 64	
Historical ondansetron minus historical placebo			27
Observed ondansetron minus historical placebo			34

The results of this modeling meta-analysis are consistent with the summaries above: placebo response rates tend to be low, ondansetron and dolasetron rates are much higher, and the results of studies PALO-99-03, -04 and -05 are in line with historical observations.

3.1.3 Study 2330 / PALO-00-01

Design

Syntex's study 2330 was designed as a phase 2 study using the IV formulation of palonosetron. It was a randomized, double-blind, multicenter, dose-ranging trial of palonosetron given to chemotherapy-naïve patients 30 minutes before the administration of highly emetogenic chemotherapy.

The enrolled population consisted of 161 subjects. Palonosetron was administered at weight-based doses of 0.3, 1, 3, 10 or 30 μg/kg. The 0.3- μg/kg dose was discontinued after two patients had been enrolled in this dose group; the applicant pooled the data from the two lowest dose groups.

Analysis

The applicant calculated the number and proportion of patients achieving complete response (CR), defined as freedom from emetic episodes and rescue medication for 24 hours after administration of chemotherapy. The applicant also calculated the number and proportion of patients achieving complete control (CC) and total response (TR), defined respectively as defined as freedom from emetic episodes and rescue medication while experiencing only mild or no nausea, for 24 hours, and freedom from emetic episodes, rescue medication, and nausea for 24 hours.

Results

Table 9 below gives response rates based on the per-protocol population. The p-value refers to the result of a test of treatment effect versus the low dose group (0.3-1 μg/kg) , based on the Cochran-Mantel-Haenszel general association test stratified by investigator.

Table 9. Response rates, 0-24 hours, weight-based dose groups

	Palonosetron dose (μg/kg)				
	0.3-1 (N=29)	3 (N=24)	10 (N=25)	30 (N=24)	90 (N=46)
Complete response					
N (%)	7 (24%)	11 (46%)	10 (40%)	12 (50%)	21 (46%)
p-value	--	0.10	0.08	0.05	0.13
Complete control					
N (%)	7 (24%)	9 (39%)	10 (40%)	11 (48%)	21 (46%)
p-value	--	0.18	0.08	0.08	0.13
Total response					
N (%)	6 (21%)	7 (30%)	6 (24%)	9 (39%)	15 (33%)
p-value	--	0.28	0.40	0.06	0.36

The four highest doses were approximately equally effective and no dose-related adverse events were observed. The applicant chose the 3 and 10 μg/kg doses, the lowest apparently effective doses, to evaluate in Phase 3 trials.

Conversion to fixed doses (PALO-00-01)

Helsinn decided to conduct Phase 3 studies using fixed doses of palonosetron in order "to simplify dosing regimens and limit the potential for dosing errors in clinical practice." (v. 273, p.59). Palonosetron doses of 0.25 mg and 0.75 mg, corresponding to approximately 3 and 10 μg/kg for a 70-kg patient, were selected. Helsinn's study PALO-00-01 is a post-hoc efficacy analysis using data from study 2330, reallocating patients and their outcomes to groups defined by fixed doses of < 0.1, 0.25, 0.75, 2, or 6 mg. These doses were chosen to correspond approximately to doses of 0.3-1, 3, 10, 30 and 90 μg/kg for a 70-kg patient. In addition, the logistic model from the meta-analysis PALO-01-23 was used to calculate a historical placebo response.

Under this reallocation scheme, all but three patients were assigned to the same grouping as in study 2330. For example, 49 out of 50 patients enrolled and randomized to receive 90 μg/kg were assigned to the group defined as receiving 6 mg; the one who was not weighed only 39 kg and received a total dose of palonosetron of 3.5 mg. This patient was reassigned and his outcome reanalyzed as part of the 2 mg dose group.

Although the groupings remained essentially the same as the original randomization assignments, the dose of palonosetron actually received by patients in any one fixed-dose group varied quite a bit. The range of doses received by patients in each fixed-dose group for the intent-to-treat population is given in table 10 below. The calculation of ranges was based on weight summary statistics in the applicant's Table 15 of the study report (v.296, p.37)

Table 10. Range of doses received, by treatment group

Mg/kg	Fixed dose in mg	N (after reallocation)	Weight Mean	Weight SD	Weight Range	Palonosetron received dose range
0.3-1	<0.1	30	68	14	45-93	0.05-0.09
3	0.25	27	75	19	48-121	0.14-0.36
10	0.75	24	74	13	57-113	0.57-1.13
30	2	27	74	17	39-104	1.2-3.1
90	6	46	78	19	45-132	4.1-11.9
Total		154				

The results for the primary efficacy outcome for study PALO-00-01, essentially the same as study 2330, are shown below for the intent-to-treat population. These support the choice of 0.25 mg as a threshold efficacy dose and confirm the results of 99-05 for highly emetogenic chemotherapy.

Table 11. Response rates, 0-24 hours, fixed-dose groups

		Palonosetron dose (mg)				
	Historical placebo	<0.1 (N=30)	0.25 (N=27)	0.75 (N=24)	2 (N=27)	6 (N=46)
Complete response						
N (%)	(9%)	9 (30%)	12 (44%)	11 (46%)	15 (56%)	23 (50%)
95% CI	(3, 18)	(15, 49)	(25, 65)	(26, 67)	(35,75)	(35, 65)
Complete control						
N (%)		7 (24%)	9 (39%)	10 (%)	11 (%)	21 (%)
Total response						
N (%)		6 (21%)	7 (30%)	6 (24%)	9 (39%)	15 (33%)

3.2 Evaluation of Safety

See medical officer's review

4. Findings in Special/Subgroup Populations

4.1 Age, Gender, Race

Age

80% of the subjects in studies PALO-99-03, 99-04, and 99-05 were between the ages of 18-64 years, with the remaining 20% older than 64. Complete response rates for 0-24 hours among patients given palonosetron were greater than among patients given the active comparators in both age groups; the differences were more pronounced (and the response rates lower) in the younger group (combined rates for the three studies were, in the younger group, 65% on palonosetron 0.25 mg and 63% on palonosetron 0.75 mg, 60% on ondansetron and 47% on dolasetron; in the older group, the rates were 77, 76, 73, and 73%, respectively.)

Gender

Gender was a prognostic factor used in the allocation algorithm to balance the treatment groups.

Based on comparison of 0-24 hours complete response, a greater proportion of the men than of the women responded to anti-emetic treatment. The differences between the genders were mostly on the order of 15-20%. Men responded markedly better than women to palonosetron 0.25 mg in study 99-04, and women to palonosetron 0.75 mg relative to the other treatments in 99-05, but there were no consistent differences between men and women among the treatments (i.e., no interaction between treatment group and gender). Both male and female subjects responded better to palonosetron than to the comparators.

For more details see section 3.1.

Race

63% of the subjects in studies PALO-99-03, 99-04, and 99-05 were non-Hispanic white, 3% black, 33% Hispanic, and 2% were Asian or Other. Complete response rates for 0-24 hours among patients given palonosetron were greater than among patients given the active comparators for both whites and Hispanics; the response rates somewhat lower among Hispanics. (71 and 71 % vs. 65 ondansetron and 64 dolasetron in whites; 61, 55 vs. 52, 49 in Hispanics.) Small numbers make discussion of rates in other races meaningless.

4.2 Other—chemotherapeutic history, corticosteroid use

Chemotherapy history (naïve or non-naïve) and corticosteroid use (yes or no) were among prognostic factors taken into consideration in the allocation algorithm to balance the treatment groups. There were no consistent or significant differences in complete response rates for 0-24 hours based on chemotherapeutic history or corticosteroid use.

For more details see section 3.1.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

A primary concern from a statistical point of view is the minimization allocation procedure used in studies PALO-99-03, PALO-99-04 and PALO-99-05 . It is not randomization, but rather a deterministic allocation with the occasional random assignment. Several drawbacks of using minimization have been cited in the literature (Scott et al, 2002). The concern in this application is that standard statistical tests, or, equivalently, confidence interval calculations, make the assumption of random allocation: more generally, "the correct statistical analysis is complex and not yet clearly worked out." (Scott et al. 2002) Permutation methods can be used to check the results of standard analyses. The two approaches are likely but not guaranteed to yield similar conclusions; there are situations where the standard methods are very misleading. These situations have not been completely characterized. The trials in this application apparently do not fall into a problematic case. For each of studies PALO-99-03, -04 and –05, the applicant computed a permutation distribution of the difference in response rates between each dose of palonosetron and the comparator. This distribution was based on 30,000 simulations of the trial; each simulation represented treatment assignments possible under the allocation scheme used and patient arrival sequence observed. The results of the permutation analysis are in accordance with the primary, standard analysis.

None of the efficacy trials done as part of this application included a placebo control. To assess trial validity and justify the value of delta used to declare non-inferiority of palonosetron to ondansetron or dolasetron, an examination and meta-analysis of results from the anti-emetic literature was carried out. In the few studies where ondansetron or dolasetron was directly compared to placebo, the active treatment reliably out-performed placebo to a greater extent than the difference between treatments in the trials in this application. A less direct comparison of the effects of setron treatments and placebo, achieved through logistic regression modeling by the applicant, yielded similar results and similar confidence in the assay sensitivity of the NDA studies. The magnitude of the differences found or modeled in the meta-analysis also was large enough to justify a conclusion of non-inferiority of palonosetron in the current trials.

In studies PALO-99-03, 99-04, and 99-05, a higher proportion of the patients responded to palonosetron than to the comparator anti-emetics. Response rates ranged from a low

of 57%, for ondansetron 32 mg following the administration of highly emetogenic chemotherapy, to a high of 81% for palonosetron 0.25 mg following moderately emetogenic chemotherapy

The applicant calculated the two-sided 97.5% confidence interval of the difference between the proportions of complete response in each dose of palonosetron and comparator (calculated as palonosetron minus comparator) to demonstrate non-inferiority of palonosetron to the comparators. In all cases, the lower boundary of the interval was above -10% , implying a reasonable certainty that the proportion of complete responders to palonosetron was no less than 10% less than the proportion among the comparators.

The applicant wishes to include a secondary outcome as part of the labeled indication, namely that palonosetron is effective for prevention of delayed nausea and vomiting. Following highly emetogenic chemotherapy (PALO-99-05), the rates of complete response are consistently higher numerically for palonosetron 0.25 mg; however, there is no time period for which palonosetron is statistically significantly higher than the comparator ondansetron (as judged by the lower limit of the confidence interval of the difference). Following moderately emetogenic chemotherapy, the rates of complete response again are consistently higher for palonosetron 0.25 mg. It is statistically significantly higher than ondansetron at all time periods other than the final 96-120 hours, when there are high response rates in all three treatment arms; its performance against dolasetron is mixed, but is statistically significantly higher for the overall time period 24-120 hours.

The results for the primary efficacy outcome for study PALO-00-01 (essentially the same as study 2330), support the choice of 0.25 mg as a threshold efficacy dose and confirm the results of 99-05 for highly emetogenic chemotherapy.

5.2 Conclusions and Recommendations

There is sufficient evidence and reasonable certainty that palonosetron 0.25 mg is efficacious in the prevention of acute nausea and vomiting following moderately and highly emetogenic cancer chemotherapy. This conclusion is based on standard statistical analyses, a permutation analysis that takes the actual allocation method in account, and a meta-analysis of historical results. While the analyses are based on comparisons to approved anti-emetics (ondansetron and dolasetron), the efficacy conclusions and claims are relative to placebo; the label should reflect this distinction.

There is also sufficient evidence that it is efficacious in the prevention of delayed emesis following moderately emetogenic chemotherapy. Again, the analyses are based on comparisons to ondansetron and dolasetron, but the efficacy conclusions and claim are relative to placebo.

References

Scott et al., *Controlled Clinical Trials 23* (2002) 662-674.

Appendix

A.1. Allocation procedure

Here is the applicant's description of the allocation procedure used in studies PALO-99-03, PALO-99-04 and PALO-99-05 (Amendment #006, p. 3) :

> Patient allocation for studies PALO-99-03, PALO-99-04 and PALO-99-05 was performed through [redacted] System) and was similarly administered for all three studies. The only differences were the stratification variables used in each of the trials. It is important to note that for all three trials, a dynamic adaptive allocation was used with no randomization component (with the exception of situations where two or three treatments had the same "imbalance" and when the selected treatment was not available at the study site: in both of these cases a randomization was applied to the attribution of the treatment). The call sequence, for patient treatment assignments, made by investigators also added to the "randomness" of patient allocation. At the beginning of the study, this procedure was slightly different, but still deterministic....While this approach is not entirely consistent with ICH E9, Guidance on Statistical Procedures for Clinical Trials, the method chosen provides a basis for the quantitative evaluation of evidence relating to treatment effects, it produces treatment groups in which the distributions of prognostic factors, known or unknown, are similar and avoids possible bias in the selection and allocation of patients arising from the predictability of treatment assignments.
>
> Initially, treatment allocation followed a completely deterministic method (basically an urn ball model), using the stratification variables: gender and previous chemotherapy history to balance allocations across treatments (99-03 and 99-04). For study PALO-99-05, concomitant dexamethasone use was also added to this list of stratification variables. This method allocated treatments based on the treatments previously assigned. Site was not used as a stratification variable.
>
> The change in treatment allocation occurred on October 16, 2000. At that time a total of 6 patients in PALO-99-03, 59 patients in PALO-99-04 and 25 patients in PALO-99-05 were already enrolled.
>
> After October 16, 2000, the treatment allocation procedure was modified using the Pocock and Simon's range method (using unweighted sum and p_i=1) presented in Scott et al. (*Controlled Clinical Trials 23* (2002) 662-674). This method assigns treatments based on the above stratification criteria (after protocol amendment 5 of August 2001, the concomitant use of dexamethasone was an additional stratification stratum for study PALO-99-04), but calculates an "imbalance score"—also referred to as a variance which should be minimized.... Using this method, if this score has equal minimum imbalance scores with two or more treatments, then a randomization using a random number generator is used. The seed for the random number generator was based on the computer clock and was not saved, until September 27, 2001. Therefore, it is not known exactly how many times a randomization occurred, but it is estimated to be 20% across all three studies.
>
> Clinical trial material, i.e., the treatment kits, was supplied in blocks of three according to a random list prepared in advance. However, since the treatments were balanced not within each individual site, but across the entire study, it was not guaranteed that a treatment assignment was available at the site, although resupply was well organized. If the patient allocation scheme assigned a treatment which was not available at the site at the time of the treatment assignment, then another method of treatment assignment was used: this method was a random selection between available treatments.
>
> The imbalance between the treatment groups for each treatment was computed by assigning the patient to this specific treatment and summing the differences of the resulting maximum and minimum number of patients in each treatment arm for each of the stratification criteria....In the event of balance, i.e., if the minimum imbalance between the treatment groups was observed in two

or all three treatment groups a random number generator was used to select one of the minimum variance treatment groups.

The change in treatment allocation occurred on October 16, 2000.

At that time a total of 6 patients in study PALO-99-03, 59 patients in study PALO-99-04 and 25 patients in study PALO-99-05 were already enrolled. These numbers refer to the randomized and treated patients, not to specific analysis populations. ...

As for the selection of drug kit, in the event to kit chosen by the —' system was not available at the site, the procedure used during the entire study period was always random selection between the available kits.

A.2. Criteria for study inclusion in meta-analysis (PALO-01-23)

A study was required to meet the following criteria to be included in the meta-analysis database (v. 368, pp.7-9):

1. Study was published in a peer reviewed journal, or FDA SBA, or FDA reviewer's summary documents for ondansetron, dolasetron, and granisetron

2. Article was published in English from studies performed in North America, Central America, Europe, Israel, Australia, New Zealand, Russia, South America, and South Africa.

3. Study involved use of anti-emetics for prevention of CINV.

4. Study was conducted under IRB review (stated as such , or stated that patients gave consent)

5. Study was randomized.

6. Study was double-blind

7. Study compared at least two different acceptable therapeutic study arms. Studies having only one acceptable study arm were also included in the meta-analysis database if the single allowed treatment arm was ondansetron, dolasetron, granisetron, or placebo.

8. Study involved patients undergoing moderately or highly emetogenic chemotherapy.

9. Study involved patients, male or female at least 18 years of age.

10. Study reported one of the following efficacy endpoints:

    No emetic episodes and no rescue medication during the period 0-24, 0-48, or 0-72 hours after chemotherapy;

No emetic episodes, no rescue medication and no more than mild nausea during the period 0-24, 0-48, or 0-72 hours after chemotherapy;

No emetic episodes and no more than mild nausea during the period 0-24, 0-48, or 0-72 hours after chemotherapy;

No emetic episodes during the period 0-24, 0-48, or 0-72 hours after chemotherapy;

No emetic episodes and no nausea during the period 0-24, 0-48, or 0-72 hours after chemotherapy;

11. Study reported either per protocol data or intent to treat data.

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