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APPLICATION NUMBER

21-372

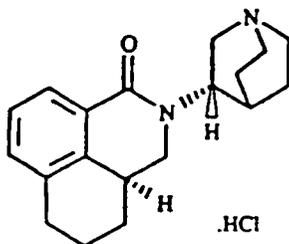
Medical Review(s)

Addendum: Medical Officer Review of NDA 21-372 Palonosetron

Date Submitted: 10 July 2003
Date Received: 11 July 2003
Date Completed: 11 July 2003

Applicant: Helsin Healthcare SA
Via Pian Scairolo
6912 Pazzallo (Lugano) - Switzerland

Drug: Generic Name - Palonosetron
Molecular Weight - 332.87
Molecular formula - $C_{19}H_{24}N_2O \cdot HCl$
Molecular structure -



Drug Class: 5-HT₃ antagonists

Formulation: 5-ml vial of palonosetron injection contains 0.25 mg palonosetron base as hydrochloride, 207.5 mg mannitol, disodium edetate and citrate buffer in water

Route of Administration: Intravenous

I. Introduction

Helsinn Healthcare submitted a New Drug Application (NDA) for the new molecular entity palonosetron on September 26, 2002. The Medical Officer's Clinical Review for this NDA was completed June 6, 2003. Subsequently, it was noted that some of the data submitted by the applicant is contradictory and possibly erroneous. This data was included in the initial clinical review unaltered. The purpose of this document is to discuss the discrepancies in applicant submission and review the implications for the NDA as a whole.

II. Review of Data

The applicant's submission consisted of 381 volumes of written material. In two places (on page 220 of Volume 1, and page 99 of Volume 96) the following table can be found.

Table II:1 Number and Percentage of Patients with Post Dose* Changes in QTc by Bazett or Fridericia Corrections

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

N= Number of patients in specific group.

Nt= Total Number of patients with ECG parameter.

n = Number of patients with changes.

% = Percentage of patients with changes.

QTcF = QT interval corrected by Fridericia formula.

QTcB = QT interval corrected by Bazett formula.

msec = Milliseconds

Source: Expert Report PALO-02-04; Appendix A.

* - post dose ECG's were obtained at 24 hours and 6-8 days after drug administration. A subset of patients had a ECG performed 15 minutes after drug administration. The data for this table was derived from the ECG that had the worst value for each patient regardless of the time of the recording.

The narrative accompanying this table goes on to state "no subject [in the palonosetron arms] had > 60 msec change from baseline." The table with the accompanying statement was incorporated in the Medical Officer's Clinical Review as Table 37 on page 77. Subsequently, it was noted that there were inconsistencies in this data. Firstly, the numbers and percentages do not correspond to each other. According to

this table, five subjects of 594 in the palonosetron 0.25 mg dose group had a change in QTcB > 60 msec. Yet, the table displays corresponding percentage as "0" rather than the correct percentage of 0.84. This happens several other times in this table for all the treatment arms. These instances where a "0" has inappropriately been listed as a percentage are shown in boldface type. In addition, the accompanying statement that no subjects had a QTc > 60 msec directly contradicts the information provided in the table.

On July 9, 2003 a telephone conversation was held between the medical officer from the Agency and Helsinn's representative Dr. Craig Lehmann to discuss these discrepancies. Consequently, Dr. Lehman spoke with Dr. _____ the cardiologist who authored this portion of the NDA submission. The applicant provided a reply in the form of a phone message and written fax response on July 10, 2003. In the response, Dr. Lehmann verifies that the numbers listed in the "n" column of the table are correct. However, the percentages were not correct due to a rounding error. On review, it seems all the percentages for all the treatment arms were rounded down. The corrected version of the table is shown below.

Revised Table with Correct Percentages (rounded to nearest tenth)

	Palonosetron 0.25 mg (N = 605) Nt = 594		Palonosetron 0.75 mg (N = 610) Nt = 601		Ondansetron 32 mg (N = 410) Nt = 404		Dolasetron 100 mg (N = 194) Nt = 192	
	n	%	n	%	n	%	n	%
QTcB 30 to 60 msec	41	6.9	54	8.9	41	10.1	13	6.7
QTcB > 60 msec	5	0.8	3	0.5	7	1.7	2	1.0
QTcB > 500 msec	1	0.2	0	0	1	0.2	1	0.5
QTcF 30 to 60 msec	27	4.5	31	5.2	32	7.9	11	5.7
QTcF > 60 msec	5	0.8	2	0.3	4	1	1	0.5
QTcF > 500 msec	0	0	0	0	0	0	1	0.5

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

The applicant's response discusses the issues of the contradictory statement as follows "Based on discussion today with Dr. _____ this statement reflects the zero percent incidence values which are incorrect as discussed." It appears the author referred to the erroneous percentage values when he stated that no patients had a change in QTc>60 msec. As the table shows 8 subjects in the palonosetron arms had QTcB changes > 60 msec and 7 subjects had QTcF changes > 60 msec.

The initial conclusion of the medical officer's clinical review in regard to cardiac safety was that palonosetron's effect on QTc was similar to that of other drugs in its class. These errors are not of a magnitude to alter this conclusion. Furthermore, the errors are of a mathematical nature and are present in all the treatment arms. They do not appear to be an attempt by the applicant to conceal or alter the side effect profile of this new molecular entity.

III. Summary

1. The percentages listed in Table III:1 entitled "Number and Percentage of Patients with Post Dose Changes in QTc by Bazett or Fridericia Corrections" is in error. This table was located on page 220 of Volume 1, and page 99 of Volume 96 in the NDA 21-372 submission for palonosetron. The table with the incorrect data was also incorporated in the Medical Officer's Clinical Review as Table 37 located on page 77. The corrected table can be found above.
2. The accompanying statement state "no subject had > 60 msec change from baseline" is also in error. This statement can be found in the narrative following the table on page 220 of Volume 1, and page 100 of Volume 96 in the NDA 21-372 for palonosetron. This incorrect statement was also incorporated into the Medical Officer's Clinical Review on page 77. The correct statement is that 8 subjects in the palonosetron arms had QTcB changes > 60 msec and 7 subjects in the palonosetron arms had QTcF changes of > 60 msec.
3. These errors are not of a magnitude to alter the medical officer's conclusion that palonosetron's effect on QTc is similar to that of other drugs in its class.
4. The errors appear to be of a mathematical nature, which are present in all the treatment arms. They do not appear to be a deliberate attempt by the applicant to conceal or alter the side effect profile of this new molecular entity.

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/s/

Narayan Nair
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MEDICAL OFFICER

Joyce Korvick
7/22/03 05:20:33 PM
MEDICAL OFFICER

**CLINICAL REVIEW STUDY 99-04
PALONOSETRON**

**Detailed Review Of Study PALO-99-04 – A Double Blind Clinical Study To
Compare Single IV Dose Of Palonosetron, 0.25 Mg or 0.75 Mg And Dolasetron, 100
mg IV, In Prevention Of Moderately Emetogenic Chemotherapy-Induced Nausea
And Vomiting**

I. OBJECTIVES

The primary objective of the study PALO-99-04 was to compare the efficacy of single IV doses of palonosetron 0.25 mg or 0.75 mg, to dolasetron 100 mg IV in preventing moderately emetogenic CINV.

The secondary objectives were to evaluate the safety and tolerability of palonosetron and its relative safety in comparison with dolasetron. In addition, the effect of anti-emetic control with palonosetron or dolasetron on the quality of life of patients receiving moderately emetogenic chemotherapy was evaluated.

II. STUDY DESIGN AND METHODOLOGY

This was a double-blind clinical study to compare single IV doses of palonosetron 0.25 mg or 0.75 mg, and dolasetron 100 mg IV, in the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. The comparator drug dolasetron is an FDA approved medication that is indicated for the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. The dose of dolasetron is the standard dose used in clinical practice. The table on the following page lists the study procedures.

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TABLE 1 : Study Flow Chart

	Screening Study Day -7 to 0	Study Day 1	Study Day 2 ^a	Study Day 5 ^b	Study Day 6-8	Study Day 15+/- 1 ^c	Study Day 15- 28 ^d
	Visit 1	Visit 2	Visit 3	Tele 1	Visit 4	Tele 2	Visit 5
Informed Consent	X						
Inc/Excl demographic	X						
Karnofsky's Index	X						
Past Medical History	X						
Blood Chemistry	X		X		X		
CBC with differential	X		X		X		
Urinalysis	X		X		X		
Pregnancy Test ^e	X						
Randomization ^f	X						
Study Medication		X					
Chemotherapy ^g		X					
Dexamethasone ^h		X					
Physical Exam	X		X ^h		X ^h		X
Vital Signs and Weight	X		X		X		X
12-Lead ECG	X	X ⁱ	X		X		
Efficacy Parameters ^j		X	X	X	X		
FLIE Questionnaire	Instruction		X ^k	X ^l	collection		
Patient's Diary and VAS ^m	Instruction	Filled in from Study Day 1 to Study Day 5 daily			collection		
Concomitant Meds	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Holter Monitoring ⁿ	initiation		termination				
PK ^o (Holter Patients)		X			X ^p		
PK ^o (selected non-Holter patients)		X	X		X ^p		X

- a) Post study medication administration
b) If Study Day 5 was a holiday or weekend day, patients were contacted the previous/next business day
c) If patient was scheduled for a clinic or hospital visit on this day, this information was obtained at that time
d) Only for those patients who enrolled in the open label protocol (PALO-99-06)
e) For females of childbearing potential only
f) After all inclusion/exclusion criteria were met the patient could be randomized to one of three treatment groups
g) 30 minutes post study medication administration
h) At the discretion of the investigator, dexamethasone, 20 mg IV could be given 15 minutes before the start of chemotherapy (in the event of a shortage of IV dexamethasone, a single 20 mg oral dose of dexamethasone or a single 125 mg IV dose of methylpredisone could be given).
i) Limited physical examination only on these days
j) 15 minutes post study medication administration in Holter patients only
k) See below for efficacy parameters and assessments
l) Referring to Study Day 1 (0-24 hours)
m) Referring to Study Days 2-4 (24-96 hours)
n) Filled in on Study Days 1-5 collected on Study Day 6-8
o) Patients at selected sites were to have Holter Monitoring from at least 2 hours before to at least 22 hours after start of study medication administration
p) Blood sampling for pharmacokinetic analysis
q) Blood sampling for pharmacokinetic analysis should be performed as close as possible to Study Day 6

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(Reference Table 5.5-a, Page 38, volume 135)

Screening Study Day -7 to 0 (Visit 1)

Patients signed an informed consent and then had their demographic information recorded. The investigator performed an initial history and physical examination. Eligibility criteria were examined and the patient underwent laboratory studies. This included 12 lead ECG, blood chemistry, complete blood count and urinalysis. A urine pregnancy test was done for females of childbearing potential as well. Patients were instructed on how to use the diaries to record nausea and episodes of emesis. If patients were randomized to get a Holter monitor, this was started 2 hours before the start of the study medication administration.

Study Day 1 (Visit 2)

Study Day 1 was defined as the day the patient received a single dose of a major chemotherapeutic agent that was considered the most emetogenic (as classified by Hesketh et al., *The Oncologist* 1999;4:191-196). The administration of this agent was not to extend greater than 4 hours.

Each patient was randomized to 1 of 3 treatment groups

- Palonosetron 0.25 mg given as a single dose over 30 seconds, 30 minutes prior to chemotherapy
- Palonosetron 0.75 mg given as a single dose over 30 seconds, 30 minutes prior to chemotherapy
- Dolasetron 100 mg given as a single dose over 30 seconds, 30 minutes prior to chemotherapy

A randomization list was prepared by the firm _____, in the United States. The study was extended into Mexico and a randomization list was prepared by a statistician not involved with the applicant using a validated SAS program. Randomization was blocked by groups of three. It was stratified by gender (male or female), previous chemotherapeutic history (naive, non-naive). A dynamic adaptive stratification type of randomization method was employed to balance the three treatment groups across these criteria. It was then checked if the study site had the supply of the selected study drug. If the kit containing the drug and dose to which the patient was randomized was not available then they would be randomly assigned to one of the other treatment arms. If the study site had only one drug available then the patient was automatically assigned to that treatment arm. The investigator called an automated telephone line and received a randomization code for the patient. Based on this randomization code, the research pharmacists would select the appropriate drug. The pharmacist would then prepare the drug for administration in unblinded fashion.

The pharmacist would deliver the drug to the investigator in a blinded fashion. A double dummy technique was utilized because the volume of the two study medications was different. Each patient received two injections: one containing the active study drug, the other inactive normal saline thus ensuring everyone received the same volume infusion regardless of treatment arm. The palonosetron or dolasetron was administered as an IV bolus over 30 seconds, 30 minutes prior to the chemotherapy. The patient remained in the clinic for a minimum of 3 hours after the administration of the study drug.

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After randomization, patients were asked if they wished to wear a Holter monitor. Holter monitor assignment was blocked if there was a difference of 10 between treatment groups or if 20 Holter patients were already in a treatment group. The plan was to have 95 patients (16.7%) wear a Holter monitor.

Medical Officer Comments: All study sites should have been provided with ample supplies of the study drug and the active control. This would have allowed true randomization. If a site only had one drug available, the patient was automatically enrolled in that treatment arm. This does not reflect true randomization. However, this only occurred in five patients (2 in each of the palonosetron arms, and 1 in the dolasetron arm). Since this is a small number, it does not invalidate the results. In addition, the applicant should have considered sending each site an unlabeled kit containing the study drug, or active control medication. This would have allowed the research pharmacist to remain blinded, and permitted all personnel at each site to be blinded to the treatment.

Study Day 2 (Visit 3)

Patients returned 24 hours after the study medication administration to the study site. They underwent a repeat physical examination, 12 lead ECG, laboratory evaluation and documentation of adverse events. For patients who were selected to have a Holter monitor it was removed 22 hours after the start of the study medication.

Study Day 5 (Telephone contact 1)

All patients were contacted by telephone for adverse events and concomitant medication recording.

Study Day 6 to 8 (Visit 4)

Patients underwent a repeat physical examination, 12 lead ECG, laboratory evaluation and documentation of adverse events. For patients who were selected to have a Holter monitor it was removed 22 hours after the start of the study medication. At this visit the 5-day patient diary was completed.

Study Day 15 (Telephone contact 2)

All patients were contacted by telephone, and adverse events and concomitant medication were recorded.

III. ELIGIBILITY CRITERIA

Male or females (females of childbearing potential using reliable contraceptive measures and a negative pregnancy test), at least 18-years of age, and who provided written informed consent were eligible for enrollment if they met the following inclusion criteria:

- Chemotherapy naïve subjects with histologically or cytologically confirmed malignant disease
- Chemotherapy non-naïve subjects with histologically proven diagnosis of cancer
- Have a Karnofsky index of $\geq 50\%$.
- Scheduled to receive a single dose of at least one of the following agents administered on Day 1 of the study: any dose of carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan or mitoxantrone; or methotrexate $> 250 \text{ mg/m}^2$; or cyclophosphamide

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<1500 mg/m² IV; doxorubicin > 25 mg/m² IV; or cisplatin ≤ 50 mg/m² IV (to be administered over 1-4 hours).^a

- If a subject has a known hepatic, renal or cardiovascular impairment and is scheduled to receive the above-mentioned chemotherapeutic agents, he/she may be enrolled in this study at the discretion of the investigator.
- If a subject experienced no more than mild nausea following any previous chemotherapy regimen, he/she could have been enrolled at the discretion of the investigator.

The following are exclusion criteria:

- Unable to understand or cooperate with study procedure
- Received any investigational drug 30 days prior to study entry
- Received any drug or were scheduled to receive any drug with anti-emetic efficacy within 24 hours of the start of treatment until Day 5 of the study
- Enrollment in a previous study with palonosetron
- Seizure disorder requiring anticonvulsant medication unless clinically stable and free of seizure activity
- Experienced any vomiting, retching, or NCI Common Toxicity Criteria grade 2 or 3 nausea in the 24 hours preceding chemotherapy.
- Ongoing vomiting from any organic etiology
- Experienced nausea (moderate to severe or vomiting following any previous chemotherapy. At the discretion of the investigator, a patient who experienced at maximum mild nausea following any previous chemotherapy might not be excluded from this study)
- Scheduled to receive any dose of a chemotherapeutic agent with an emetogenicity level 5 according to Hesketh et al Classification (The Oncologist 1999; 4:191-196) or were scheduled to receive any chemotherapeutic agent with an emetogenicity level 3 or higher during Days 2-6
- Known contraindication to 5-HT₃ antagonist
- Scheduled to receive radiotherapy of the upper abdomen or cranium during Study Day 2

Medical Officer Comments: The inclusion criteria are adequate. These doses of chemotherapy are considered moderately emetogenic according to the classification by Hesketh, et al., The Oncologist 1999. The exclusion criteria are adequate with one exception. The protocol excludes patients who had previous nausea or vomiting with previous chemotherapy. This could introduce bias into the study. Patients who are not chemotherapy naïve and enter the study are subjects who tolerate chemotherapy well with respect to emetogenicity. This could make the results appear more favorable in this subset of patients. However, the agency did agree to these criteria in a Special Protocol Assessment dated December 1999. The results demonstrated that naïve subjects had a better response than non-naïve.

IV. STATISTICAL ANALYSIS

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PALO-99-04 was an active comparator, non-inferiority analysis that employed a 15% delta. The primary efficacy parameter in these trials was the proportion of subjects considered to have achieved a complete response (CR) during the first 24 hours after administration of chemotherapy. CR is defined as no emesis and no rescue medication during the first 24 hours after chemotherapy.

The lower bound of 97.5% CI for the difference (palonosetron minus active comparator) between the proportion of subjects with a complete response during the first 24 hours after administration of chemotherapy was calculated and compared to the pre-set threshold (-15% difference) to demonstrate non-inferiority. To demonstrate that the two palonosetron doses were equal with respect to CR (0–24 hours), the bounds of the two-sided 95% CI of the difference between the proportions of CR (0–24 hours) were compared to the pre-set threshold ($\pm 15\%$). The intent to treat (ITT) population was used in the primary analysis. Table 2 displays the various statistical methods used for the secondary efficacy parameters at various time intervals.

TABLE 2 – Statistical Test Utilized for Secondary Efficacy Parameters

Parameters	Statistical Test
Complete Control (CC)	
0-24 hr	Chi-square
24-48 hr	Chi-square
48-72 hr	Chi-square
72-96 hr	Chi-square
96-120 hr	Chi-square
0-48 hr	Chi-square
0-72 hr	Chi-square
0-96 hr	Chi-square
0-120 hr	Chi-square
Number of Emetic Episodes (EE)	
0-24 hr	Kruskal-Wallis/Wilcoxon
24-48 hr	Kruskal-Wallis/Wilcoxon
48-72 hr	Kruskal-Wallis/Wilcoxon
72-96 hr	Kruskal-Wallis/Wilcoxon
96-120 hr	Kruskal-Wallis/Wilcoxon
0-120 hr	Kruskal-Wallis/Wilcoxon
Time to First EE	Log Rank
Severity of Nausea	
0-24 hr	Kruskal-Wallis/Wilcoxon
24-48 hr	Kruskal-Wallis/Wilcoxon
48-72 hr	Kruskal-Wallis/Wilcoxon
72-96 hr	Kruskal-Wallis/Wilcoxon
96-120 hr	Kruskal-Wallis/Wilcoxon

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Due to ethical concerns, a placebo-controlled trial was not feasible for CINV. Thus to ensure validity, the applicant developed a meta-analysis (PALO-01-23) which used data from a published literature to predict the complete response for CINV. A literature search was performed to select articles using placebo, dolasetron, granisetron, ondansetron and other anti-emetics for CINV). This meta-analysis database consisted of 78 treatment arms from published trials and included 7274 subjects. Helsinn used this database to perform a logistic regression to identify which covariates were relevant in predicting complete response for various treatments and produce a model to calculation of historical placebo and historical active comparator complete response.

Validity was demonstrated if:

- the lower limit of the 95% CI of complete response in the active comparator group was greater than the upper limit of the 95% CI of the complete response rate of the modeled historical placebo; and
- the complete response rate achieved in the active comparator group was similar to modeled historical comparator.

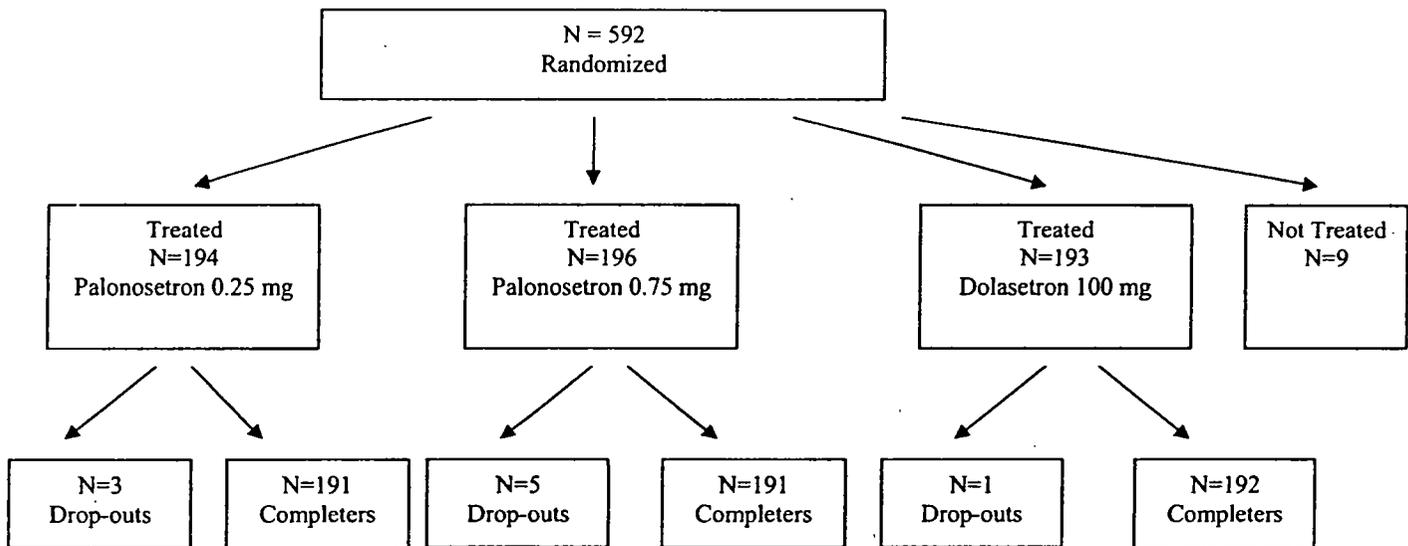
Medical Officer Comments: The Agency and the applicant agreed to this approach to validation in pre-NDA meetings and end of Phase II meetings held in spring of 1999.

V. RESULTS

A. Demographics and Disposition of Patients

Sixty-one centers enrolled 593 patients. Of these, 592 were randomized to one of the three treatment groups (1 patient was not randomized and did not receive treatment). The following figure shows the disposition of patients.

FIGURE 1 – Disposition of Patients



From Figure 6.1-1, Volume 135, pg. 72

Of the eight patients in the palonosetron arms who withdrew from the study:

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- 3 dropped out because of patient decision
 - 3 dropped out due to serious adverse event or death (1 patient who received 0.25 mg and 2 in the 0.75 mg group)
 - 1 dropped out because of violation of exclusion criteria
 - 1 patient lost to follow-up.
- One patient who received dolasetron was lost to follow-up.

The following table shows the number of patients by region.

TABLE 3 – List of Patients by Region

Country (Active centers)	Patients Randomized	Gender		Chemotherapeutic History		Holter Monitor Performed	Corticosteroid Use	
		Male	Female	Naïve	Non- Naïve		Yes	No
U.S. East (13)	93	24	69	38	94	3	7	86
U.S. West (15)	40	12	28	25	29	2	13	27
California (13)	128	30	98	34	30	3	7	121
Mexico South (6)	76	10	66	28	30	8	1	75
Mexico Center (10)	172	22	150	57	64	11	2	170
Mexico North (4)	83	8	75	63	86	22	1	82
Total (61)	592	106	486	237	333	49	31	561

(Reference: Table 6.1-a, pg. 71, Volume 135)

Mexico Center and California were the regions in which the largest number of patients were enrolled.

The following table shows the number of patients by gender, corticosteroid use and the number of chemotherapy naïve or non-naïve patients.

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TABLE 4 - Gender/Chemotherapeutic History

	Palonosetron 0.25 mg (N=189)	Palonosetron 0.75 mg (N=189)	Dolasetron 100 mg (N=191)
	N.(%)	N.(%)	N.(%)
Gender			
Male	34 (18.0)	33 (17.5)	35 (18.3)
Female	155 (82.0)	156 (82.5)	156 (81.7)
Chemotherapeutic History			
Naïve	124 (65.6)	131 (69.3)	125 (65.4)
Non-naïve	65 (34.4)	58 (30.7)	66 (34.6)
Corticosteroid Use			
Yes	11 (5.8)	12 (6.3)	8 (4.2)
No	178 (94.2)	177 (93.7)	183 (95.8)

(Reference: Table 6.3-b, pg. 76, Volume 135)

Medical Officer Comments: The distribution of patients by gender, corticosteroid use and chemotherapeutic history is similar across treatment groups. The majority of patients were female and naïve. This is because moderate emetogenic chemotherapy is most frequently given for breast cancer. The number of patients who received corticosteroids was small. This is because its use was allowed by amendment to the protocol that was implemented 5 months prior to the study ended.

The next table displays the type of cancer for which chemotherapy was given.

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TABLE 5 -Type of Cancer (by MedDRA preferred term) for which Chemotherapy was given

Type of Cancer	Palonosetron 0.25 mg (N=193)	Palonosetron 0.75 mg (N=195)	Dolasetron 100 mg (N=194)
	N (%)	N (%)	N (%)
Breast Cancer female – nos	106 (54.9)	95 (48.7)	110 (56.7)
Breast Cancer invasive –nos	22 (11.4)	20 (10.3)	19 (9.8)
Lung Cancer	8 (4.1)	10 (5.1)	7 (3.6)
Non-Hodgkins lymphoma- nos	8 (4.1)	13 (6.7)	8 (4.1)
Non-small cell lung cancer	5 (2.6)	2 (1.0)	2 (1.0)
Ovarian cancer- nos	4 (2.1)	9 (4.6)	3 (1.5)
Breast Cancer stage II	3 (1.6)	1 (0.5)	2 (1.0)
Cervical cancer carcinoma	3 (1.6)	2 (1.0)	2 (1.0)
Small cell lung cancer stage unspecified	3 (1.6)	6 (3.1)	4 (2.1)
Colon Cancer nos	2 (1.0)	3 (1.5)	0 (0.0)
Prostate cancer nos	1 (0.5)	1 (0.5)	3 (1.5)
Acute lymphocytic leukemia	0 (0.0)	2 (1.0)	4 (2.1)

(Reference: Table 6.4.2-a, pg. 89, Volume 135)

Medical Officer Comments: Breast cancer was the most frequently reported primary cancer in all treatment groups. A higher number of small cell lung cancer and colon cancer was seen in the palonosetron groups versus the dolasetron group. However, these differences should not have affected the results of the study.

The following table gives detailed information about the demographic data of the patients enrolled.

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TABLE 6 – Demographic Data of Patients

	Palonosetron 0.25 mg (N=193)	Palonosetron 0.75 mg (N=195)	Dolasetron 100 mg (N=194)
	N (%)	N (%)	N (%)
Gender			
Male	34 (17.6)	34 (17.4)	36 (18.6)
Female	159 (82.4)	161 (82.6)	158 (81.4)
Ethnic Group			
White	61 (31.6)	68 (34.9)	62 (32.0)
Black	12 (6.2)	8 (4.1)	10 (5.2)
Hispanic	115 (59.6)	114 (58.5)	115 (59.3)
Asian	3 (1.6)	4 (2.1)	6 (3.1)
Other	2 (0.0)	5 (2.6)	1 (0.5)
Tobacco Use			
Non-smoker	128 (66.3)	114 (58.5)	114 (58.8)
Ex-smoker	38 (19.7)	52 (26.7)	51 (26.4)
Smoker	27 (14.0)	29 (14.9)	29 (14.9)
Alcohol consumption			
No	126 (65.3)	128 (65.6)	5 (2.6)
Rarely	26 (13.5)	31 (15.9)	25 (12.9)
Occasionally	32 (16.6)	26 (13.3)	20 (10.3)
Regularly	9 (4.7)	9 (4.6)	14 (7.2)

(Reference: Table 6.41-a, pg. 80, Volume 135)

Medical Officer Comments: Overall the treatment arms were balanced in regard to baseline demographic characteristics. Due to the many of the clinical sites being located in Mexico a large number of subjects were Hispanic.

The following table gives physical characteristics of the patients in each treatment arm.

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TABLE 7 – Age, Height, Weight, and Karnofsky Index for Each Treatment Arm

	Palonosetron 0.25 mg (N=193)		Palonosetron 0.75 mg (N=195)		Dolasetron 100 mg (N=194)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	53.6	13.1	55.7	13.2	54.0	13.0
Height (cm)	159.7	9.5	160.3	8.9	160.6	9.1
Weight (kg)	71.6	17.3	71.0	16.0	72.5	18.5
Karnofsky Index (%)	94.7	8.2	93.6	9.9	94.3	8.8

(Reference Table 6.4.1-a, pg. 80, Volume 135)

Medical Officer Comments: Each treatment arm was similar in regards to age, height and weight. They also were balanced in regards to Karnofsky index.

TABLE 8 –Risk Factors for Patients

	Palonosetron 0.25 mg (N=189)	Palonosetron 0.75 mg (N=189)	Dolasetron 100 mg (N=185)
	N (%)	N (%)	N (%)
Renal Impairment			
Yes	2 (1.1)	1 (0.5)	2 (1.0)
No	187 (98.9)	188 (99.5)	189 (99.0)
Hepatic Impairment			
Yes	2 (1.1)	4 (2.1)	3 (1.6)
No	187 (98.9)	185 (97.9)	188 (98.4)
Cardiac Impairment			
Yes	7 (3.7)	7 (3.7)	6 (3.1)
No	182 (96.3)	182 (96.3)	185 (96.9)

(Reference: Table 6.4.1-b, pg. 85, Vol. 135)

Medical Officer Comments: There were small numbers of patients with organ impairment. The most common organ impairment was cardiac.

The protocol defined prior diseases as those starting before Visit 1 and not ongoing after Visit 1. Concomitant diseases were defined as those starting before Visit 1 and ongoing

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after Visit 1. The following table lists prior and concomitant diseases. Diseases are listed by the system organ class followed by preferred term according to MedDRA.

TABLE 9 – Most Common Prior and Concomitant Diseases¹

System Organ Class ² Preferred Term ³ (MedDRA)	Palonosetron 0.25 mg (N=193)	Palonosetron 0.75 mg (N=193)	Dolasetron 100 mg (N=194)
	N (%)	N (%)	N (%)
Any prior Disease	129 (66.8)	130 (66.8)	126 (64.9)
Infections and infestations	46 (23.8)	47 (24.1)	43 (22.2)
Gastrointestinal disorders	43 (22.3)	44 (22.6)	44 (22.7)
Reproductive system and breast disorders	25 (13.0)	29 (14.9)	28 (14.4)
Any concomitant diseases	156 (80.8)	163 (83.6)	143 (73.7)
Metabolism and nutrition disorders	60 (31.1)	55 (28.2)	46 (23.7)
Diabetes mellitus nos	18 (9.30)	23 (11.8)	15 (7.7)
Reproductive system and breast disorders	50 (25.9)	48 (24.6)	50 (25.8)
Menopause	41 (21.2)	40 (20.5)	38 (19.6)
Vascular disorders	48 (24.9)	62 (31.8)	65 (33.5)
Hypertension nos	41 (21.2)	48 (24.6)	50 (25.8)
Musculo-skeletal, connective tissue and bone disorders	43 (22.3)	56 (28.7)	52 (26.8)
Gastrointestinal disorders	41 (21.2)	46 (23.6)	41 (21.1)
Immune system disorders	32 (16.6)	40 (20.5)	32 (16.5)
Drug hypersensitivity	24 (15.5)	35 (17.9)	30 (15.5)
Respiratory disorders	32 (16.6)	22 (11.3)	29 (14.9)
Blood and lymphatic system	30 (15.5)	24 (12.3)	30 (15.5)
Anemia	24 (12.4)	16 (8.2)	22 (11.3)
Cardiac disorders	27 (14.0)	22 (11.3)	23 (11.9)
Nervous system disorders	24 (12.4)	34 (17.4)	33 (17.0)

¹ Multiple answers possible

² Incidence at least 14% of patients in treatment group

³ Incidence at least 10% of patients in treatment group

(Reference: Table 6.4.4-a, pg. 94, Vol. 135)

Medical Officer Comments: *There were no significant differences between treatment groups with regard to prior and concomitant disease. Hypertension was the most frequently reported concomitant disease in all treatment groups.*

The next table displays concomitant medications (defined as intake between receiving the study drug and the last date of contact or intake before randomization that continued after receiving the study drug).

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TABLE 10 – Concomitant Medication¹

Concomitant Medication ²	Palonosetron 0.25 mg (N=193)	Palonosetron 0.75 mg (N=193)	Dolasetron 100 mg (N=194)
	N (%)	N (%)	N (%)
Any concomitant medication	145 (75.1)	140 (64.1)	144 (74.2)
Analgesics	58 (30.1)	76 (39.0)	64 (33.0)
Opioids	10 (5.2)	22 (11.3)	12 (6.2)
Other analgesics and antipyretics	50 (25.9)	57 (29.2)	55 (28.4)
Antacids	44 (22.8)	43 (22.1)	51 (26.3)
drugs for treatment peptic ulcer	38 (19.7)	36 (18.5)	46 (23.7)
Antianemic preparations	16 (8.3)	16 (8.2)	22 (11.3)
Antibacterial for systemic use	18 (9.3)	32 (16.4)	19 (9.8)
Anti-inflammatory and anti-rheumatic products	27 (14.0)	22 (11.3)	25 (12.9)
Non-steroid anti-inflammatory/anti- rheumatic products	27 (14.0)	22 (11.3)	25 (12.9)
Antithrombotic agents	12 (6.2)	22 (11.3)	18 (9.3)

¹ Multiple answers possible

² Incidence at least 10% of patients in treatment group
(Reference: Table 6.4.5-a, pg. 96, Vol. 135)

Medical Officer Comments: *The treatment groups were comparable in regards to concomitant medication. The most common medication in all 3 treatment groups was analgesics.*

Prior anti-emetic treatments were defined as intake within 12 months before randomization. By this criteria 70 (36%) patients of the 0.25 mg palonosetron group, 71 (36.4%) patients of the 0.75 mg palonosetron group, and 65 (33.5%) of the dolasetron group had prior anti-emetic treatment. Concomitant anti-emetic treatment included all medication taken after Study Day 5. Anti-emetic treatment taken between the administration of the study drug and Study Day 5 was considered rescue therapy and is included in the efficacy results. Concomitant anti-emetic treatment was seen in 26 (13.5%) patients of the 0.25 mg palonosetron group, 28 (14.4%) patients of the 0.75 mg palonosetron group, and 29 (14.9%) of the dolasetron group. Dexamethasone was the most common concomitant anti-emetic treatment in the palonosetron groups (4.7% and 6.2%) while ondansetron was most frequently taken by patients in the dolasetron group (3.6%).

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The following table displays the chemotherapy agent administered on Study Day 1, the day the patients received either palonosetron or dolasetron.

TABLE 11 - Chemotherapeutic treatment administered on Study Day 1¹

Substance	Palonosetron 0.25 mg (N=189)	Palonosetron 0.75 mg (N=189)	Dolasetron 100 mg (N=191)
	N (%)	N (%)	N (%)
Cyclophosphamide	138 (73.0)	129 (68.3)	146 (76.4)
Doxorubicin	91 (48.1)	77 (40.7)	93 (48.7)
Epirubicin	39 (20.6)	44 (23.3)	43 (22.5)
Carboplatin	30 (15.9)	38 (20.1)	26 (13.6)
Cisplatin	14 (7.4)	8 (4.2)	7 (3.7)
Methotrexate	7 (3.7)	9 (4.8)	6 (3.1)
Mitoxantrone	4 (2.1)	5 (2.6)	8 (4.2)
Irinotecan	2 (1.1)	4 (2.1)	3 (1.6)
Ifosfamide	2 (1.1)	0 (0.0)	1 (0.5)
Idarubicin	2 (1.1)	0 (0.0)	0 (0.0)

¹ Multiple answers possible
(Reference: Table 6.4.3-a, pg. 91, Volume 135)

Medical Officer Comment: The treatment groups were similar in chemotherapy agents received. The chemotherapy agents in the study groups are moderately emetogenic. Although cisplatin can be considered highly emetogenic, the dose used here ($\leq 50 \text{ mg/m}^2$ IV) is considered moderately emetogenic.

B. Protocol Deviations

The investigators conducted a blinded review meeting in which they defined major and minor protocol violations. The following table displays major protocol violations.

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**TABLE 12 – Major Protocol Violations¹
(All patients randomized, N=569)**

Reason	Palonosetron 0.25 mg (N=189)		Palonosetron 0.75 mg (N=189)		Dolasetron 100 mg (N=191)	
	N	(%)	N	(%)	N	(%)
Intake of rescue medication before first episode on Day 1	21	(11.1)	23	(12.2)	16	(8.4)
Code broken	6	(3.2)	6	(3.2)	5	(2.6)
Forbidden anti-emetics on Day 0	3	(1.6)	5	(2.6)	8	(4.2)
Difference between start chemo and start bolus ≤ 5 minutes	4	(2.1)	3	(1.6)	4	(2.1)
Patient unable to understand or cooperate with study procedure	1	(0.5)	2	(1.1)	2	(1.0)
No diary card available	3	(1.6)	2	(1.1)	0	(0.0)
Emetic episode within 24 hours before chemotherapy	2	(1.1)	0	(0.0)	2	(1.0)
Primary endpoint could not be calculated	0	(0.0)	1	(0.5)	3	(1.6)
Start time of chemo missing	1	(0.5)	1	(0.5)	1	(0.5)
Difference between start of chemo and start bolus ≥ 160 minutes	0	(0.0)	1	(0.5)	1	(0.5)
Lead investigator unblinded	1	(0.5)	1	(0.5)	0	(0.0)
No primary cancer	0	(0.0)	0	(0.0)	1 ²	(0.5)
Wrong informed consent signed	0	(0.0)	1	(0.5)	0	(0.0)
Total number of patients with major protocol violations	33	(17.5)	38	(20.1)	35	(18.3)

¹ Multiple answers possible

² Diagnosis Lupus

(Reference: Table 6.2-a, pg. 74, Volume 135)

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Medical Officer Comments: There were a large number of protocol violations in this study. However, the percentage of patients with major protocol violations was similar in all treatment arms. The most notable protocol violations were the intake of rescue medication before the first emetic episode on Day 1 and the use of forbidden anti-emetics on Day 0. These patients were considered treatment failures in the intent to treat analysis.

The following table shows minor protocol violation for the study.

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TABLE 13 – Minor Protocol Violations¹
(All patients randomized, N=569)

Reason	Palonosetron	Palonosetron	Dolasetron
	0.25 mg (N=189) N (%)	0.75 mg (N=189) N (%)	100 mg (N=191) N (%)
Violation of Time window	51 (27.0)	44 (23.3)	41 (21.5)
Intake of rescue medication before first episode after day 1	12 (6.3)	10 (5.3)	11 (5.8)
Exclusion criterion marked yes or missing	10 (5.3)	11 (5.8)	8 (4.2)
Time between infusion and chemotherapy <25 or >45 minutes	4 (2.1)	5 (2.6)	8 (4.2)
Ongoing prior anti-emetic PRN	4 (2.1)	2 (1.1)	7 (3.7)
Unknown stability of seizure disorder	2 (1.1)	2 (1.1)	4 (2.1)
Inclusion criterion missing	2 (1.1)	4 (2.1)	1 (0.5)
End time of chemotherapy missing	1 (0.5)	1 (0.5)	1 (0.5)
Nausea and vomiting following previous chemotherapy	1 (0.5)	1 (0.5)	1 (0.5)
Forbidden chemotherapy on days 2-6	1 (0.5)	1 (0.5)	1 (0.5)
Start time of bolus missing	1 (0.5)	1 (0.5)	0 (0.0)
Duration of chemotherapy >255 minutes	0 (0.0)	1 (0.5)	1 (0.5)
Karnofsky Index < 50% or missing	1 (0.5)	1 (0.5)	0 (0.0)
Dexamethasone received in time but patients not randomized to	0 (0.0)	1 (0.5)	0 (0.0)
Forbidden chemotherapy on day 1	0 (0.0)	1 (0.5)	0 (0.0)
QTc >500 msec at baseline	1 (0.5)	0 (0.0)	0 (0.0)
Total number of patients with minor protocol violations	73 (38.6)	70 (37.0)	64 (33.5)

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¹ Multiple answers possible (Reference: From Table 3, pg. 238, Volume 135)

Medical Officer Comments: There was a large number of patients with minor protocol violations. However, the percentage of patients with minor protocol violations was similar in all treatment arms. Again, patients who had inappropriate intake of rescue medication were considered treatment failures in the intent to treat analysis.

C. Efficacy Results

1. Primary Efficacy Parameter

The primary efficacy was complete response (defined as no emetic episode and no rescue medication) during the first 24 hours after administration of chemotherapy.

The following table displays the complete response rates for the first 24 hours after chemotherapy.

TABLE 14-Complete Response Rates During the First 24 Hours After Chemotherapy: Moderately Emetogenic CINV Studies PALO-99-04 (ITT Cohort; N = 569)

Treatment Group	Complete Response (CR) During the First 24 Hours			97.5% CI for the Difference in CR Rates During the First 24 Hours Between Palonosetron and Active Comparator	
	N	n (%)	95% CI	Palonosetron 0.25 mg Minus Active Comparator	Palonosetron 0.75 mg Minus Active Comparator
Palonosetron 0.25 mg	189	119 (63.0)	[55.6%, 69.8%]		
Palonosetron 0.75 mg	189	108 (57.1)	[49.8%, 64.2%]		
Dolasetron 100 mg	191	101 (52.9)	[45.6%, 60.1%]	[-1.7%, 21.9%]	[-7.7%, 16.2%]

CR = Complete Response (defined as no emetic episode and no rescue medication) during the first 24 hours after chemotherapy.

N = Number of subjects in treatment group.

n (%) = number and percentage of subjects with CR.

CI = Confidence Interval.

* = 97.5% CIs for the difference between palonosetron and active comparator (dolasetron) indicating palonosetron superiority ($p < 0.05$).

Medical Officer Comments: The lower limit of the 97.5% confidence interval for the difference in complete response rates during the first 24 hours after chemotherapy was above the preset 15% delta. The comparator was adequate. The comparator drug dolasetron is an FDA approved medication that is indicated for the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. Based on this data, the non-inferiority of both palonosetron doses to dolasetron 100 mg was demonstrated for the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting during the first 24 hours after chemotherapy. The lower limit of the 97.5% CI for the comparison of palonosetron 0.25 mg to dolasetron was slightly below zero. It is not

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clear why the higher dose of palonosetron seemed to have less efficacy. The follow up rate at 24 hours for patients who received the study drug was 97%.

For trial validation, the 95% confidence interval of the proportion of complete response in the active comparator group was compared to the complete response rate of the modeled historical placebo group and modeled history dolasetron group. The following table displays the results.

	Modeled Historical Dolasetron at 24 hours	Modeled Historical Placebo at 24 hours	Dolasetron 100 mg (N=191)
CR	59.7%	15.1%	52.9%
95% CI of the proportion of patients with CR	[51.3%, 67.6%]	[11.3%, 20.1%]	[45.6%, 60.1%]

(Reference: Table 7.1.1.2 g, page 106, Volume 135)

Medical Officer Comments: Since the use of placebo is not ethically acceptable in the CINV subject population, a literature-based meta-analysis (PALO-01-23) was performed to provide historical placebo control data. Since the dolasetron performed similarly to the modeled historical dolasetron and far better than in the modeled historical placebo, the applicant demonstrated validity of the trial for the 24 hour end-point.

2. Secondary Efficacy Endpoints

There were several secondary efficacy endpoints as listed below:

- Complete response over 120 hours
- Complete control (defined as a complete response and no more than mild nausea)
- Total response (subjects free from emetic episodes, rescue medication, and nausea over time)
- Number of emetic episodes
- Time to first emetic episode
- Time to rescue medication
- Time to treatment failure (time to first emetic episode or administration of rescue medication, whichever occurred first)
- Severity of nausea (Likert Scale)
- Subject global satisfaction with therapy (VAS; visual analog scale)
- Quality of life questionnaire (FLIE; Functional Living Index)

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Complete Response over 120 hours

Table 15 on the following page displays one of the secondary endpoints – complete response over 120 hours.

TABLE 15- Subjects with Complete Response After Chemotherapy, By Day (Acute and Delayed): (ITT Cohort; N = 663)

Time Period (Hours)	Number and Percentage (%) of Subjects with Complete Response			Difference in Complete Response Rates, 97.5% Confidence Intervals	
	Palonosetron 0.25 mg (N = 189)	Palonosetron 0.75 mg (N = 189)	Dolasetron 100 mg (N = 185)	Palonosetron 0.25 mg Minus Dolasetron 100 mg	Palonosetron 0.75 mg Minus Dolasetron 100 mg
Acute^a					
0-24	119 (63.0)	108 (57.1)	101 (52.9)	[-1.7%, 21.9%]	[-7.7%, 16.2%]
Delayed^b					
24-48	118 (62.4)	118 (62.4)	85 (44.5)	[6.1%, 29.7%]*	[6.1%, 29.7%]*
48-72	128 (67.7)	138 (73.0)	107 (56.0)	[0.1%, 23.3%]*	[5.6%, 28.3%]*
72-96	149 (78.8)	155 (82.0)	137 (71.7)	[-3.3%, 17.5%]	[0.1%, 20.4%]*
96-120	167 (88.4)	162 (85.7)	156 (81.7)	[-2.0%, 15.4%]	[-5.0%, 13.0%]

^a = Primary efficacy endpoint.

^b = Secondary endpoint.

* = 97.5% CIs for the difference between palonosetron and active comparator (dolasetron or dolasetron)

The following table displays CR over cumulative time periods.

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**TABLE 16 -Subjects with Complete Response After Chemotherapy, Cumulative Time Periods: Moderately Emetogenic CINV
Studies PALO-99-04 (ITT Cohort; N = 569)**

Time Period (Hours)	Palonosetron 0.25 mg (N = 189)	Palonosetron 0.75 mg (N = 189)	Dolasetron 100 mg (N = 191)	Palonosetron 0.25 mg Minus Dolasetron 100 mg	Palonosetron 0.75 mg Minus Dolasetron 100 mg
0-24	119 (63.0)	108 (57.1)	101 (52.9)	[-1.7%, 21.9%]	[-7.7%, 16.2%]
0-48	96 (50.8)	95 (50.3)	74 (38.7)	[0.2%, 23.9%]*	[-0.4%, 23.4%]
0-72	89 (47.1)	93 (49.2)	69 (36.1)	[-0.8%, 22.8%]	[1.3%, 24.9%]*
0-96	88 (46.6)	90 (47.6)	68 (35.6)	[-0.8%, 22.7%]	[0.2%, 23.8%]*
0-120	87 (46.0)	89 (47.1)	65 (34.0)	[0.3%, 23.7%]*	[1.3%, 24.8%]*
24-120	102 (54.0)	107 (56.6)	74 (38.7)	[3.4%, 27.1%]*	[6.0%, 29.7%]*

* = 97.5% CIs for the difference between palonosetron and active comparator (ondansetron or dolasetron) indicating palonosetron superiority ($p < 0.05$).

For secondary endpoints p-values not adjusted for multiple comparisons.
(Reference: Table 7.1.2.1-a and Table 7.1.2.1.b, page 109, Volume 135).

Medical Officer Comments: During all study days, complete response rates were higher in the 2 palonosetron groups than in the dolasetron group. Higher rates were observed in the palonosetron 0.25 mg group compared to the 0.75 mg group. The lower limit of the confidence interval of the difference of each palonosetron dose versus dolasetron was above the pre-set threshold of -15%, indicating non-inferiority of palonosetron to dolasetron. Although the palonosetron seems to demonstrate some efficacy at 120 hours some factors need to be considered. The p-values were not adjusted for multiple endpoints. Since there were multiple secondary endpoints, there may be issues with multiplicity. In addition, the comparator arm Dolasetron is not indicated for prevention of CINV at 120 hours. Thus, what the results may be demonstrating is that the nausea from the chemotherapy is simply wearing off.

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Complete Control

Table 17 shows the proportion of patients who were considered to have complete control. Complete control was another secondary efficacy endpoint and was defined as patient who had a complete response and no more than mild nausea.

TABLE 17 – Patients with complete control after chemotherapy, overall time periods (ITT cohort, N=563)

Time Period (Hours)	Palonosetron 0.25 mg (N = 189)		Palonosetron 0.75 mg (N = 189)		Dolasetron 100 mg (N = 191)	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
0-24	108 (57.2)	[49.8%, 64.2%]	100 (52.9)	[45.5%, 60.2%]	91 (47.6)	[40.4%, 55.0%]
0-48	86 (45.5)	[38.3%, 52.6%]	87 (46.0)	[38.8, 53.4%]	66(34.6)	[27.9%,41.8%]
0-72	81 (42.9)	[35.8%, 50.2%]	86 (45.5)	[38.3%, 52.9%]	63 (33.0)	[26.5%, 40.2%]
0-96	80 (42.3)	[35.3%, 49.7%]	83 (43.9)	[36.8%, 51.3%]	60 (45.4)	[25.0%, 38.6%]
0-120	79 (41.8)	[34.7%, 49.2%]	81 (42.9)	[35.8%, 50.2%]	59 (30.9)	[24.5%, 38.0%]

(Reference: Table 7.1.2.2-a, page 115, Volume 135)

Medical Officer Comments: Both palonosetron groups demonstrated higher complete control rates at all time periods when compared to dolasetron. During the 0-24 hours period the palonosetron 0.25 mg group had a higher proportion of patients that had complete control than the 0.75 mg group. Pairwise comparison of the treatment groups revealed statistically significant differences between both palonosetron and the dolasetron for each observation period.. There were no statistically significant differences between the two palonosetron groups.

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Number of Emetic Episodes

Table 18 shows the number of emetic episodes during the observation period.

TABLE 18 – Number of emetic episodes during the observation period

Time Period	Palonosetron 0.25 mg (N=189)		Palonosetron 0.75 mg (N=189)		Dolasetron 100 mg (N=191)	
	N	(%)	N	(%)	N	(%)
ACUTE						
0-24						
0 episodes	136	(72.0)	123	(65.1)	112	(58.6)
1 episode	19	(10.1)	21	(11.1)	25	(13.1)
2 episodes	4	(2.1)	6	(3.2)	15	(7.9)
≥3 episodes	30	(15.9)	39	(20.6)	39	(20.4)
DELAYED						
24-48						
0 episodes	134	(70.9)	142	(75.1)	110	(57.6)
1 episode	24	(12.7)	23	(12.2)	34	(17.8)
2 episodes	9	(4.8)	11	(5.8)	18	(9.4)
≥3 episodes	22	(11.6)	13	(6.9)	29	(15.2)
48-72						
0 episodes	147	(77.8)	159	(84.1)	139	(72.8)
1 episode	20	(10.6)	15	(7.9)	31	(16.2)
2 episodes	9	(4.8)	5	(2.6)	11	(5.8)
≥3 episodes	13	(6.9)	10	(5.3)	10	(5.2)
72-96						
0 episodes	170	(89.9)	168	(88.9)	158	(82.7)
1 episode	10	(5.3)	12	(6.3)	20	(10.5)
2 episodes	2	(1.1)	3	(1.6)	8	(4.2)
≥3 episodes	7	(3.7)	6	(3.2)	5	(2.6)
96-120						
0 episodes	181	(95.8)	175	(92.6)	168	(88.0)
1 episode	2	(1.1)	9	(4.8)	15	(7.9)
2 episodes	2	(1.1)	1	(0.5)	2	(1.0)
≥3 episodes	4	(2.1)	4	(2.1)	6	(3.1)

(Reference: Table 7.1.2.3-a, from page 118 Volume 135)

Medical Officer Comments: The percentage of patients without an emetic episode was higher in both palonosetron groups than in the dolasetron group. The 0.25 mg palonosetron group had a higher rate of patients without emetic episodes on Day 1 compared to the 0.75 mg group. Pair wise testing revealed a statically significant difference between palonosetron 0.25 mg group and the dolasetron group on Study Day

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1, 2 and 5. Pairwise testing revealed a difference on Day 2 and 3 between dolasetron and the 0.75 mg group. However, multiple analyses were performed and this result was not adjusted for multiplicity.

Time to First Emetic Episode

Table 18 shows the median time to the first emetic episode.

TABLE 19 –Median Time to first emetic episode

Time Period	Palonosetron 0.25 mg (N=189)		Palonosetron 0.75 mg (N=189)		Dolasetron 100 mg (N=191)	
	Q1	Median	Q1	Median	Q1	Median
0-120 hours	13.5	>120	9.8	>120	7.9	>120

Q1= first quartile

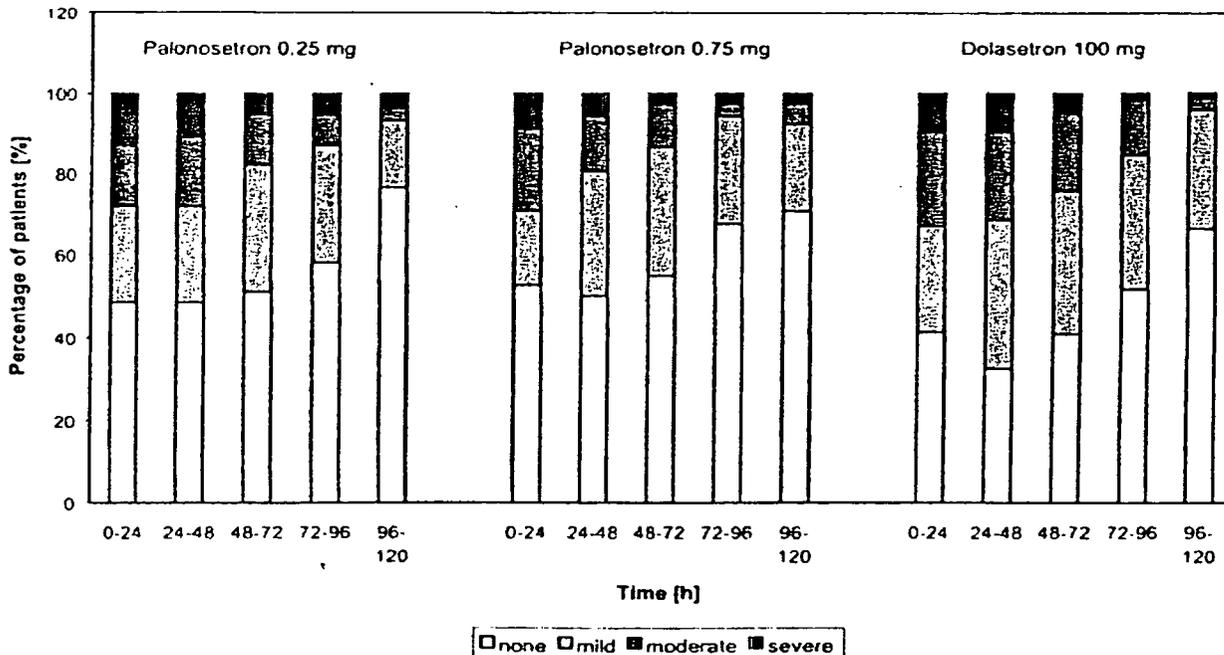
(Reference: Table 7.2.3-b, page 113, Volume 135)

Medical Officer Comments: The median time to first emetic episode was above 120 hours for all groups. When the applicant performed further analysis of the first quartile of patients, they found that the first quartile showed that time to first emetic episode was longer in the 0.25 mg group. This was an unplanned analysis that was done after the primary analysis failed to show a difference. Thus, it is unclear if this is clinically significant.

Severity of Nausea

The following figure shows the severity of nausea during study Day 1,2,3 and 4

**FIGURE 2: Severity of nausea during Study Day 1, 2, 3, 4, and 5
ITT cohort N=569 (Scanned from figure 7.1.2.4-a, page 121, Volume 135)**



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Medical Officer Comments: The rate of patients without nausea was higher in the palonosetron groups compared to the dolasetron group. For Day 1 the difference was not significant. For Days 2,3,4, there was a statistically significant difference between groups in favor of the 0.25 mg dose of palonosetron. When pairwise testing (using the Wilcoxon test) was done with the 0.25 mg palonosetron group versus dolasetron, statistically significant differences were seen on Day 2, and 3 but not for Day 4 or 5.

Time to Rescue Medication

The following table shows the time to first use of rescue medication.

TABLE 20– Median Time to First Administration of Rescue Medication

Time Period	Palonosetron 0.25 mg (N=189)		Palonosetron 0.75 mg (N=189)		Dolasetron 100 mg (N=191)	
	Q1	Median	Q1	Median	Q1	Median
0-120 hours	>28.1	>120	>24.0	>120	23.9	>120

Q1= first quartile

(Reference: Tables 7.1.2.5-b, from page 124, Volume 135)

Medical Officer Comments: The median time to first use of rescue medication was greater than 120 hours for all groups. However, the sponsor did an analysis of the first quartile of patients and found that the time to first administration of rescue medication tended to be shorter in the dolasetron group. It is unclear what the clinical relevance of this finding is since this was an unplanned analysis. Overall, few patients took rescue medication during this study. There was no statistical difference between treatment groups in the number of patients who took rescue medication for any study day.

Time to Treatment Failure

The median time to treatment failure (time to first emetic episode or administration of rescue medication, whichever occurred first) is displayed on the following table.

TABLE 21 –Median time to Treatment failure (ITT cohort, N=563)

Time Period	Palonosetron 0.25 mg (N=189)		Palonosetron 0.75 mg (N=189)		Dolasetron 100 mg (N=191)	
	Q1	Median	Q1	Median	Q1	Median
0-120 hours	8.3	51.1	7.4	52.8	6.9	24.6

Q1= first quartile

(Reference: Table 7.1.2.6-a, page 127, Volume 135).

Medical Officer Comments: The median time to treatment failure was longer in the palonosetron groups than in the dolasetron group.

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Quality of Life Questionnaire

The quality of life was assessed by using a modified and validated Functional Living Index Emesis (FLIE). This consisted of 18 questions divided into 2 domains (nausea, and vomiting). The questions were assessed by using a visual analog scale (VAS). A high score reflects less impairment from nausea and vomiting.

TABLE 22 – Quality of Life VAS scores for nausea and vomiting

Time Period (hours)	Palonosetron 0.25 mg (N=189)	Palonosetron 0.75 mg (N=189)	Dolasetron 100 mg (N=191)
	Median	Median	Median
0-24 hours			
Nausea	831	841	789
Vomiting	884	874	874
Overall score	1686	1700	1629
24-96 hours			
Nausea	826	833	728
Vomiting	882	885	873
Overall score	1672	1683	1599

(Reference: Table 7.1.2.8-a ,page 126, Volume 135)

Medical Officer Comments: Median quality of life scores were similar in all the treatment groups. Statistical testing found no difference between the groups for nausea, vomiting and the overall score during the 0-24 hours time period. There was statistical difference for the nausea score for the time period 24-96 hours between palonosetron 0.25 mg and dolasetron (p=0.031).

Global Satisfaction with Therapy

The global satisfaction of the patients with the anti-emetic therapy was recorded on a VAS for the entire 120-hour interval. Global satisfaction was evaluated daily. Again, the applicant performed an unplanned analysis of the first quartile. The results are shown in the following table.

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**TABLE 23– Global Satisfaction with Anti-emetic therapy
(ITT cohort, N=569)**

Time Period (hours)	Palonosetron 0.25 mg (N=189)	Palonosetron 0.75 mg (N=189)	Dolasetron 100 mg (N=191)
	Median	Median	Median
Acute			
0-24 hours	95	93	90
Delayed			
24-48	95	92	85
48-72	95	95	90
72-96	97	97	93
96-120	98	98	96

(Reference: Table 7.1.2.7-a, page 130, Volume 135)

Medical Officer's Comments: A statistical difference between treatment groups was found by Kruskal-Wallis testing for Day 2 (p=0.008) but not the other days). A pair wise test between 0.25 mg of palonosetron and dolasetron showed a significant difference (0.022) in favor to palonosetron for Day 4.

Summary of Results for Secondary Efficacy Endpoints

The table on the following page displays a summary of the statistical analysis regarding the secondary efficacy endpoints.

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TABLE 24– Statistical Analysis Results of Secondary Efficacy Endpoints

Parameters	Statistical Test	Overall	PALO 0.25 mg vs Dola 100 mg	PALO 0.75 mg vs Dola 100 mg	PALO 0.25 mg vs PALO 0.75 mg
Complete Control (CC)					
0-24 hr	Chi-square	0.1780	--	--	--
24-48 hr	Chi-square	0.0010	0.0040	0.0010	0.6040
48-72 hr	Chi-square	0.0010	0.0050	0.0010	0.2340
72-96 hr	Chi-square	0.0120	0.1310	0.0030	0.1410
96-120 hr	Chi-square	0.2270	--	--	--
0-48 hr	Chi-square	0.0380	0.0290	0.0230	0.9180
0-72 hr	Chi-square	0.0320	0.0470	0.0120	0.6050
0-96 hr	Chi-square	0.0250	0.0270	0.0120	0.7550
0-120 hr	Chi-square	0.0290	0.0270	0.0160	0.8350
Number of Emetic Episodes (EE)					
0-24 hr	KW/Wilcoxon	0.0462	0.0135	0.2047	0.2208
24-48 hr	KW/Wilcoxon	0.0009	0.0153	0.0003	0.2732
48-72 hr	KW/Wilcoxon	0.0441	0.3745	0.0121	0.1160
72-96 hr	KW/Wilcoxon	0.0917	--	--	--
96-120 hr	KW/Wilcoxon	0.0228	0.0073	0.1334	0.2064
0-120 hr	KW/Wilcoxon	0.0018	0.0036	0.0016	0.8442
Time to First EE	Log Rank	0.0083	0.0101	0.0075	0.8327
Severity of Nausea					
0-24 hr	KW/Wilcoxon	0.1907	--	--	--
24-48 hr	KW/Wilcoxon	0.0014	0.0240	0.0003	0.2732
48-72 hr	KW/Wilcoxon	0.0069	0.0415	0.0019	0.3202
72-96 hr	KW/Wilcoxon	0.0026	0.2643	0.0006	0.0259
96-120 hr	KW/Wilcoxon	0.1696	--	--	--
Need of Rescue Medication					
0-24 hr	Chi-square	0.3090	--	--	--
24-48 hr	Chi-square	0.1230	--	--	--
48-72 hr	Chi-square	0.2210	--	--	--
72-96 hr	Chi-square	0.5840	--	--	--
96-120 hr	Chi-square	0.3430	--	--	--
0-120 hr	Chi-square	0.2950	--	--	--
Time to Rescue	Log Rank	0.3015	--	--	--
Subject Global Satisfaction					
0-24 hr	KW/Wilcoxon	0.4754	--	--	--
24-48 hr	KW/Wilcoxon	0.0494	0.0559	0.0212	0.8714
48-72 hr	KW/Wilcoxon	0.0538	--	--	--
72-96 hr	KW/Wilcoxon	0.0078	0.0217	0.0032	0.4686
96-120 hr	KW/Wilcoxon	0.0592	--	--	--
Function Living Index-Emesis					
FLIE #1 Nausea	KW/Wilcoxon	0.1779	--	--	--
FLIE #1 Vomiting	KW/Wilcoxon	0.5042	--	--	--
FLIE #1 Total	KW/Wilcoxon	0.2159	--	--	--
FLIE #2 Nausea	KW/Wilcoxon	0.0130	0.0307	0.0048	0.5619
FLIE #2 Vomiting	KW/Wilcoxon	0.2029	--	--	--
FLIE #2 Total	KW/Wilcoxon	0.0159	0.0393	0.0055	0.5174

PALO = Palonosetron; ONDA = Dolasetron;; EE = Emetic Episode; KW = Kruskal-Wallis.

Legend

bold means statistically significant difference (i.e., $p < 0.05$).
 means difference in favor of PALO 0.25 mg.
 means difference in favor of PALO 0.75 mg.

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3. Subgroup Analysis

Gender

The primary efficacy parameter was complete response during the first 24 hours after chemotherapy. The following table displays complete response by gender for each of the treatment arms.

TABLE 25 – Patients with Complete Response by Gender

	Number and Percentage (%) of Subjects with Complete Response								
	Palonosetron 0.25 mg (N = 189)			Palonosetron 0.75 mg (N = 189)			Dolasetron 100 mg (N = 191)		
	N	N*	%	N	N*	%	N	N*	%
Male	34	30	(88.2)	33	21	(63.6)	35	22	(62.9)
Female	155	89	(57.4)	156	87	(55.8)	156	79	(50.6)

N = number of female or male patients

N* = number of patients with response

(Reference: Table 7.2.1-a, page 135, Volume 135)

Medical Officer Comments: Male patients had a higher complete response rate than female patients. The applicant does not offer an explanation why this was so but it has been noted in previous studies of other anti-emetics. The lower limits of a 97.5% confidence interval for the difference in complete response rates between the 0.25 mg palonosetron dose and dolasetron 100 mg was above the pre-set threshold of -15 % in male and female patients. For the palonosetron 0.75 mg the confidence interval's lower limit was -28.4% for males and -8.2% for the females. This result for the palonosetron 0.75 mg dose in the males does not meet the pre-set threshold.

Chemotherapeutic History

The following table displays complete response stratified by chemotherapeutic history during the first 24 hours.

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TABLE 26- Patients with Complete Response by Chemotherapeutic history

	Number and Percentage (%) of Subjects with Complete Response								
	Palonosetron 0.25 mg (N = 189)			Palonosetron 0.75 mg (N = 189)			Dolasetron 100 mg (N = 191)		
	N	N*	%	N	N*	%	N	N*	%
Naïve	124	75	(60.5)	131	73	(55.7)	125	58	(46.4)
Non-naïve	65	44	(67.7)	58	35	(60.3)	66	43	(65.2)

N = number of naïve or non-naïve patients

N* = number of patients with response

(Reference: Table 7.3.1-a, page 150, Volume 135)

Medical Officer Comments: In naïve patients, the lower limits of the 97.5% confidence intervals for the difference between both palonosetron doses and dolasetron were above the preset threshold of -15% (-0.7%, -5.4% respectively). This indicates non-inferiority of palonosetron 0.25 mg to dolasetron in the naïve patients. However, in non-naïve patients the lower limits of the 97.5% confidence intervals for the difference in complete response rates were below the pre-set -15% threshold (-17.5%, -25.9% respectively). This study did not establish non-inferiority of palonosetron for non-naïve subjects. The exclusion criteria for this study excluded non-naïve patients who had moderate to severe nausea with prior chemotherapy. This could have led to bias with a more favorable response in the non-naïve group. The overall results of this study may be driven by the effect in the naïve group.

VI. Safety Evaluation

Most patients were observed for 14 days after the study drug was administered. A subset of patients were enrolled in a follow-up study PALO-99-06, that extended the observation period to 27 days. The following table displays treatment emergent adverse events.

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TABLE 27 – Treatment Emergent Adverse Events overview (Safety cohort, N=582)

Number of patients with adverse events	Palonosetron 0.25 mg (N = 193)		Palonosetron 0.75 mg (N = 195)		Dolasetron 100 mg (N = 194)				
	N	%	N	%	N	%			
All	148	76.7	156	80.0	149	76.8			
Related ¹	45	23.3	58	29.7	61	31.4			
By category									
All AEs/Non-Lab, Non-ECG	134	69.4	143	73.3	135	69.6			
All AEs/Laboratory	55	28.5	67	34.4	69	35.6			
All AEs/ECG	5	2.6	8	4.1	3	1.5			
Related ¹ AEs/Non-Lab, Non-ECG	45	23.3	53	27.2	57	29.4			
Related ¹ AEs/Laboratory	0	0.0	2	1.0	7	3.6			
Related ¹ AEs/ECG	2	1.0	5	2.6	0	0.0			
Serious adverse events									
All SAEs	4	2.1	13	6.7	9	4.6			
Related ¹ SAEs	0	0.0	0	0.0	0	0.0			
Withdrawn due to AEs									
All	1	0.5	2	1.0	0	0.0			
Related ¹	0	0.0	0	0.0	0	0.0			
	N*	N	%	N*	N	%	N*	N	%
Subgroup: gender									
All AEs/male	34	25	73.5	34	29	85.3	36	29	80.6
All AEs/female	159	123	77.4	161	127	78.9	158	120	75.9
Related ¹ AEs/male	34	4	11.8	34	10	29.4	36	9	25.0
Related ¹ AEs/female	159	41	25.8	161	48	29.8	158	52	32.9
Subgroup: chemotherapeutic history									
All AEs/naive	127	99	78.0	132	100	75.8	126	98	77.8
All AEs/non-naive	66	49	74.2	63	56	88.9	68	51	75.0
Related ¹ AEs/naive	127	37	29.1	132	40	30.3	126	42	33.3
Related ¹ AEs/non-naive	66	8	12.1	63	18	28.6	68	19	27.9

(continued)

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TABLE 27 - Treatment Emergent Adverse Events (Cont'd)

Number of patients with adverse events	Palonosetron 0.25 mg (N = 103)			Palonosetron 0.75 mg (N = 195)			Dolasetron 100 mg (N = 194)		
	N*	N	%	N*	N	%	N*	N	%
U.S. East									
All AEs	29	23	79.3	31	28	90.3	31	24	77.4
Related ¹ AEs	29	2	6.9	31	1	3.2	31	4	12.9
U.S. West									
All AEs	14	12	85.7	16	13	81.3	8	7	87.5
Related ¹ AEs	14	3	21.4	16	4	25.0	8	4	50.0
California									
All AEs	42	34	81.0	39	36	92.3	45	38	84.4
Related ¹ AEs	42	4	9.5	39	7	17.9	45	7	15.6
Mexico South									
All AEs	25	20	80.0	25	18	72.0	25	22	88.0
Related ¹ AEs	25	8	32.0	25	12	48.0	25	15	60.0
Mexico Center									
All AEs	55	39	70.9	55	39	70.9	59	40	67.8
Related ¹ AEs	55	15	27.3	55	17	30.9	59	20	33.9
Mexico North									
All AEs	28	20	71.4	29	22	75.9	26	18	69.2
Related ¹ AEs	28	13	46.4	29	17	58.6	26	11	42.3

Source: Appendix B-1.3.1, Tables 1, 3

¹ Adverse events which had a definite, possible, probable or unknown relationship to study medication or for which no information about relationship to the study medication was available

N = number of patients

N* = number of patients in specific group

% = percentage of patients with adverse events

(Scanned from Table 8.1.1, page 170-171, Volume 117)

Medical Officer Comments: *There was a high rate of treatment adverse events in all three study arms. The rate was highest for the patients in the palonosetron 0.75 mg group. Cancer patients undergoing chemotherapy generally have a high rate of complications and co-morbid illness so the high rate is not unexpected. Adverse events that were rated by the investigator as definite, possible, probable or unknown relationship to the study drug were characterized as related adverse events. The number of serious adverse events was highest in the palonosetron 0.75 mg group. Chemotherapy*

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naïve and non-naïve patients had a similar rate of adverse events except in the 0.75 mg palonosetron arm where more non-naïve patients had AE's.

B. Adverse Events by Body System

The following table displays adverse events by body system.

TABLE 28– Treatment Emergent Adverse events by body System and preferred term¹ (Safety Cohort, N=562)

System organ class ² Preferred term ² (MedDRA)	Palonosetron 0.25 mg (N = 193)			Palonosetron 0.75 mg (N = 195)			Dolasetron 100 mg (N = 194)		
	N	%	n	N	%	n	N	%	n
Any adverse event	148	76.7	445	156	80.0	498	149	76.8	458
Nervous system disorders	67	34.7	84	68	34.9	81	66	34.0	82
Headache nos ³	51	26.4	56	47	24.1	49	52	26.8	56
Insomnia nec ³	6	3.1	6	10	5.1	10	8	4.1	8
Gastrointestinal disorders	65	33.7	89	67	34.4	89	58	29.9	83
Constipation	23	11.9	24	29	14.9	30	18	9.3	18
Diarrhea nos ³	14	7.3	14	12	6.2	12	14	7.2	15
Dyspepsia	12	6.2	13	5	2.6	5	6	3.1	6
General disorders and administration site conditions	40	20.7	51	52	26.7	66	47	24.2	58
Fatigue	21	10.9	21	26	13.3	26	24	12.4	25
Blood and lymphatic system disorders	37	19.2	58	47	24.1	69	49	25.3	71
Leucopenia nos ³	19	9.8	19	17	8.7	17	19	9.8	19
Lymphopenia	12	6.2	12	21	10.8	21	12	6.2	12
Neutropenia	12	6.2	12	15	7.7	15	23	11.9	23
Investigations	23	11.9	32	25	12.8	38	21	10.8	23
Metabolism and nutrition disorders	16	8.3	19	30	15.4	30	22	11.3	25
Appetite decreased ncs ³	5	2.6	5	11	5.6	11	8	4.1	8
Musculo-skeletal, connective tissue and bone disorders	14	7.3	18	17	8.7	25	20	10.3	24
Skin and subcutaneous tissue disorders	13	6.7	13	15	7.7	15	19	9.8	25
Alopecia	11	5.7	11	8	4.1	8	11	5.7	11
Infection and infestations	12	6.2	13	18	9.2	20	18	9.3	21

(continued)

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TABLE 28 –(Cont'd)

System organ class ² Preferred term ² (MedDRA)	Palonosetron 0.25 mg (N = 193)			Palonosetron 0.75 mg (N = 195)			Dolasetron 100 mg (N = 194)		
	N	%	n	N	%	n	N	%	n
Cardiac Disorders	10	5.2	15	15	7.7	15	8	4.1	8
Respiratory, thoracic and mediastinal disorders	10	5.2	16	10	5.1	11	10	5.2	10

Source: Appendix B-1 3 1, Table 4

N = number of patients

% = percentage of patients with adverse events

n = number of adverse events

¹ Multiple answers possible. ² Incidence of at least 5% of patients in any treatment group

³ Not otherwise specified, not elsewhere classified

(Scanned from Table 8.1.2.2-a page 175, Volume 135)

Medical Officer Comment: Adverse events of the nervous system were most common in all treatment groups. These were equally spread out in all treatment groups. General disorders were more commonly reported in the palonosetron 0.75 mg arm. Gastrointestinal disorders were slightly more common in the palonosetron arms compared to dolasetron.

D. Adverse Events by Severity and Relationship to Treatment

The following table shows adverse events by treatment group and severity.

TABLE 28 – Number of Adverse Events by Intensity

Severity	Palonosetron 0.25 mg (N=193)		Palonosetron 0.75 mg (N=195)		Dolasetron 100 mg (N=194)	
	N	(%)	N	(%)	N	(%)
Mild	308	(69.2)	299	(60.0)	291	(63.5)
Moderate	121	(27.2)	167	(33.5)	146	(31.9)
Severe	16	(3.6)	3	(0.6)	2	(0.4)
TOTAL	445	100	498	100	458	100

(Reference: Table 8.1.2.2-a, page 167, Volume 135)

Medical Officer Comments: The majority of adverse events in all treatment arms were of mild intensity. The rate of severe adverse events was higher in the palonosetron groups compared to the dolasetron group. The body system most frequently involved for severe adverse events was blood and lymphatic system and was secondary to chemotherapy.

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The following table displays the number of adverse events by relationship to treatment.

TABLE 29 – Number of Adverse Events by Relationship to Treatment

	Palonosetron 0.25 mg (N=193)		Palonosetron 0.75 mg (N=195)		Dolasetron 100 mg (N=194)	
	N	(%)	N	(%)	N	(%)
Unrelated	322	(72.4)	345	(69.3)	310	(67.7)
Unlikely	44	(9.9)	61	(12.2)	48	(10.5)
Possible	51	(11.5)	49	(9.8)	48	(10.5)
Probable	27	(6.1)	35	(7.0)	34	(7.4)
Definite	1	(0.2)	4	(0.8)	6	(1.3)
Unknown	0	(0.0)	4	(0.0)	10	(2.2)
TOTAL	273	100	498	100	458	100

(Reference: Table 8.1.2.2-b, page 168, Volume 135)

Medical Officer Comments: The majority of adverse events were judged by the investigator to be unrelated to the study drug in all three treatment groups. The incidence of possibly and probably related adverse events was slightly higher in the dolasetron group.

The following table shows the treatment emergent related adverse events by body system.

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TABLE 30 – Treatment Emergent Related Adverse Events by Body System and Preferred Term² (Safety cohort, N=582)

System organ class ³ Preferred term (MedDRA)	Palonosetron 0.25 mg (N = 193)			Palonosetron 0.75 mg (N = 195)			Dolasetron 100 mg (N = 194)		
	N	%	n	N	%	n	N	%	n
	Any related adverse event	45	23.3	79	58	29.7	92	61	31.4
Nervous system disorders	30	15.5	35	36	18.5	39	33	17.0	42
Headache nos ⁴	28	14.5	30	30	15.4	32	32	16.5	35
Dizziness (exc. vertigo)	3	1.6	3	2	1.0	2	4	2.1	4
Insomnia nec ⁴	0	0.0	0	1	0.5	1	3	1.5	3
Gastrointestinal disorders	18	9.3	21	22	11.3	26	21	10.8	24
Constipation	14	7.3	14	18	9.2	19	12	6.2	12
Diarrhea nos ⁴	3	1.6	3	3	1.5	3	4	2.1	4
Abdominal pain nos ⁴	1	0.5	1	1	0.5	1	3	1.5	3
Psychiatric disorders	5	2.6	5	0	0.0	0	1	0.5	1
Anxiety nec ⁴	4	2.1	4	0	0.0	0	0	0.0	0
Cardiac disorders	4	2.1	4	4	2.1	4	1	0.5	1
Tachycardia nos ⁴	3	1.6	3	2	1.0	2	0	0.0	0
General disorders and administration site conditions	4	2.1	4	9	4.6	10	7	3.6	7
Fatigue	2	1.0	2	2	1.0	2	4	2.1	4
Asthenia	1	0.5	1	4	2.1	4	1	0.5	1
Ear and labyrinth disorders	3	1.6	3	0	0.0	0	1	0.5	1
Vascular disorders	3	1.6	3	0	0.0	0	1	0.5	1
Hypotension nos ⁴	3	1.6	3	0	0.0	0	1	0.5	1
Investigations	1	0.5	1	3	1.5	3	2	1.0	3

(continued)

**CLINICAL REVIEW STUDY 99-04
PALONOSETRON**

TABLE 30 – (Cont'd)

System organ class ³ Preferred term (MedDRA)	Palonosetron 0.25 mg (N = 193)			Palonosetron 0.75 mg (N = 195)			Dolasetron 100 mg (N = 194)		
	N	%	n	N	%	n	N	%	n
	Metabolism and nutrition disorders	1	0.5	1	4	2.1	4	5	2.6
Musculoskeletal, connective tissue and bone disorders	0	0.0	0	3	1.5	3	4	2.1	4
Skin & subcutaneous tissue disorders	0	0.0	0	1	0.5	1	4	2.1	4

Source: Appendix B-1.3.1, Table 9

N = number of patients

% = percentage of patients with adverse events

n = number of adverse events

¹ Adverse events which had a definite, possible, probable or unknown relationship to study medication or for which no information about relationship was available

study medication

² Multiple answers possible

³ Incidence of at least 1.5% of patients in any treatment group

⁴ Not otherwise specified, not elsewhere classified

Scanned from Table 8.1.2.2.2-c, page 179, Volume 135

Medical Officer Comments: The rate of patients with related adverse events was higher dolasetron group than in the 2 palonosetron groups. The nervous system was the most often involved in all 3 treatment arms. The most common related adverse events were headache for all treatment groups. Psychiatric disorders occurred more often in the palonosetron 0.25 mg group. Tachycardia was reported in 3 patients in the palonosetron 0.25 mg group and 2 in the 0.75 mg group but none in the dolasetron group.

The individual case report tabulation forms were reviewed for the treatment related adverse events. The following are the highlights of this review.

Nervous System Disorders

Headache was the most common adverse event.

- 51 (26.4%) of the 0.25 mg palonosetron group suffered headaches.
 - 27 (14.0%) were judged to be related to the study drug
 - Of those judged to be related to the study drug:
 - 21 (10.9%) were mild in intensity.
 - 4 (2.1%) were moderate in intensity.
 - 2 (1.0%) were severe in intensity