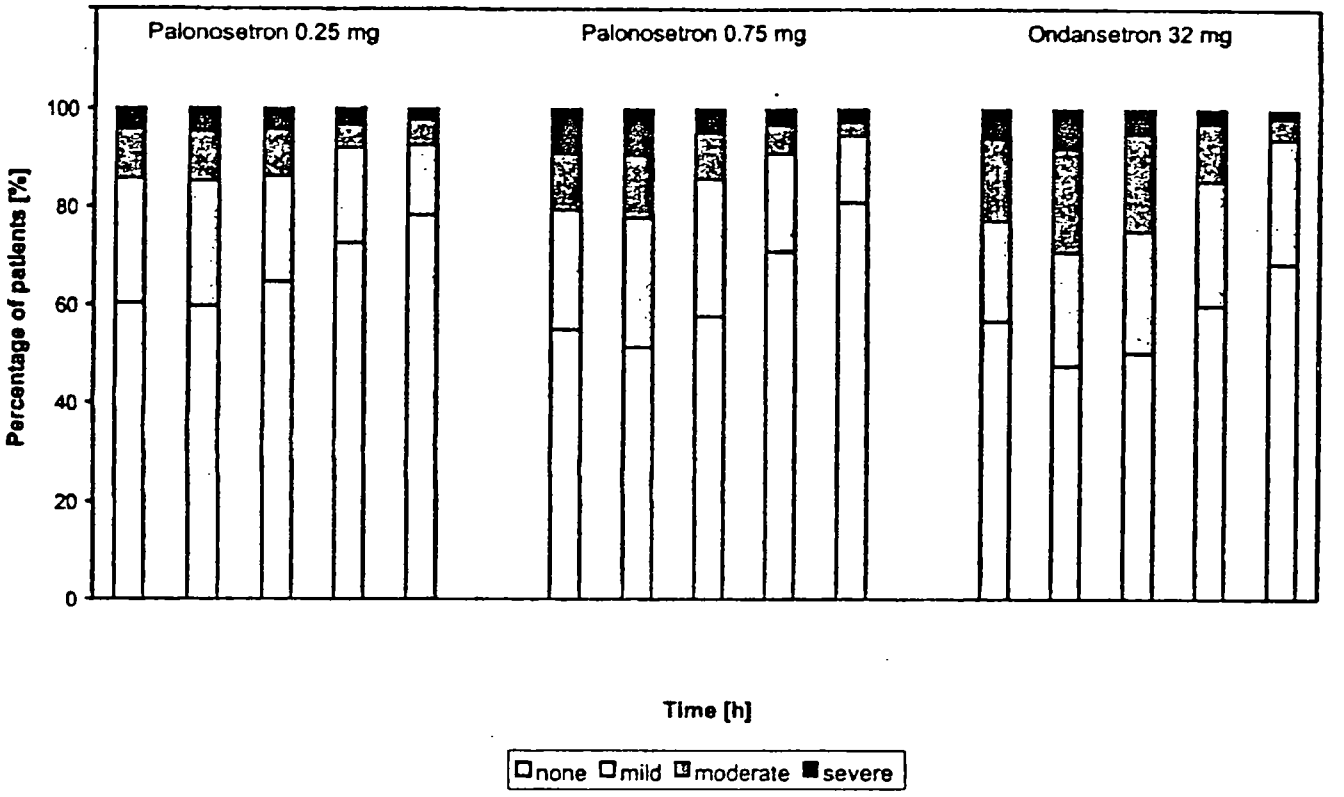
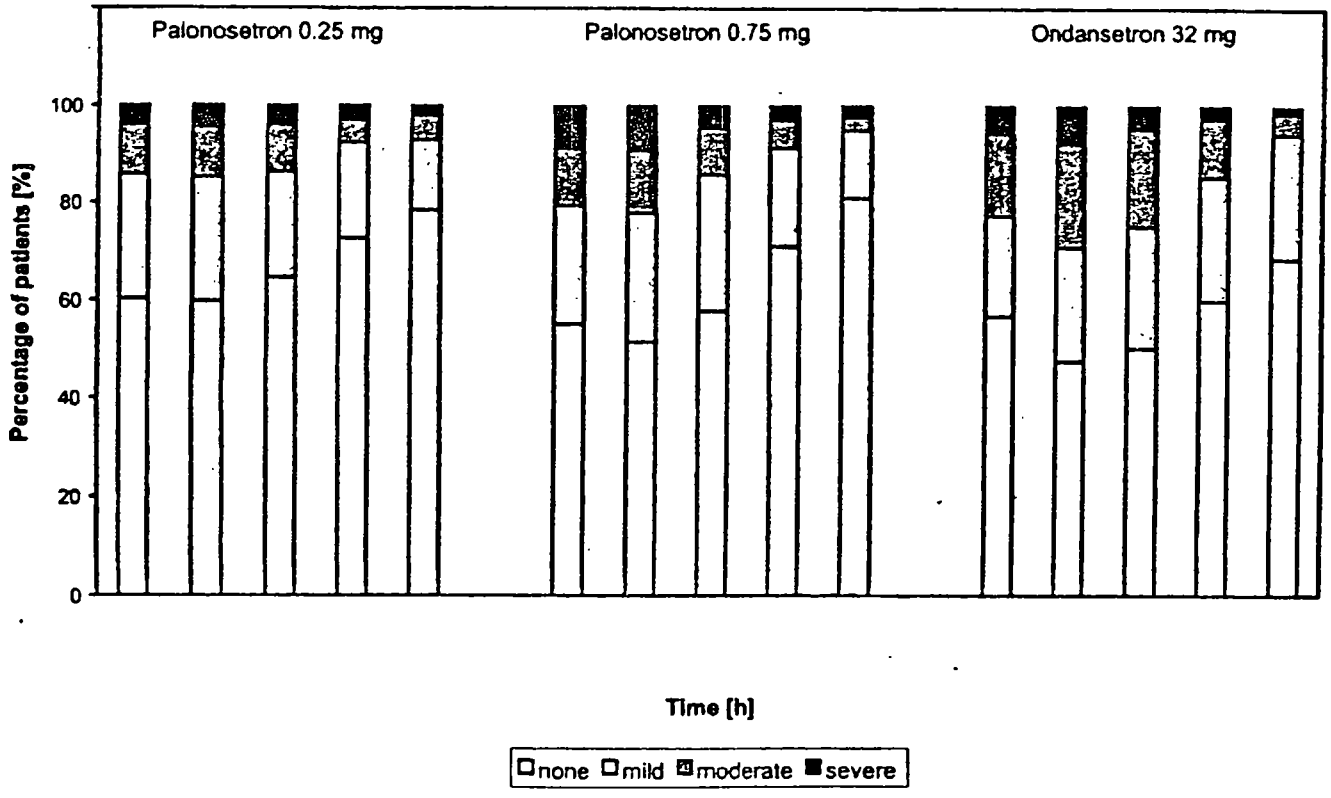
FIGURE 1: Severity of nausea during Study Day 1, 2, 3, 4, and 5
PALO-99-03 (top), PALO-99-04 (bottom) (Scanned from figure 7.1.2.4-a,)





Medical Officer Comments: For PALO 99-03, the rate of patients without nausea was highest in the palonosetron 0.25 mg group and lowest in the ondansetron group. For Day 1 the difference was not significant (p-value 0.318 using Kruskal-Wallis test). For Days 2,3,4,5 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 ondansetron statistically significant differences were seen on Day 2, 3, and 4. This is consistent with the pharmacologic properties of palonosetron, which has a longer half-life than ondansetron.

For PALO-99-04, 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.

Secondary Efficacy Endpoint – Time to Rescue Medication

The median time to first use of rescue medication was greater than 120 hours for all groups in both studies. 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 mediation during this study. There was no statistical difference between treatment groups in the number of patients who took rescue medication for any study day.

Secondary Efficacy Endpoint – Time to Treatment Failure

The median time to treatment failure (time to first emetic episode or administration of rescue medication, whichever occurred first) was again greater than 120 hours for all groups in both studies. Analysis of the first quartile of patients found that the time to treatment failure was longest in the 0.25 mg Palonosetron group.

Secondary Efficacy Endpoint – 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. The following tables display the results for both PALO-99-03, and PALO-99-04 respectively.

TABLE 21: PALO-99-03 - Quality of Life VAS scores for nausea and vomiting

Time Period (hours)	Palonosetron 0.25 mg (N=189)	Palonosetron 0.75 mg (N=189)	Ondansetron 32 mg (N=185)
	Median	Median	Median
0-24 hours			
Nausea	872	866	851
Vomiting	900	897	899
Overall score	1587	1749	1721
24-96 hours			
Nausea	861	866	828
Vomiting	899	896	889
Overall score	1740	1734	1680

(Reference: Table 7.1.2.8-a ,page 126, Volume 117)

TABLE 22: PALO-99-04 - 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: *For Study PALO-99-03, 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 total score for the time period 24-96 hours between palonosetron 0.25 mg and ondansetron (p=0.014). No statistical difference was found between the higher dose of palonosetron and ondansetron,(p=0.130) nor between the 2 doses of palonosetron (p=0.369).*

For Study PALO-99-04, again 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).

Secondary Efficacy Endpoint -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. The results are shown in the following tables

TABLE 23: PALO-99-03 - Global Satisfaction with Anti-emetic therapy (ITT cohort, N=563)

Time Period (hours)	Palonosetron 0.25 mg (N=189) Median	Palonosetron 0.75 mg (N=189) Median	Ondansetron 32 mg (N=185) Median
Acute			
0-24 hours	97	96	97
Delayed			
24-48	97	94	93
48-72	98	96	94
72-96	99	98	97
96-120	99	99	98

(Reference: Table 7.1.2.7-a, page 124, Volume 117)

TABLE 24: PALO-99-04 - Global Satisfaction with Anti-emetic therapy (ITT cohort, N=569)

Time Period (hours)	Palonosetron 0.25 mg (N=189) Median	Palonosetron 0.75 mg (N=189) Median	Dolasetron 100 mg (N=191) 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: *For PALO-99-03, a statistical difference between treatment groups was found by Kruskal-Wallis testing for Day 3 (p=0.045) but not the other days (0.05). A pair wise test between 0.25 mg of palonosetron and ondansetron showed a significant difference (0.015) in favor to palonosetron for Day 3 also. No difference was seen between the two palonosetron groups or between 0.75 mg palonosetron and ondansetron.*

For PALO-99-04, a statistical difference between treatment groups was found by Kruskal-Wallis testing for Day 2 (p=0.008) but not the other days). A pairwise 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 for PALO-99-03, and 99-04

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

TABLE 25: Statistical Analysis Results of Secondary Efficacy Parameters for Phase 3 Moderately Emetogenic CINV Pivotal Studies (PALO-99-03 and PALO-99-04)

		PALO-99-03				PALO-99-04			
Parameters	**Statistical Test**	**Overall**	**PALO 0.25 mg vs ONDA 32 mg**	**PALO 0.75 mg vs ONDA 32 mg**	**PALO 0.25 mg vs PALO 0.75 mg**	**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	0.0720	--	--	--	0.1780	--	--	--
24-48 hr	Chi-square	**0.0030**	**0.0010**	0.4870	**0.0100**	**0.0010**	**0.0040**	**0.0010**	0.6040
48-72 hr	Chi-square	**0.0010**	**0.0010**	**0.0040**	0.3960	**0.0010**	**0.0050**	**0.0010**	0.2340
72-96 hr	Chi-square	**0.0030**	**0.0030**	**0.0060**	0.7780	**0.0120**	0.1310	**0.0030**	0.1410
96-120 hr	Chi-square	0.2050	--	--	--	0.2270	--	--	--
0-48 hr	Chi-square	**0.0040**	**0.0020**	0.5490	**0.0100**	**0.0380**	**0.0290**	**0.0230**	0.9180
0-72 hr	Chi-square	**0.0010**	**0.0010**	0.0990	**0.0460**	**0.0320**	**0.0470**	**0.0120**	0.6050
0-96 hr	Chi-square	**0.0020**	**0.0010**	0.0980	0.0600	**0.0250**	**0.0270**	**0.0120**	0.7550
0-120 hr	Chi-square	**0.0020**	**0.0010**	0.0970	0.0610	**0.0290**	**0.0270**	**0.0160**	0.8350
Number of Emetic Episodes (EE)									
0-24 hr	KW/Wilcoxon	**0.0166**	**0.0042**	0.2131	0.0983	**0.0462**	**0.0135**	0.2047	0.2208
24-48 hr	KW/Wilcoxon	**0.0001**	**0.0001**	0.2245	**0.0025**	**0.0009**	**0.0153**	**0.0003**	0.2732
48-72 hr	KW/Wilcoxon	**0.0004**	**0.0001**	**0.0300**	0.0786	**0.0441**	0.3745	**0.0121**	0.1160
72-96 hr	KW/Wilcoxon	0.5591	--	--	--	0.0917	--	--	--
96-120 hr	KW/Wilcoxon	0.9116	--	--	--	**0.0228**	**0.0073**	0.1334	0.2064
0-120 hr	KW/Wilcoxon	**0.0004**	**0.0001**	0.0587	**0.0356**	**0.0018**	**0.0036**	**0.0016**	0.8442
Time to First EE	Log Rank	**0.0004**	**0.0001**	0.0789	**0.0306**	**0.0083**	**0.0101**	**0.0075**	0.8327
Severity of Nausea									
0-24 hr	KW/Wilcoxon	0.3183	--	--	--	0.1907	--	--	--
24-48 hr	KW/Wilcoxon	**0.0117**	**0.0032**	0.3358	**0.0488**	**0.0014**	**0.0240**	**0.0003**	0.2732
48-72 hr	KW/Wilcoxon	**0.0094**	**0.0029**	0.0565	0.2328	**0.0069**	**0.0415**	**0.0019**	0.3202
72-96 hr	KW/Wilcoxon	**0.0157**	**0.0088**	**0.0242**	0.7148	**0.0026**	0.2643	**0.0006**	**0.0259**
96-120 hr	KW/Wilcoxon	**0.0253**	0.0616	**0.0097**	0.4988	0.1696	--	--	--

PALO = Palonosetron; ONDA = Ondansetron; DOLA = 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.

TABLE 25 :Statistical Analysis Results of Secondary Efficacy Parameters for Phase 3 Moderately Emetogenic CINV Pivotal Studies (PALO-99-03 and PALO-99-04) (continued)

		PALO-99-03				PALO-99-04			
Parameters	**Statistical Test**	**Overall**	**PALO 0.25 mg vs Onda 32 mg**	**PALO 0.75 mg vs Onda 32 mg**	**PALO 0.25 mg vs PALO 0.75 mg**	**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**
Need of Rescue Medication									
0-24 hr	Chi-square	0.8380	--	--	--	0.3090	--	--	--
24-48 hr	Chi-square	0.2740	--	--	--	0.1230	--	--	--
48-72 hr	Chi-square	0.2030	--	--	--	0.2210	-	-	-
72-96 hr	Chi-square	0.1890	--	--	--	0.5840	--	--	--
96-120 hr	Chi-square	0.5300	--	--	--	0.3430	--	--	--
0-120 hr	Chi-square	0.1430	--	--	--	0.2950	--	--	--
Time to Rescue	Log Rank	0.1699	--	--	--	0.3015	--	--	--
Subject Global Satisfaction									
0-24 hr	KW/Wilcoxon	0.7132	--	--	--	0.4754	--	--	--
24-48 hr	KW/Wilcoxon	0.0703	--	--	--	**0.0494**	0.0559	**0.0212**	0.8714
48-72 hr	KW/Wilcoxon	**0.0452**	**0.0152**	0.2628	0.1393	0.0538	--	--	--
72-96 hr	KW/Wilcoxon	0.1200	--	--	--	**0.0078**	**0.0217**	**0.0032**	0.4686
96-120 hr	KW/Wilcoxon	0.0768	--	--	--	0.0592	--	--	--
Function Living Index-Emesis									
FLIE #1 Nausea	KW/Wilcoxon	0.4221	--	--	--	0.1779	--	--	--
FLIE #1 Vomiting	KW/Wilcoxon	0.1520	--	--	--	0.5042	--	--	--
FLIE #1 Total	KW/Wilcoxon	0.2794	--	--	--	0.2159	--	--	--
FLIE #2 Nausea	KW/Wilcoxon	0.0953	--	--	--	**0.0130**	**0.0307**	**0.0048**	0.5619
FLIE #2 Vomiting	KW/Wilcoxon	0.0565	--	--	--	0.2029	--	--	--
FLIE #2 Total	KW/Wilcoxon	0.0472	**0.0138**	0.1298	0.3687	**0.0159**	**0.0393**	**0.0053**	0.5174

PALO = Palonosetron; ONDA = Ondansetron; DOLA = 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.

(Reference: Table 3.8.3:6, page 133, Volume 1)

b.) Highly Emetogenic Chemotherapy (Study PALO-99-05)

For Study PALO-99-05, 76 centers located in Europe, and North America enrolled 680 patients. Of these 671 were randomized to one of the three treatment groups.

There were comparable number of male and female subjects enrolled. This study contained slightly more chemotherapy-naïve subjects than non-naïve subjects. Standard of care in patients receiving highly emetogenic chemotherapy entails the use of corticosteroids. Thus, twice as many subjects with concomitant corticosteroid use than without corticosteroid use participated in this trial. A large majority of subjects received highly emetogenic doses of cisplatin.

As with the studies related to moderately emetogenic chemotherapy, the primary efficacy endpoint 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 26: Complete Response Rates During the First 24 Hours After Chemotherapy: Highly Emetogenic CINV Study PALO-99-05 (ITT Cohort; N = 667)

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 Ondansetron	
	N	n (%)	95% CI	Palonosetron 0.25 mg Minus Ondansetron	Palonosetron 0.75 mg Minus Ondansetron
Palonosetron 0.25 mg	223	132 (59.2)	[52.4%, 65.6%]		
Palonosetron 0.75 mg	223	146 (65.5)	[58.8%, 71.6%]		
Ondansetron 32 mg	221	126 (57.0)	[50.2%, 63.6%]	[-8.8%, 13.1%]	[-2.3%, 19.2%]

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.
Source: Final Study Report PALO-99-05; Table 7.1.1.1-a and Table 7.1.1.1-b.
(Reference: Table 3.8.3:7, page 137, Volume 1)

Medical Officer Comment: *The palonosetron 0.75 mg group had the highest proportion of subjects (65.5%) with a complete response during the first 24 hours after chemotherapy. The palonosetron 0.25 mg group had a complete response rate of 59.2% and the complete response rate was slightly less for the ondansetron group (57.0%).*

The lower limit of the 97.5% CI for the difference of complete response rates during the first 24 hours after chemotherapy was above the –15% pre-set threshold indicating non-inferiority of both palonosetron doses to ondansetron 32 mg in prevention of highly emetogenic acute CINV. The comparator drug was an FDA approved medication for the prevention of highly emetogenic CINV.

Complete response, by day (0 to 24, 24 to 48, 48 to 72, 72 to 96, and 96 to 120 hours) and cumulative time periods (0 to 48, 0 to 72, 0 to 96, 0 to 120, and 24 to 120 hours) is shown for Study PALO-99-05 in the following table.

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TABLE 27: Subjects with a Complete Response After Chemotherapy, By Day and Cumulative Time Periods: PALO-99-05 (ITT Cohort; N = 667)

	Number and Percentage (%) of Subjects with Complete Response at 24 Hours			Difference in Complete Response Rates, 97.5% Confidence Intervals	
Daily					
Time Period (Hours)	**Palonosetron 0.25 mg (N = 223)**	**Palonosetron 0.75 mg (N = 223)**	**Ondansetron 32 mg (N = 221)**	**Palonosetron 0.25 mg Minus Ondansetron 32 mg**	**Palonosetron 0.75 mg Minus Ondansetron 32 mg**
Acute[a]					
0–24	132 (59.2)	146 (65.5)	126 (57.0)	[-8.8%, 13.1%]	[-2.3%, 19.2%]
Delayed[b]					
24–48	127 (57.0)	129 (57.8)	109 (49.3)	[-3.4%, 18.7%]	[-2.5%, 19.5%]
48–72	137 (61.4)	139 (62.3)	118 (53.4)	[-2.9%, 19.0%]	[-2.0%, 19.9%]
72–96	149 (66.8)	164 (73.5)	142 (64.3)	[-8.0%, 13.1%]	[-1.0%, 19.5%]
96–120	165 (74.0)	170 (76.2)	156 (70.6)	[-6.6%, 13.4%]	[-4.2%, 15.5%]
Cumulative					
0–24	132 (59.2)	146 (65.5)	126 (57.0)	[-8.8%, 13.1%]	[-2.3%, 19.2%]
0–48	108 (48.4)	110 (49.3)	92 (41.6)	[-4.2%, 17.8%]	[-3.3%, 18.7%]
0–72	98 (43.9)	99 (44.4)	79 (35.7)	[-2.6%, 19.0%]	[-2.2%, 19.5%]
0–96	93 (41.7)	95 (42.6)	75 (33.9)	[-3.0%, 18.5%]	[-2.1%, 19.4%]
0–120	91 (40.8)	94 (42.2)	73 (33.0)	[-2.9%, 18.5%]	[-1.6%, 19.8%]
24-120	101 (45.3)	107 (48.0)	86 (38.9)	[-4.6%, 17.3%]	[-1.9%, 20.0%]

[a] = Primary efficacy endpoint.
[b] = Secondary endpoint.
Source: Final Study Report PALO-99-05; Table 7.1.2.1-a, Table 7.1.2.1-b, Table 7.1.2.1-d, and Table 7.1.2.1-e.
(Reference: Table 3.8.3:8, page 139, Volume 1)

Medical Officer Comments: *For all cumulative time periods following the first 24 hours, the proportion of subjects with complete response in the two palonosetron doses were similar. There were no statistically significant differences between the complete response rate in the palonosetron groups compared to the ondansetron group. It is significant to note that ondansetron is not indicated for delayed treatment of highly emetogenic CINV. The applicant has demonstrated non-inferiority to ondansetron when using the –15% preset threshold. However, the comparator has not been proven to efficacious in this setting and must be assumed to have the same efficacy as placebo. Thus, to show efficacy of palonosetron for delayed prevention of highly emetogenic CINV, the applicant should show superiority to ondansetron. For all the time periods the lower limit for the 97.5% confidence intervals for the difference in complete response rates was below zero. Palonosetron did not show efficacy for delayed prevention of highly emetogenic CINV.*

The following table displays other secondary efficacy parameters for PALO-99-05, including complete control, number of emetic episodes, time to first emetic episode, severity of nausea, need of rescue medication, time to rescue medication, global satisfaction and quality of life (Function Living Index-Emesis; FLIE). Statistically significant differences are in bold type.

TABLE 28: Statistical Analysis Results of Secondary Efficacy Parameters for Phase 3 Highly Emetogenic CINV Pivotal Study (PALO-99-05)

Parameter	Statistical Test	Overall	PALO 0.25 mg vs ONDA 32 mg	PALO 0.75 mg vs ONDA 32 mg	PALO 0.25 mg vs PALO 0.75 mg
Complete Control (CC)					
0-24 hr	Chi-square	0.1360	--	--	--
24-48 hr	Chi-square	0.1820	--	--	--
48-72 hr	Chi-square	0.0620	--	--	--
72-96 hr	Chi-square	**0.0230**	0.5100	**0.0080**	**0.0440**
96-120 hr	Chi-square	0.3010	--	--	--
0-24 hr	Chi-square	0.0800	--	--	--
0-72 hr	Chi-square	0.0690	--	--	--
0-96 hr	Chi-square	0.1090	--	--	--
0-120 hr	Chi-square	0.0950	--	--	--
Number of Emetic Episodes					
0-24 hr	KW/Wilcoxon	**0.0222**	0.1599	**0.0053**	0.2065
24-48 hr	KW/Wilcoxon	0.2494	--	--	--
48-72 hr	KW/Wilcoxon	0.1555	--	--	--
72-96 hr	KW/Wilcoxon	0.1404	--	--	--
96-120 hr	KW/Wilcoxon	0.5516	--	--	--
0-120 hr	KW/Wilcoxon	**0.0222**	0.0842	**0.0061**	0.3721
Time to First EE	Log-Rank	**0.0122**	**0.0228**	**0.0062**	0.6793
Severity of Nausea					
0-24 hr	KW/Wilcoxon	0.2261	--	--	--
24-48 hr	KW/Wilcoxon	0.6187	--	--	--
48-72 hr	KW/Wilcoxon	0.3354	--	--	--
72-96 hr	KW/Wilcoxon	0.2181	--	--	--
96-120 hr	KW/Wilcoxon	0.2432	--	--	--
Need of Rescue Medication					
0-24 hr	Chi-square	0.3360	--	--	--
24-48 hr	Chi-square	0.1640	--	--	--
48-72 hr	Chi-square	0.1310	--	--	--
72-96 hr	Chi-square	0.4450	--	--	--
96-120 hr	Chi-square	0.8650	--	--	--
0-120 hr	Chi-square	0.3310	--	--	--
Time to Rescue	Log-Rank	0.3075	--	--	--

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

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.

TABLE 28: Statistical Analysis Results of Secondary Efficacy Parameters for Phase 3 Highly Emetogenic CINV Pivotal Study (PALO-99-05) (continued)

Parameter	Statistical Test	Overall	PALO 0.25 mg vs ONDA 32 mg	PALO 0.75 mg vs ONDA 32 mg	PALO 0.25 mg vs PALO 0.75 mg
Subject Global Satisfaction					
0-24 hr	KW/Wilcoxon	0.4884	--	--	--
24-48 hr	KW/Wilcoxon	0.4362	--	--	--
48-72 hr	KW/Wilcoxon	0.5843	--	--	--
72-96 hr	KW/Wilcoxon	0.6915	--	--	--
96-120 hr	KW/Wilcoxon	0.4813	--	--	--
Function Living Index-Emesis					
FLIE #1 Nausea	KW/Wilcoxon	0.7920	--	--	--
FLIE #1 Vomiting	KW/Wilcoxon	0.6597	--	--	--
FLIE #1 Total	KW/Wilcoxon	0.8291	--	--	--
FLIE #2 Nausea	KW/Wilcoxon	0.9636	--	--	--
FLIE #2 Vomiting	KW/Wilcoxon	0.7070	--	--	--
FLIE #2 Total	KW/Wilcoxon	0.9415	-	-	-

PALO = Palonosetron; ONDA = Ondansetron; 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.

(Reference: Table 3.8.3:9, page 144, Volume 1)

Medical Officer Comments: *The only secondary endpoint with a statistical significant difference in favor of palonosetron 0.25 mg was the time to first emetic episode. There was a statistical difference in favor of the 0.75 mg dose of palonosetron for complete control on day 4, number of emetic episodes and time to first emetic episode.*

Supportive Study PALO-00-01

The applicant submitted PALO-00-01 as a supportive trial for highly emetogenic CINV. It consisted of a re-analysis of efficacy data from Study 2330, a Phase 2 dose-response study that did not employ a comparator agent. A literature-based meta-analysis (PALO-01-23) was performed to provide historical placebo control data since the use of placebo is not ethically acceptable in the CINV subject population. The study design was similar to the pivotal trials in that it was a randomized, multi-center double-blind trial. The endpoints were identical to the pivotal trial with the exception being the omission of a quality of life questionnaire and the time assessed was 168 hours versus 120 hours of the pivotal trials. In the original protocol subjects received one of the following doses 0.3, 1, 3, 10 and 30 µg/kg. In the re-analysis these weight based cohorts were converted to fixed milligram doses in the following manners. Subjects were assigned to the following groups based on the original dose of medication they received.

- < 0.25 mg group included any dose less than 0.1 mg
- 0.25 mg group included 0.1 mg to less than 0.5 mg
- 0.75 mg group included 0.5 mg to less than 1.3735 mg
- >0.75 mg group included 1.375 mg or greater

The following table shows the primary efficacy variable complete response rate during the first 24 hours.

TABLE 29: Complete Response Rates During the First 24 Hours After Chemotherapy: Highly Emetogenic CINV Efficacy Analysis PALO-00-01 (Helsinn Data Set, ITT Cohort; N = 154)

	Historical Placebo	Palonosetron Fixed Dose				
		< 0.1 mg	0.25 mg	0.75 mg	2 mg	6 mg
N	70	30	27	24	27	46
CR, n (%)	6 (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%]
99% CI	[2%; 21%]	[11%; 55%]	[21%; 70%]	[21%; 73%]	[30%; 79%]	[31%; 69%]
p-value	--	0.012	< 0.001	< 0.001	< 0.001	< 0.001

N = Number of subjects in treatment group.
CR = Complete Response (defined as no emetic episode and no rescue medication).
n (%) = Number and percentage of subjects with CR.
CI = Confidence Interval.
Note: p-value = Treatment effect versus historical placebo using Fisher's exact test.
Source: Final Study Report PALO-00-01; Table 21.

Medical Officer Comments: *The palonosetron doses of 0.25 mg to 6 mg were significantly superior to the historical placebo group ($p < 0.01$). Complete response rates ranged from 44% to 56% for the 0.25 mg to 6 mg fixed-dose groups, compared with a modeled historical placebo complete response rate of 9%.*

The proportion of subjects who had complete response following highly emetogenic chemotherapy for cumulative time periods up to seven days is displayed by fixed dose group in the following table.

TABLE 30: Complete Control After Chemotherapy: Highly Emetogenic CINV Efficacy Analysis PALO-00-01 (Helsinn Data Set, ITT Cohort; N = 154)

Time Period (hours)	Palonosetron Fixed Doses				
	< 0.1 mg	0.25 mg	0.75 mg	2 mg	6 mg
	Number and Percentage (%) of Subjects with Complete Control (CC)				
	(n = 31)	(n = 24)	(n = 25)	(n = 25)	(n = 47)
0-24	9 (29)	11 (46)	11 (44)	13 (48)	22 (49)
0-48	6 (19)	6 (25)	7 (28)	8 (32)	13 (28)
0-72	6 (19)	3 (13)	7 (28)	8 (32)	12 (26)
0-96	6 (19)	3 (13)	6 (24)	8 (32)	11 (23)
0-120	6 (19)	3 (13)	6 (24)	8 (32)	11 (23)
0-144	6 (19)	3 (13)	6 (24)	8 (32)	10 (21)
0-168	6 (19)	2 (8)	6 (24)	6 (24)	10 (21)

CC = Complete Control (defined as no emetic episode and no rescue medication, experiencing no more than mild nausea).

Source: Final Study Report PALO-00-01; Table 32.

Medical Officer Comments: *The results from this study supported the pivotal trial PALO-99-05, that 0.25 mg of palonosetron is efficacious for prevention of CINV in the acute setting for highly emetogenic chemotherapy. The data from the supportive trial does not substantiate the claim that palonosetron is efficacious for delayed prevention of CINV for highly emetogenic chemotherapy.*

D. Efficacy Conclusions

Moderately emetogenic chemotherapy

The applicant has demonstrated the efficacy of 0.25 mg palonosetron for the prevention of moderately emetogenic CINV. This assessment of efficacy is based on two adequate and well controlled pivotal Phase 3 efficacy trials, PALO-99-03 and PALO-99-04, that used standard, accepted efficacy and safety endpoints, and FDA-approved active comparators. The primary efficacy parameter was complete response within the first 24 hours after chemotherapy that was has been used as the basis for approval of other medications for this indication. The results demonstrated the non-inferiority of both palonosetron 0.25 mg and 0.75 mg when compared to ondansetron and dolasetron. The lower limit of the 97.5% confidence interval for the difference in complete response rates between the ondansetron and the palonosetron groups during the first 24 hours after chemotherapy was above the preset 15% delta. These trials also demonstrated that palonosetron 0.25 mg was efficacious for delayed prevention (24-120 hours) of moderately emetogenic CINV.

Highly emetogenic chemotherapy

The applicant has demonstrated the efficacy of 0.25 mg palonosetron for the prevention of highly emetogenic CINV. This assessment of efficacy is based on the adequate and well controlled pivotal Phase 3 efficacy trial PALO-99-05 and PALO-00-01(a Phase 2 supportive trial). PALO-99-05 used standard, accepted efficacy and safety endpoints, and FDA-approved active comparators. The trial design and endpoints were identical to PALO-99-03. The results demonstrated the non-inferiority of both palonosetron 0.25 mg and 0.75 mg when compared to ondansetron. Again, the lower limit of the 97.5% confidence interval for the difference in complete response rates between the ondansetron and the palonosetron groups during the first 24 hours after chemotherapy was above the preset 15% delta. However, these trials did not establish that palonosetron 0.25 mg was efficacious for delayed prevention (24-120 hours) of highly emetogenic CINV. While the results did show non-inferiority to the comparator arms, the comparator drug is not indicated for delayed prevention of CINV. Thus, in order to show efficacy the study drug should demonstrate superiority to the comparator drug. It did not do so. There was no statistically significant difference between palonosetron and ondansetron for delayed prevention of highly emetogenic CINV. The evidence the applicant has presented does not substantiate an efficacy claim for this indication.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The clinical Integrated Summary of Safety (ISS) of this NDA includes all safety data collected in 3137 unique subjects enrolled in the 18 palonosetron clinical trials of whom 2360 received palonosetron. Review of this data demonstrates that palonosetron when given as single dose prior to chemotherapy was well tolerated. A wide dose range was studied (less than 0.25 mg to approximately 6 mg). No deaths occurred that were attributable to the study drug. An extensive review of cardiac safety was conducted which included analysis of ECG (performed in 2172 subjects) and Holter tracings (143 subjects) using high-resolution methods and a centralized review by a blinded cardiologist. No dose response on QTc interval was observed. The cardiac safety profile for palonosetron is similar to that of other drugs in this class. No signal for adverse effects of the study drug on laboratory or vital signs was detected.

The most common adverse reactions seen with palonosetron (≥ 2%) were constipation and headache. Incidences of these reactions were similar across all palonosetron dose groups and the active comparator 5-HT_3 receptor antagonists, ondansetron and dolasetron. All other adverse reactions were seen at incidences equal to or less than 1%. Nearly all episodes of constipation were self-limiting and not severe. However, two subjects who took palonosetron in Phase 2 trials suffered from constipation that required treatment in a hospital. The current package insert for another already approved 5-HT_3 antagonists ondansetron states that constipation occurred in 11% of chemotherapy patients receiving multiday ondansetron. The package insert for dolasetron reports a 3.2% incidence of constipation in chemotherapy patients.

C. Description of Patient Exposure

This Integrated Review of Safety is comprised of data from 16 studies with 3125 subjects in the palonosetron clinical development program. It consists single-dose administration of palonosetron by the intravenous and oral routes in healthy volunteers, special populations, and PONV and CINV patients. The 16 studies included nine controlled studies (active or placebo) and seven uncontrolled studies (no comparator). A total of 2348 palonosetron-treated subjects were in these 16 studies: 198 in Phase 1; 937 in Phase 2; and 1213 in Phase 3 studies.

The following table summarizes the number of subjects exposed to palonosetron and comparators in the 16 clinical trials in the Integrated Safety Database

TABLE 31: Enumeration of Subjects Exposed to Palonosetron (All Doses) and Comparators in Various Analysis Populations in the Integrated Summary of Safety

	Palonosetron (all doses)			Active Comparators		Placebo	Total
	IV	Oral	Total	Ondansetron	Dolasetron		
No. subjects	n (%)	N (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All trials	1838 (100)	510 (100)	2348 (100)	410 (100)	194 (100)	173 (100)	3125 (100)
Phase 3 trials	1213 (66.0)	–	1213 (51.7)	410 (100)	194 (100)	–	1817 (58.1)
Phase 2/3 Pivotals[a]	1374 (74.8)	–	1374 (58.5)	410 (100)	194 (100)	–	1978 (63.3)
Phase 2/3 trials	1693 (92.1)	457 (89.6)	2150 (91.6)	410 (100)	194 (100)	127 (73.4)	2881 (92.2)
Phase 2 trials[b]	480 (26.1)	457 (89.6)	937 (39.9)	–	–	127 (73.4)	1064 (34.0)
Phase 1 trials	145 (7.9)	53 (10.4)	198 (8.4)	–	–	46 (26.6)	244 (7.8)

[a] Includes studies PALO-99-03, PALO-99-04, PALO-99-05 and 2330.
[b] Study 2330 is included in Phase 2 trials and Phase 2/3 Pivotal trials.
(Reference: Volume 1, Table 3.8.4:1, page 165).

2348 subjects in the Integrated Safety Database received palonosetron while 410, 194, and 173 received ondansetron, dolasetron, and placebo, respectively. A total of 1838 (78.3 %) of

subjects received IV palonosetron while 510 (21.7 %) received the oral formulation. The following table displays the exposure in the CINV patients.

TABLE 32: Exposure in CINV in Integrated Safety Database

		Palonosetron	Comparator	Total
Phase 3	IV	1213	604	1817
Phase 2/3 pivotal[a]	IV	1374	604	1978
Phase 2[b]	IV Oral	163 169	– –	332
Overall exposure in CINV		1545	604	2149

[a] Includes PALO-99-03, PALO-99-04, PALO-99-05 and 2330.
[b] Study 2330 and Study 2120 for IV and 2332 for PO.
(Reference Table 3.8.4:2, Volume 1, page 165)

Two-thousand one hundred and fifty subjects were exposed to palonosetron in the Integrated Phase 2/3 trials. Seventy-two percent were treated for CINV, including 763 subjects in moderately emetogenic studies (PALO-99-03, PALO-99-04) and 782 in highly emetogenic studies (PALO-99-05, 2330, 2332, and 2120). The remaining 28% were enrolled in post-operative nausea and vomiting (PONV) trials (2500 and 2502).

The applicant proposes a dose of 0.25 mg IV in this NDA. In the Integrated Review of safety database most subjects received either 0.25 mg or 0.75 mg doses, (38% and 33.8 %, respectively). The following table summarizes exposure in clinical trials according to palonosetron dose level

TABLE 33: Exposure in the Integrated Safety Database of Palonosetron by Dose

Number of Subjects	Palonosetron (mg)					Comparators			Total
	< 0.25	0.25	0.75	> 0.75	Total	Onda 32 mg	Dola 100 mg	Placebo	
Phase 3	0	605	608	0	1213	410	194	–	1817
Phase 2	329	212	118	278	937	–	–	127	1064
Phase 1	12	24	93	69	198	–	–	46	244
Total Phase 2/3	329	817	726	278	2150	410	194	127	2881
Total all integrated trials	341	841	819	347	2348	410	194	173	3125

Onda = Ondansetron; Dola = Dolasetron.
(Reference: Table 3.8.4.3, page 166, Volume 1)

A total of 2150 subjects were exposed to palonosetron in the Phase 2/3 trials. Of these, 1693 (78.7%) received IV doses (in studies PALO-99-03, PALO-99-04, PALO-99-05, 2330, 2120, and 2500) and 457 (21.3%) received oral doses (in studies 2332 and 2502).

The mean age of palonosetron-treated subjects was 49.7 years. Four-hundred and seventeen subjects (18%) subjects were ≥ 65 years. More females (64%) than males (36%) were

exposed to palonosetron. The majority of subjects were Caucasian, with 785 (33%) subjects representing non-Caucasian races. Fifty-six percent of the subjects were from North America.

C. Methods and Specific Findings of Safety Review

The applicant did not include two trials in the Integrated Safety Database that investigated repeated dosing of palonosetron. These were PALO-99-06, a repeat-cycle, open-label, extension trial involved 895 patients from the Phase 3 pivotal trials and PALO-99-34 comprised 12 healthy subjects. They did, however, include deaths and serious adverse events from these studies with the other data.

1. Deaths

Of subjects who received palonosetron in all Phase 1, 2 and 3 trials, 31 (1.3%) died. In the studies with comparator arms, four (0.7 %) subjects who had received ondansetron died and no deaths occurred among dolasetron or placebo subjects. Fifteen of the deaths in the palonosetron group occurred during the Phase 2 studies including two deaths in subjects receiving palonosetron for PONV. The remaining 16 deaths occurred during Phase 3 studies in subjects receiving moderately or highly emetogenic chemotherapy for cancer.

Twenty-three subjects who died received intravenous formulation of palonosetron and the remaining 8 subjects received the oral formulation. The dose was > 0.75 mg in six deaths, 0.75 mg in 14 deaths, 0.25 mg in eight deaths and < 0.25 mg in three deaths. Sixteen of the 31 deaths occurred within 2 weeks of receiving the dose of palonosetron, nine deaths occurred more than 2 weeks after receiving the palonosetron and the timing was unknown for six of the deaths. Below are listed a summary of the case reports for all subjects who died within two weeks of receiving palonosetron or for those in which the time of death was uncertain.

Study PALO-99-04

- Subject #2228 was a 68 year old female with Non-Hodgkins lymphoma who died of septic shock. She received 0.75 mg of palonosetron IV. The death was thought to be unlikely related to the study drug by the investigator and the sponsor.
- Subject #4007 was a 71 year old male who suffered from pancreatic cancer. He experienced gastrointestinal bleeding and died 2 days after receiving 0.75 mg palonosetron IV. The death was thought to be unlikely related to the study drug by the investigator and the sponsor.
- Subject #4343 was a 75 year old female who suffered from lung cancer. She was hospitalized for pleural effusion secondary to her cancer 3 days after receiving 0.25 mg palonosetron IV. She died of urosepsis two weeks after receiving the palonosetron. The death was assessed to be unrelated to the study drug by the investigator and the sponsor.

Study PALO-99-05

- Subject #8091 was a 66 year old female who suffered from small cell lung cancer. She was hospitalized for respiratory failure six days receiving 0.25 mg palonosetron IV. She was intubated and post-intubation developed bradycardia followed by idioventricular cardiac rhythm. Attempts at resuscitation were unsuccessful and the patient died eight days after receiving the study drug. No autopsy was performed but the cause of death was listed as respiratory failure secondary to lung cancer. The death was assessed to be unlikley to be related to the study drug by the investigator and the sponsor.

- Subject #4343 was a 75 year old female who suffered from lung cancer. She was hospitalized for pleural effusion secondary to her cancer 3 days after receiving 0.25 mg palonosetron IV. She died of urosepsis two weeks after receiving the palonosetron. The death was assessed to be unrelated to the study drug by the investigator and the sponsor.
- Subject #9187 was a 58 year old male who suffered from urinary bladder cancer. He was hospitalized with acute renal failure 5 days after receiving 0.75 mg palonosetron IV. He died of renal failure the next day. The renal failure was thought to be secondary to either displacement of the nephrostomy tube or pyleonephritis. No autopsy was performed. The death was assessed to be unlikely to be related to the study drug by the investigator and the sponsor.
- Subject #9607 was a 41 year old male who suffered from malignant mesothelioma. He died at his home 12 days after receiving 0.25 mg palonosetron IV. The cause of death was listed as respiratory insufficiency secondary to lung cancer. No autopsy was performed. The death was assessed to be unrelated to the study drug by the investigator and the sponsor.
- Subject #9745 was a 71 year old female who suffered from Stage IV broncho-alveloar carcinoma. The patient suffered from severe bronchospasm one day after receiving 0.75 mg IV palonosetron. She died one day later. The cause of death was bronchospasm. She had a history of chronic obstructive pulmonary disease. The death was assessed to be unlikely to be related to the study drug by the investigator and the sponsor.
- Subject #9773 was a 82 year old female who suffered from oral cancer. She suffered a myocardial infarction 13 days after receiving 0.75 mg palonosetron IV. The death was assessed to be unrelated to the study drug by the investigator and the sponsor.

Study 2330

- Subject #2402 was a 61 year old male who suffered from advanced head and neck cancer. He died of complications related to disseminated intravascular coagulation 12 days after receiving palonosetron. The death was assessed to be unrelated to the study drug by the investigator and the sponsor.
- Subject #2505 was a 59 year old male who suffered poorly differentiated metastatic carcimona. He died at his home 13 days after receiving palonosetron 1 µg/kg IV. The cause of death was unknown but listed as possible related to neutropenia. The death was assessed to be unrelated to the study drug by the investigator and the sponsor.
- Subject #302 was a 69 year old male who died of sepsis 14 days after receiving palonosetron 3 µg/kg IV. The death was assessed to be unrelated to the study drug by the investigator and the sponsor.
- Subject #008 was a 69 year old male who died of stroke 12 days after receiving palonosetron 3 µg/kg IV. The death was assessed to be unrelated to the study drug by the investigator and the sponsor.
- Subject #009 was a 60 year old male who died of infectious and hemorrhagic complications of pancytopenia 13 days after receiving palonosetron 10 µg/kg IV. The death was assessed to be unrelated to the study drug by the investigator and the sponsor.

Study 2332

- Subject #1502 was a 71 year old male who died of acute renal failure 5 days after receiving palonosetron 30 µg/kg IV. The cause of the renal failure was listed as cisplatin. The death was assessed to be unrelated to the study drug by the investigator and the sponsor.
- Subject #706 was a 62 year old female with terminal lung cancer. She died at home with hospice care 12 days after receiving palonosetron 30 µg/kg IV. The cause of death was lung cancer. The death was assessed to be unrelated to the study drug by the investigator and the sponsor.

Study 2500

- Subject #586 was a 39 year old female who underwent a hysterectomy. She received palonosetron 3 µg/kg IV for PONV. She died 7 days later of a pulmonary embolism. The death was assessed to be unrelated to the study drug by the investigator and the sponsor.

Medical Officer Comments: *All deaths among subjects who received palonosetron were reviewed. All the deaths were judged as unrelated or unlikely to be related to the study drug by both the sponsor and the investigator. After careful review, this medical officer concurs with this assessment. The cancer population for which this drug is intended has multiple co-morbidities and typically has a high mortality. Many of the deaths occurred as progression or as typical sequale of cancer and its treatment. In the palonosetron group none of the causes of deaths had a clearly discernible pattern that would suggest they were related to the study drug. In addition the timing of the deaths make it unlikely to be related to the palonosetron given it's 40 hour half-life. The death rate for patients was comparable for patients in the comparator arms in studies that had a comparator.*

2. Serious Adverse Events

Of 2348 palonosetron-treated subjects, 134 (5.7%) experienced an SAE, eight of which were considered related to palonosetron. Below are listed the most common SAEs among these 2348 palonosetron-treated subjects

- general disorders (n = 30 subjects)
- gastrointestinal (n = 30)
- metabolic (n = 29)
- infection (n = 27)
- blood disorders (n = 24)

Five percent of the 604 subjects in active comparator groups experienced a SAE as listed below:

- blood disorders (n = 9 subjects)
- general (n = 7)
- vascular (n = 6)
- infection (n = 5)
- gastrointestinal (n = 4)
- metabolic (n = 4)

The following table displays the rate of adverse events in various palonosetron dose groups:

TABLE 34: Serious Adverse Events in All Integrated Phase 1,2,3 Trials by Number of Subjects

	Palonosetron (mg)					Active Comparators			Placebo
	< 0.25 n (%)	0.25 n (%)	0.75 n (%)	> 0.75 n (%)	Total	Onda n (%)	Dola n (%)	Com-bined	n (%)
No SAE	321(94)	800 (95)	773(94)	319 (92)	2213 (94)	389 (95)	185 (95)	574 (95)	168 (97)
Any SAE	20 (6)	41 (5)	46 (6)	28 (8)	135 (6)	21 (5)	9 (5)	30 (5)	5 (3)

Onda = Ondansetron; Dola = Dolasetron.
(Reference: Table 8.9.5:5, page 54, Volume 96)

The rate of events across different palonosetron dose groups was similar (range 5% to 8%).

The following lists further details about the subjects who were considered to have SAEs possibly or probably related to the study drug.

- Subject #2590 was a 72 year old female subject who was enrolled in Study 2502. She received 10 µg/kg of palonosetron for prophylaxis of PONV. Three days later she was hospitalized for constipation. She responded to laxatives and was discharged after three days of hospitalization. This adverse event was thought to be possibly related to the study drug.
- Subject #951 was a 29 year old male who was enrolled in PALO-99-35. He received 0.75 mg of palonosetron IV. Four days later he had severe abdominal pain that caused an episode of syncope. He presented to the emergency room and was noted on abdominal x-ray to have a large amount of stool in the colon. He was treated with stool softeners and an enema and discharged. This adverse event was assessed as possibly related to the study drug.
- Subject #802 was a 61 year old male who was enrolled in Study 2332. He received a single dose of oral palonosetron at 1 µg/kg for prophylaxis of CINV. After receiving chemotherapy, he was noted to have an elevated creatinine. The level increased three days after receiving the palonosetron and chemotherapy and continued to rise for the next week. It responded to intravenous hydration. This adverse event was characterized as possibly related to the study drug, although the investigator noted the patient's chemotherapy was nephrotoxic.
- Subject #1211 was a 51 year old female who was enrolled in Study PALO-99-06. She received 0.75 mg IV of palonosetron for CINV. Approximately three hours later while receiving an IV infusion of pamidronate disodium she developed an anaphylactic reaction with hypotension and tachycardia. She responded to intravenous steroids and had no sequelae. This patient had a history of urticaria to an unknown drug. This adverse event was characterized as possibly related to the study drug although it was noted that pamidronate can be rarely associated with anaphylaxis.
- Subject #4434 was 54 year old male who was enrolled in PALO-99-06. He received 0.75 mg of palonosetron IV for CINV. One hour after the study drug was infused he became hypotensive and had a brief syncopal episode lasting two seconds. He was admitted to the hospital and monitored but no abnormalities were reported. This adverse event was characterized as probably related to the study drug by the investigator.
- Subject # 601 was a 54 year old male who received 1 µg/kg of palonosetron for CINV. He was admitted a week later with fever and granulocytopenia. The case report form lists the fever as possibly related to the study drug.

- Subject #1309 was enrolled in Study 2332/ She was 56 year old female who received 1 μg/kg of palonosetron for CINV. She was admitted 3 days later with dehydration and vomiting. The investigator characterized this adverse event as possibly related to the study drug due to lack of efficacy.
- Subject #3302 was a 29 year old male who received 90 μg/kg of palonosetron IV for CINV. He was hospitalized with abdominal pain, fever and neutropenia one week after receiving the study drug. He responded to antibiotics. Both the investigator and the sponsor felt his symptoms were not related to the study drug. However, there was some discrepancy in the case report forms from Syntex, so Helsinn has opted to include this as one of the 8 cases of SAEs possibly related to the study drug.

Medical Officer Comments: *Of these SAEs, three are likely unrelated to the study drug. Subjects # 802, 601, 1309 and 3302 more likely suffered toxicity from chemotherapy than related to the palonosetron.*

Two subjects suffered from constipation that required treatment in a hospital. The current package insert for another already approved 5-HT_3 antagonists ondansetron states that constipation occurred in 11% of chemotherapy patients receiving multiday ondansetron. The package insert for dolasetron reports a 3.2% incidence of constipation in chemotherapy patients. Another 5-HT_3 antagonist indicated for severe diarrhea predominant irritable bowel syndrome, alosetron, has been associated with severe complications from constipation. It should be noted that Subject #2590 did not have a bowel movement for at least 4 days prior to receiving the palonosetron. Thus, it may be possible that the study drug exacerbated a pre-existing problem. Labeling for this product should reflect the potential for constipation as a serious adverse event.

3. Treatment-Emergent Adverse Events

A total of 1693 (72%) palonosetron-treated subjects who participated in the 16 Phase 1, 2 and 3 clinical trials reported at least one AE. The following table displays the adverse events reported by System Organ Class(SOC) level.

TABLE 35: Adverse Events by SOC in All Phase 1, 2 and 3 Trials

SOC	Palonosetron										Active Comparators						Placebo	
	< 0.25 mg (n = 341)		0.25 mg (n = 841)		0.75 mg (n =819)		> 0.75 mg (n = 347)		Total (n = 2348)		Onda 32 mg (n = 410)		Dola 100 mg (n = 194)		Total (n = 604)		(n = 173)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
No AE	105	31	245	29	213	24	92	27	655	28	127	31	45	23	172	28	67	39
Any AE	236	69	596	71	606	76	255	73	1693	72	283	69	149	77	432	72	106	61
Blood	20	6	129	15	150	18	18	5	317	14	92	22	49	25	141	23	4	2
Cardiac	11	3	46	5	50	6	17	5	124	5	28	7	8	4	36	6	5	3
Ear	3	1	17	2	10	1	5	1	35	1	5	1	2	1	7	1	0	0
Endocrine	1	<1	2	<1	0	0	4	<1	0	0	0	0	0	0	0	0	0	0
Eye	4	1	8	1	8	1	3	1	23	1	4	1	0	0	4	1	1	1
Gastrointestinal	105	31	223	27	246	30	134	39	708	30	83	20	58	30	141	23	43	25
General	56	16	171	20	181	22	72	21	480	20	86	21	47	24	133	22	23	13
Hepatic	1	<1	5	1	10	1	0	0	16	1	6	1	1	1	7	1	1	1
Immune system	0	0	1	<1	4	<1	0	0	5	<1	1	<1	0	0	1	<1	0	0
Infection	34	10	62	7	65	8	31	9	192	8	18	4	18	9	36	6	14	8
Injury/Poisoning	2	1	5	1	4	<1	6	2	17	1	1	<1	0	0	1	<1	1	1
Investigational	16	5	92	11	114	14	27	8	249	11	56	14	21	11	77	13	13	8

Onda = Ondansetron; Dola = Dolasetron

TABLE 35: Adverse Events by SOC in All Phase 1, 2 and 3 Trials (continued)

SOC	Palonosetron										Active Comparators						Placebo	
	< 0.25 mg (n = 341)		0.25 mg (n = 841)		0.75 mg (n =819)		> 0.75 mg (n = 347)		Total (n = 2348)		Onda 32 mg (n = 410)		Dola 100 mg (n = 194)		Total. (n = 604)		(n = 173)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Metabolic	21	6	99	12	104	13	40	12	264	11	61	15	23	12	84	14	1	1
Musculoskeletal	14	4	45	5	46	6	20	6	125	5	22	5	20	10	42	7	5	3
Neoplasm	2	1	8	1	11	1	3	1	24	1	2	<1	1	1	3	<1	1	1
Nervous	99	29	206	24	214	26	113	33	632	27	106	26	67	35	173	29	44	25
Psychiatric	10	3	27	3	15	2	16	5	68	3	2	<1	4	2	6	1	1	1
Renal	15	4	26	3	28	3	15	4	84	4	10	2	6	3	16	3	12	7
Reproductive	3	1	7	1	8	1	1	<1	19	1	0	0	3	2	3	<1	0	0
Respiratory	28	8	40	5	51	6	45	13	164	7	12	3	10	5	22	4	10	6
Skin	56	16	57	7	50	6	44	13	207	9	22	5	19	10	41	7	16	9
Surgical	0	0	0	0	0	0	1	<1	1	<1	0	0	0	0	0	0	1	1
Vascular	22	6	40	5	43	5	23	7	128	5	22	5	6	3	28	5	12	7

Onda = Ondansetron; Dola = Dolasetron
(Reference: Table 3.8.4:4, page 172, Volume 1)

Medical Officer Comments: *Gastrointestinal AEs were most common in all treatment groups. In the Phase 3 trials and were reported for 30% of palonosetron and dolasetron subjects (708/2348 and 58/194, respectively), 25% of placebo subjects (43/173) and 20% of ondansetron subjects (83/410). The incidence of gastrointestinal AEs varied with dose ranging from 27% at the 0.25 mg dose to 39% at the > 0.75 mg dose.*

The active comparators combined had a lower incidence of gastrointestinal AEs (23%), with a difference between ondansetron and dolasetron groups (20% and 30%, respectively). For the Phase 2/3 trials the most commonly reported AEs were gastrointestinal (28%), nervous system (25%), general (24%), and blood and lymphatic system (21%) events. The incidence of AEs was slightly higher in the 0.75 mg dose group than in the 0.25 mg dose group. The active comparator arms displayed similar incidences although nervous system disorders were slightly more frequent (26% for ondansetron, 35% for dolasetron, 29% combined). Constipation, diarrhea, and abdominal pain were the most common gastrointestinal AEs in palonosetron groups (11%, 6% and 4% respectively). Headache was the predominant complaint in nervous system AEs (19%). Fatigue (6%), pyrexia (4%), asthenia (5%), and weakness (4%) were the most commonly noted adverse events in the general disorders category for all palonosetron doses combined. The incidences of constipation, headache, lymphopenia, and leukopenia were slightly higher at the 0.75 mg dose versus the 0.25 mg dose. A similar adverse event profile was observed in the active comparator groups, However, the dolasetron groups had slightly higher incidences of headache (27%), fatigue (12%), and constipation (10%) compared to the ondansetron groups (17%, 5%, and 6%, respectively).

The majority of AEs were judged by the investigators to be unlikely related to the study drug. Gastrointestinal and nervous system AEs were most likely to be assessed as possibly or probably related to study drug in both palonosetron and active comparator groups.
The following table displays incidences for events that are possibly or probably related to palonosetron occurring in greater than or equal to 2% of palonosetron-treated subjects.

TABLE 36: Summary of Number (%) of Patients Reporting Adverse Events by SOC and MedDRA Preferred Term Adverse Events Which are Considered Probably or Possibly Related in Pivotal Phase 2/3 Trials with an Incidence of Greater Than or Equal to 2%

SOC	Preferred Term	Palonosetron Doses (mg)										Active Comparators					
		< 0.25		0.25		0.75		> 0.75		Total		Onda 32 mg		Dola 100 mg		Total	
		n = 31		n = 633		n = 633		n = 77		n = 1374		n = 410		n = 194		n = 604	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Cardiovascular	**Any AEs**	**0**	**(0)**	**15**	**(2)**	**15**	**(2)**	**2**	**(3)**	**32**	**(2)**	**9**	**(2)**	**1**	**(1)**	**10**	**(2)**
Gastrointestinal	**Any AEs**	**2**	**(6)**	**42**	**(7)**	**55**	**(9)**	**13**	**(17)**	**112**	**(8)**	**19**	**(5)**	**21**	**(11)**	**40**	**(7)**
	Constipation	1	(3)	29	(5)	42	(7)	9	(12)	81	(6)	8	(2)	12	(6)	20	(3)
	Diarrhoea NOS	1	(3)	8	(1)	6	(1)	0	(0)	15	(1)	7	(2)	4	(2)	11	(2)
	Abdominal pain NOS	1	(3)	1	(< 1)	3	(< 1)	3	(4)	8	(1)	2	(< 1)	3	(2)	5	(1)
	Hiccups	1	(3)	1	(< 1)	1	(< 1)	0	(0)	3	(< 1)	1	(< 1)	0	(0)	1	(< 1)
General	**Any AEs**	**2**	**(6)**	**14**	**(2)**	**27**	**(4)**	**1**	**(1)**	**44**	**(3)**	**10**	**(2)**	**7**	**(4)**	**17**	**(3)**
	Fatigue	0	(0)	3	(< 1)	5	(1)	0	(0)	8	(1)	4	(1)	4	(2)	8	(1)
	Chest pain NEC	2	(6)	0	(0)	0	(0)	0	(0)	2	(< 1)	0	(0)	0	(0)	0	(0)
Investigations	**Any AEs**	**0**	**(0)**	**6**	**(1)**	**16**	**(3)**	**1**	**(1)**	**23**	**(2)**	**7**	**(2)**	**2**	**(1)**	**9**	**(1)**
Metabolism	**Any AEs**	**0**	**(0)**	**11**	**(2)**	**8**	**(1)**	**0**	**(0)**	**19**	**(1)**	**6**	**(1)**	**5**	**(3)**	**11**	**(2)**
Musculoskeletal	**Any AEs**	**0**	**(0)**	**1**	**(< 1)**	**4**	**(1)**	**1**	**(1)**	**6**	**(< 1)**	**1**	**(< 1)**	**4**	**(2)**	**5**	**(1)**

Onda = Ondansetron
Dola = Dolasetron.
Source: ISS End-of-Text Tables O.1

TABLE 36: Summary of Number (%) of Patients Reporting Adverse Events by SOC and MedDRA Preferred Term Adverse Events Which are Considered Probably or Possibly Related in All Pivotal Phase 2/3 Trials with an Incidence of Greater Than or Equal to 2% (continued)

SOC	Preferred Term	Palonosetron Doses (mg)										Active Comparators					
		< 0.25		0.25		0.75		> 0.75		Total		Onda 32 mg		Dolas 100 mg		Total	
		n = 31		n = 633		n = 633		n = 77		n = 1374		n = 410		n = 194		n = 604	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nervous	**Any AEs**	**10**	**(32)**	**68**	**(11)**	**86**	**(14)**	**16**	**(21)**	**180**	**(13)**	**45**	**(11)**	**33**	**(17)**	**78**	**(13)**
	Headache NOS	9	(29)	60	(9)	73	(12)	12	(16)	154	(11)	34	(8)	32	(16)	66	(11)
	Dizziness (exc vertigo)	0	(0)	8	(1)	8	(1)	3	(4)	19	(1)	9	(2)	4	(2)	13	(2)
	Insomnia NEC	0	(0)	1	(< 1)	4	(1)	1	(1)	6	(< 1)	3	(1)	3	(2)	6	(1)
	Neurological disorder NOS	1	(3)	0	(0)	0	(0)	0	(0)	1	(< 1)	0	(0)	0	(0)	0	(0)
Psychological	**Any AEs**	**1**	**(3)**	**6**	**(1)**	**0**	**(0)**	**0**	**(0)**	**7**	**(1)**	**1**	**(< 1)**	**1**	**(1)**	**2**	**(< 1)**
	Confusion	1	(3)	0	(0)	0	(0)	0	(0)	1	(< 1)	0	(0)	0	(0)	0	(0)
Skin	**Any AEs**	**0**	**(0)**	**2**	**(< 1)**	**3**	**(< 1)**	**1**	**(1)**	**6**	**(< 1)**	**4**	**(1)**	**4**	**(2)**	**8**	**(1)**
Vascular	**Any AEs**	**0**	**(0)**	**8**	**(1)**	**5**	**(1)**	**0**	**(0)**	**13**	**(1)**	**7**	**(2)**	**1**	**(1)**	**8**	**(1)**

Onda = Ondansetron
Dola = Dolasetron.
Source: ISS End-of-Text Tables O.1
(Reference: Table 3.8.4:5, page 175, Volume 1)

Headache and constipation consisted of the majority of events considered related to the study drug. The incidences of constipation for various doses of palonosetron ranged from 3% at the < 0.25 mg dose to 12% at the > 0.75 mg dose, while the comparator incidences ranged from 2% to 6% in the ondansetron and dolasetron groups, respectively. The incidence of headache ranged from 9% to 16% in the palonosetron groups (0.25 mg to > 0.75 mg), and from 8% to 16% in the ondansetron and dolasetron subjects, respectively. Of note a higher incidence (29%) of subjects with headache was observed in the < 0.25 mg dose group. This is likely due to the smaller sample size compared to the other treatment groups.

Medical Officer Comments: *The adverse event profile for palonosetron appears to be similar to that of other drugs in this class.*

4. Cardiovascular Safety

Particular attention was paid to cardiovascular affects of palonosetron. Like other 5-HT_3 antagonists, palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarization and to prolong action potential duration. Preclinical data did show prolonged action potential duration *in vitro* in canine Purkinje fibers. Thus, all findings regarding cardiac safety were reviewed in detail.

Cardiovascular Deaths

Three subjects suffered a cardiovascular related cause of death in all clinical trials. None of the deaths were thought to be related to the palonosetron.

- Subject #4703 was a 66 year old man with a history of hypertension who died at home 15 days after receiving 90 µg/kg of palonosetron IV as part of protocol 2330.
- Subject #9745 died of cardiac arrest secondary to bronchospasm. This case was discussed in the section devoted to deaths.
- Subject #9773 was a 82 year old female with a history of diabetes and renal insufficiency who died 13 days after receiving 0.75 mg palonosetron IV as part of study PALO-99-06.

Medical Officer Comment: *The timing and medical history related to these deaths makes it unlikely any of them were related to the study drug. There were no cardiovascular related deaths in the patients who received ondansetron and dolasetron.*

Cardiovascular Adverse Events

The following adverse events were considered selected cardiovascular events.

TABLE 37: Selected Cardiovascular Events for ISS Analysis

SYSTEM ORGAN CLASS: CARDIAC	
- Atrioventricular Block First Degree	- Atrioventricular Block Nos
- Atrioventricular Block Second Degree	- Arrhythmia Nos
- Bradycardia Nos	- Extrasystoles Nos
- Nodal Arrhythmia	- Tachycardia Aggravated
- Tachycardia Nos	- Atrial Fibrillation
- Sinus Arrhythmia	- Sinus Bradycardia
- Sinus Tachycardia	- Supraventricular Arrythmia Nos
- Supraventricular Extrasystoles	- Pulsus Bigeminus
- Ventricular Extrasystoles	- Ventricular Tachycardia
- Palpitations	- Angina Pectoris
- Angina Unstable	- Myocardial Infarction
- Myocardial Ischaemia	- Cardiac Failure Congestive
- Cardiomegaly Nos	- Cardiac Arrest
SYSTEM ORGAN CLASS: GENERAL	
- Chest Pain Aggravated	- Chest Pain Nec
SYSTEM ORGAN CLASS: INVESTIGATIONS	
- Electrocardiogram Abnormal Nos	- Electrocardiogram Change Nos
- Electrocardiogram QT Corrected Interval	- Electrocardiogram QT Prolonged
- Electrocardiogram T Wave Amplitude Decreased	- Electrocardiogram U Wave Appearance
- Heart Rate Increased	- Heart Rate Irregular
SYSTEM ORGAN CLASS: NEUROLOGICAL	
- Syncope	
SYSTEM ORGAN CLASS: VASCULAR	
- Blood Pressure Increased	- Blood Pressure Systolic Increased
- Cerebral Ischaemia	- Orthostatic Collapse
- Hypotension Nos	- Postural Hypotension
- Hypertensive Crisis	- Hypertension Aggravated
- Hypertension Nos	- Collapse

(Reference: Table 3.8.4:6, Volume 1, page 178)

The cardiac selected AEs occurred in 9% of the palonosetron subjects, 13 % of the ondansetron subjects, 6 %of the dolasetron subjects and 8 %of the placebo subjects. None of these selected cardiovascular events occurred as a SAE at an incidence greater than 1% and

there were no apparent differences across treatment groups. In the palonosetron-treated subjects, chest pain and atrial fibrillation was experienced in three subjects, syncope, cardiac arrest and congestive heart failure in two subjects. For the comparator arms myocardial infarction, chest pain, and hypertensive crisis were each reported for one ondansetron subject, syncope was reported for four ondansetron subjects and tachycardia was reported for one placebo subject.

One palonosetron subject, (# 4434 from Study PALO-99-06) was considered to have a cardiac SAE related to the study drug. This patient experienced hypotension and brief syncope and was discussed in the SAE section.

Chest pain was reported for 1% of subjects in palonosetron, active comparator, and placebo groups.

Increased blood pressure was reported for 2% of ondansetron subjects versus < 1% for palonosetron across all doses and 0% for dolasetron and placebo.

Hypertension was reported for 2% of the palonosetron group, 1% active comparators, and 4% placebo.

Syncope was reported in less than one percent of subjects treated with palonosetron and in 1% of subjects treated with comparator.

For all clinical studies, tachycardia occurred in 1% of all groups but occurred slightly more commonly in the 0.75 mg palonosetron and the ondansetron groups (2% for both treatments). In the Phase 3 trials, 31 subjects experienced tachycardia, 23 of whom were on palonosetron. The 23 palonosetron subjects who experienced tachycardia in Phase 3 had the following characteristics:

- 14 were considered possibly or probably related to the study drug.
- 19 were mild in severity
- 4 were moderate in severity (only 1 of the 4 was considered related to the study drug)
- all resolved without sequelae

The following table displays the Selected Cardiovascular events, which were considered possibly, probably or definitely related, or whose causality was unknown.

TABLE 38: Selected Cardiovascular AEs by Preferred Term Considered Related[a] to Study Drug in Pivotal Phase 2/3 Trials (Number of Subjects)

	Palonosetron										Active Comparators					
	< 0.25 mg (n = 31)		0.25 mg (n = 633)		0.75 mg (n = 635)		> 0.75 mg (n = 77)		Total (n = 1376)		Ondansetron 32 mg (n = 410)		Dolasetron 100 mg (n = 194)		Combined (n = 604)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
No selected cardiac AE of interest	27	87	576	91	571	90	65	84	1239	90	357	87	183	94	540	89
Any selected cardiac AE of interest	4	13	57	9	62	10	12	16	135	10	53	13	11	6	64	11
SOC																
Cardiac (any related[a] AE of interest)	**0**	**0**	**15**	**2**	**15**	**2**	**2**	**3**	**32**	**2**	**8**	**2**	**1**	**1**	**9**	**1**
Tachycardia NOS	0	0	6	1	7	1	0	0	13	1	2	< 1	0	0	2	< 1
Braadycardia NOS	0	0	5	1	1	< 1	0	0	6	< 1	3	1	0	0	3	< 1
Extrasystoles NOS	0	0	1	< 1	1	< 1	0	0	2	< 1	1	< 1	0	0	1	< 1
Atrioventricular block, 1st degree	0	0	0	0	3	< 1	0	0	3	< 1	0	0	0	0	0	0
Myocardial ischaemia	0	0	1	< 1	1	< 1	0	0	2	< 1	0	0	0	0	0	0
Palpitations	0	0	0	0	0	0	1	1	1	< 1	0	0	1	1	1	< 1
Angina pectoris	0	0	0	0	0	0	0	0	0	0	1	< 1	0	0	1	< 1
Atrial fibrillation	0	0	0	0	0	0	0	0	0	0	1	< 1	0	0	1	< 1
Sinus tachycardia	0	0	1	< 1	0	0	0	0	1	< 1	1	< 1	0	0	1	< 1
Sinus bradycardia	0	0	0	0	1	< 1	0	0	1	< 1	0	0	0	0	0	0
Tachycardia aggravated	0	0	0	0	1	< 1	0	0	1	< 1	0	0	0	0	0	0
Arrhythmia NOS	0	0	0	0	0	0	1	1	1	< 1	0	0	0	0	0	0
Sinus arrhythmia	0	0	1	< 1	0	0	0	0	1	< 1	0	0	0	0	0	0
Supraventricular extrasystoles	0	0	1	< 1	0	0	0	0	1	< 1	0	0	0	0	0	0
General (any related AE of interest)	**2**	**6**	**8**	**1**	**6**	**1**	**4**	**5**	**20**	**1**	**5**	**1**	**2**	**1**	**7**	**1**
Chest pain NEC	2	6	0	0	0	0	0	0	2	< 1	0	0	0	0	0	0

Sources: ISS End-of-Text Tables H.3, O.1

[a] Includes AEs judged by the investigator to be possibly or probably related to study drug.

TABLE 38: Selected Cardiovascular AEs by Preferred Term Considered Related[a] to Study Drug in Pivotal Phase 2/3 Trials (Number of Subjects) (continued)

	Palonosetron										Active Comparators					
	< 0.25 mg (n = 31)		0.25 mg (n = 633)		0.75 mg (n = 635)		> 0.75 mg (n = 77)		Total (n = 1376)		Ondansetron 32 mg (n = 410)		Dolasetron 100 mg (n = 194)		Combined (n = 604)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
No selected cardiac AE of interest	27	87	576	91	571	90	65	84	1239	90	357	87	183	94	540	89
Any selected cardiac AE of interest	4	13	57	9	62	10	12	16	135	10	53	13	11	6	64	11
SOC																
Inv (any related AE of interest)	**0**	**0**	**6**	**1**	**16**	**3**	**1**	**1**	**23**	**2**	**7**	**2**	**2**	**1**	**9**	**1**
Blood pressure increased	0	0	0	0	2	< 1	0	0	2	< 1	2	< 1	0	0	2	< 1
Electrocardiogram QT prolonged	0	0	1	< 1	3	< 1	0	0	4	< 1	0	0	0	0	0	0
Electrocardiogram abnormal NOS	0	0	0	0	2	< 1	0	0	2	< 1	0	0	0	0	0	0
Electrocardiogram QT corr interval	0	0	0	0	1	< 1	0	0	1	< 1	0	0	0	0	0	0
Heart rate irregular	0	0	0	0	0	0	0	0	0	0	2	< 1	0	0	2	< 1
Nervous System (any related AE of interest)	**10**	**32**	**68**	**11**	**86**	**14**	**16**	**21**	**180**	**13**	**45**	**11**	**33**	**17**	**78**	**13**
Syncope	0	0	0	0	0	0	1	1	1	<1	0	0	0	0	0	0
Vasc (any related AE of interest)	**3**	**10**	**13**	**2**	**18**	**3**	**5**	**6**	**39**	**3**	**11**	**3**	**3**	**2**	**14**	**2**
Hypotension NOS	0	0	4	1	2	< 1	0	0	6	< 1	2	< 1	1	< 1	3	< 1
Hypertension NOS	0	0	3	< 1	0	0	0	0	3	< 1	1	< 1	0	0	1	< 1
Hypertension aggravated	0	0	0	0	1	< 1	0	0	1	< 1	0	0	0	0	0	0
Hypertesnsive crisis	0	0	0	0	1	< 1	0	0	1	< 1	1	< 1	0	0	0	0

Sources: ISS End-of-Text Tables H.3, O.1

[a] Includes AEs judged by the investigator to be possibly or probably related to study drug.

Medical Officer Comments: *Selected cardiovascular events related to the study drug occurred in 10% of the palonosetron subjects and 11% of the comparator subjects. The cardiac adverse event profile for palonosetron appears similar to that of other drugs in this class. Although, there seemed to be more subjects with tachycardia in the palonosetron group versus the comparator arms (1% versus 0.5%).*

ECG Data

Standard 12-lead electrocardiograms were recorded during all the 16 studies included in the Integrated Safety Database. In the early Phase 1 and 2 trials conducted by Syntex, the ECGs were interpreted solely by the investigator. In the studies conducted by Helsinn, ECGs were interpreted by the investigator and by a blinded cardiologist at a central location. Digitization software was utilized to provide high-resolution measurement of cardiac intervals and morphological assessment. The previous ECGs collected by Syntex were re-analyzed using these methods.

A retrospective analysis of ECGs obtained in the early Phase 1, 2 trials performed by Syntex was performed. Helsinn was successful in obtaining 80% of the ECGs from these trials. The analysis collected ECGs from five Phase 1 trials in healthy volunteers (2216, 2092, 2236, 0100, and 0101) and two Phase 2 trials in cancer patients (2330 and 2332). They did not collect ECGs from two PONV studies. All of these studies were dose ranging, double-blind placebo-controlled studies except for Study 2216. For the two early Phase 1 trials (0100 and 0101), the tracings were obtained at baseline and either one or four hours post-dose respectively and then in both studies, at 24, 48, 72 and 96 hours after palonosetron injection. For the other three Phase 1 studies included in the re-analysis (2092, 2236 and 2216), ECGs were recorded at baseline and then a single tracing was recorded on Day 7, 8 or 11 post-dose, respectively. For two Phase 2 CINV trials, 2330 (IV route) and 2332 (oral route), the tracings were recorded at baseline and 24 hours after dosing and repeated on Day 7 post-dose in case the 24-hour tracing was abnormal. Since the ECG's were collected at disparate times, the post dose values from the ECGs were recorded at different time-points. To rectify this the post dose values for Studies 0100 and 0101 were computed from the mean of one hour or four hour post dose ECG and the 24 hours post-dose data. For Studies 2092, 2236, 2216, the ECGs obtained on Day 7, 8, 9, and 11 were used for the post dose analysis respectively. For studies 23330, 2332 the 24 hour ECGs were utilized to compute post dose values.

Medical Officer Comments: *Ideally, an ECG should be obtained at Cmax to detect any ECG changes. This would have been shortly after injection. However, it should be noted that these studies were performed by Syntex and Helsinn is conducting a retrospective analysis.*

The following parameters were evaluated

- 25% change from baseline and a rate ≤ 50 or ≥ 120 bpm
- Change in PR interval ≥ 25% from baseline
- QRS duration ≥ 25% change from baseline
- QTc evaluation performed using the Bazett correction
- QTc evaluation performed using the Fridericia correction
- Presence of abnormal U-waves

The results revealed for heart rate, 1.5% of the subjects treated at 3.0 μg/kg, 1.3% at 10 and 1.7% at 30 and 2.6% at 90 μg/kg had a ≥ 25% change from baseline and a rate ≤ 50 or ≥ 120 bpm, whereas no subject met this criterion on placebo.

For PR interval, 8.3% for the subjects who received 20 μg/kg and 1.3% of dose administered 90 μg/kg had a ≥ 25% change from baseline. No subject on placebo showed such changes.

For QRS duration, only one subject (1.5%) receiving 3.0 μg/kg had a ≥ 25% change from baseline, while no subject on placebo met this criterion.

The QTc evaluation performed using the Bazett correction (QTcB) showed a change from baseline of 2, 1, 5, –2 and 4 msec in the dose groups 1, 3, 10, 30 and 90 µg/kg respectively, which presented the largest sample sizes. The mean change from baseline in the placebo group was of 1 msec. Using Bazett correction one subject who received 3 µg/kg (1.5%) and two subjects who received 10 µg/kg (2.6%) and one subject who received 40 µg/kg (20%) had a 60 or more msec QTc change from baseline. One subject in the 10 µg/kg group had a new 500 msec absolute QTcB. No subjects who received placebo had these findings

Using the Frederica correction of QTc only one subject in the 3 µg/kg group and one in the 10 µg/kg had an increase of 60 msec.

Medical Officer Comment: *This analysis consisted of 45 subjects who received placebo and 370 subjects exposed to a 300-fold dose range of palonosetron. The data seems to indicate that palonosetron does not cause a clinically meaningful effect on QTc. No dose response could be seen. The 90 µg/kg subjects had a lower percentage of QTc abnormalities than the 0.3 µg/kg subjects did. This data is not conclusive, however, because of its retrospective nature and the widely varying times the post dose ECG was obtained. It also should be noted many of the dosages had very few subjects.*

In the pivotal Phase 3 trials a prospective evaluation of ECGs was performed. ECGs were collected at baseline, at 24 hours post-dose and six to eight days after dosing. A subset of patients who were Holter monitored also had an ECG recorded 15 minutes post-dose.
The following table displays the number and percentage of patients in each treatment group across the Phase 3 clinical studies who had a post dose change by 30 to 60 and > 60 msec in QTc by Bazett or Fridericia.

TABLE 39 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.
(Reference: Table 3.8.4:8, page 185, Volume 1)

The mean change from baseline QTc ranged -1 to +3 msec without any dose trends and without any case of major change versus baseline. When all the Phase 3 ECG data was pooled, the effect on the QTc parameter by Bazett or Fridericia correction was 2 msec at both palonosetron doses. No subject had > 60 msec change from baseline. In the comparator arms the QTc mean changes from baseline were larger at 4–5 msec. There were several cases of new absolute QTcB or QTcF > 500 msec but these were equally distributed in all treatment arms.

Medical Officer Comment: *This phase 3 analysis provides useful information for several reasons. The Phase 3 trials did not exclude subjects with a cardiac history. Thus, the population was representative of the patients who would receive the drug if approved. The patients were randomized and the addition of a comparator arm would allow a signal of cardiac toxicity to reveal itself. No such signal was discovered. There were no clinically relevant effect on PR and QRS interval or morphological findings (conduction blocks, ST-T waves and myocardial infarction patterns). A wide range of doses of palonosetron were tested from the suggested dose of 0.25 mg to 6 mg an (8 fold range). No dose effect on cardiac toxicity was seen.*

Holter Data

A subset of patients in the Phase 3 trials underwent Holter monitoring. Evaluable Holters in 193 subjects were obtained from two-hours before dosing to 22-hours after dosing. The following table displays the interpretable data summarized in these four trials as a mean change from baseline (two hours before dosing) as compared to 22 hours post dosing for each study medication.

TABLE 40: Overall Holter Measurement Results (Mean Change From Baseline)

Mean Change	Palonosetron 0.25 mg	Palonosetron 0.75 mg	Ondansetron 32 mg	Dolasetron 100 mg
N total	57	102	46	6
N evaluable	51	92	44	6
High HR (bpm)	19	13	17	21
Low HR (bpm)	-1	4	0	9
Mean HR (bpm)	-40	-35	-36	-78
Pauses per hour	0	-0.01	0.05	0
SVT ≥ 10 beats	0.01	0	0.01	0.03
SVT Events/ hr	-0.01	0	0.06	0.12
VT Runs of > 1 0 beats	0	-0.01	0	0
VT Runs of 6–9 beats	0	-0.04	0	0
VT Runs of 3 beats	0.04	0	0	0
Ventricular Pairs	-0.14	0.31	0.13	0.01
VE beats total	2.36	-2.12	-2.97	-0.56
Beats in VT	0.17	-0.45	0.02	0

N = Number of subjects
HR = Heart rate
SVT = Supraventricular tachycardia, i.e., 3 or more beats of supraventricular ectopy in a row.
VT = Nonsustained ventricular tachycardia
VE = Ventricular ectopic beats
bpm = Beats per minute
(Reference: Table 8.9.6:5, Volume96, page 108)

Individual infrequent cases of Mobitz Type II block, sinus pauses, and occasional runs of nonsustained ventricular tachycardia were identified, however no difference in treatment groups was seen. Many of the subjects had underlying cardiopulmonary disease in addition to suffering from cancer and the physiologic stress of undergoing chemotherapy. Thus, there was a significant background rate of events but no clinically relevant difference seen between palonosetron at two different doses compared to ondansetron and dolasetron.

5. Laboratory Data

Laboratory data was pooled from the four Pivotal Phase 2 and 3 studies in CINV subjects as well as for all eight Phase 2/3 Studies (CINV, PONV subjects). Since the Phase 1 trials consisted of healthy volunteers they were not included in the applicant's analysis. Patients on chemotherapy typically have changes in many laboratory parameters secondary to their cancer or its treatment. The applicant performed four analyses of the lab data to include mean worst post-baseline value, mean worst change from baseline value, worst post baseline toxicity grade and worst change in toxicity grade.

Hematology

Changes in hematology parameters were equivalent among between treatment groups, and were attributed to chemotherapy. The mean worst post-baseline value, mean worst change from baseline value, worst post baseline toxicity grade and worst change in toxicity grade showed no differences across treatment arms. Of all palonosetron patients in Phase 2/3 studies the AEs related to hematology results were as follows: leukopenia NOS (135 subjects; 6%), lymphopenia (128 subjects; 5%), neutropenia (70 subjects; 3%), and anemia NOS (56 subjects; 2%). For the treatment arms, the same four AEs (leucopenia NOS, lymphopenia, neutropenia and anemia NOS) were reported most frequently for subjects treated with ondansetron 32 mg and dolasetron 100 mg. These AEs occurred at a higher proportion of subjects in the ondansetron and dolasetron groups compared with subjects treated with palonosetron.

Chemistry

In regards to the chemistry parameters, the mean worst post-baseline value, mean worst change from baseline value, worst post baseline toxicity grade and worst change in toxicity grade showed no differences across treatment arms. The percentage of AEs related to pertinent clinical chemistry parameters was similar across treatment groups: 385 events were reported among the 2348 subjects treated with palonosetron, 74 among the 410 subjects treated with ondansetron 32 mg, and 18 among the 194 subjects treated with dolasetron 100 mg. In the placebo group, (containing Phase 1 healthy volunteers and PONV subjects) 15 subjects had an AE related to clinical chemistry. No clinically relevant patterns could be seen. In the pivotal studies it was noted that the liver function tests increased in all treatment groups after chemotherapy. However, they decreased 6-8 days after chemotherapy.

6. Vital Signs

The applicant provided descriptive statistics for heart rate, diastolic and systolic blood pressure for subjects in eight Phase 2 and Phase 3 studies. Vital signs were taken prior to and after palonosetron administration. The mean, maximum, minimum and worst changes from baseline for blood pressure, and heart rate in the palonosetron and active comparator groups revealed no apparent clinical significant difference.

D. Adequacy of Safety Testing

The applicant has included safety data collected in 3137 subjects enrolled in the 18 palonosetron clinical trials of whom 2360 received palonosetron. Adverse events, ECG, and laboratory parameters were evaluated. Initially, the Agency requested roughly 300 patients undergo Holter monitor for 72 hours. The applicant had difficulty in obtaining this number due to the high number of cancer patients who refused to undergo Holter monitor because of discomfort and inconvenience. The applicant has provided Holter data on 193 subjects for 22 hours. Although less than originally requested, this data is adequate to help establish safety

because the monitoring included the time period with the highest drug concentration and the dose's studied included 0.75 mg which is three-fold the recommended dose for treatment.

E. Summary of Critical Safety Findings and Limitations of Data

Review of this data demonstrates that palonosetron when given as single dose prior to chemotherapy was well tolerated. A wide dose range was studied (less than 0.25 mg to approximately 6 mg). No deaths occurred that were attributable to the study drug. An extensive review of cardiac safety was conducted which included analysis of ECG (performed in 2172 subjects) and Holter tracings (143 subjects) using high-resolution methods and a centralized review by a blinded cardiologist. No dose response on QTc interval was observed. The cardiac safety profile for palonosetron is similar to that of other drugs in this class. No signal for adverse effects of the study drug on laboratory or vital signs was detected.

The most common adverse reactions seen with palonosetron (≥ 2%) were constipation and headache. Incidences of these reactions were similar across all palonosetron dose groups and the active comparator 5-HT_3 receptor antagonists, ondansetron and dolasetron. All other adverse reactions were seen at incidences equal to or less than 1%. Constipation was mild in nearly all subjects, however, two subjects who took palonosetron in Phase 2 trials suffered from constipation that required treatment in a hospital. Both subjects' symptoms resolved with treatment and neither needed surgical intervention.

The safety database is limited in several ways. Although the numbers of patients was relatively large, a signal could not have been detected for an adverse event that has a low incidence. The majority of subjects did not have an ECG performed at CMAX when cardiac changes would be most likely to occur. The applicant was unable to recruit the requested 300 patients to undergo Holter monitoring. Despite these limitations, the applicant was able to demonstrate safety of palonosetron.

VIII. Dosing, Regimen, and Administration Issues

The applicant proposes a dose of 0.25 mg palonosetron intravenously given over 30 seconds, 30 minutes prior to chemotherapy being dosed. This is based on the pivotal studies that demonstrated that the 0.25 mg dose of palonosetron was more efficacious than the 0.75 mg dose. Palonosetron is to be supplied as a single-use sterile, clear, colorless solution in glass 5 ml vials ready for intravenous injection.

In Phase 1 and Phase 2 trials, palonosetron was shown to be well tolerated at 30-second IV bolus doses up to 90 µg/kg. The maximum dose tested was approximately 6 mg as a fixed dose. The selection of doses for Phase 3 trials was based primarily on efficacy data. Study 2330 was a Phase 2 study in which subjects received one of the following doses of palonosetron: 0.3, 1, 3, 10, and 30 µg/kg . Based on efficacy data from this study, the 3-µg/kg and 10-µg/kg doses were selected as the doses to evaluate in Phase 3 trials. These were converted to the fixed doses of 0.25 mg and 0.75 mg in order to simplify dosing regimens in clinical practice.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The applicant has adequately evaluated the effects of gender on efficacy and safety. For the moderately emetogenic CINV Studies PALO-99-03 and PALO-99-04, the majority of subjects were female. Subgroup analyses by gender demonstrated that male subjects had a trend for greater complete response rates during the first 24 hours after chemotherapy than female subjects (90% complete response for males versus 67% for females). However, palonosetron did show non-inferority in female subjects to the comparator drugs. In addition, both male and female subjects in both palonosetron groups showed greater response rates than subjects in the ondansetron 32 mg (Study PALO-99-03) and dolasetron 100 mg (Study PALO-99-04) groups.

For the highly emetogenic CINV Study PALO-99-05, there were roughly equal numbers of male and female subjects. Again, it was noted that male subjects had a higher complete response rate than females (67% versus 52.2%). However, the palonosetron did not show non-inferiority to ondansetron in male subjects. The 97.5% confidence interval was slightly lower than the −15% delta. For female subjects, palonosetron did demonstrate non-inferiority.

In regards, to safety no relevant difference was seen in adverse events, severe adverse events or deaths based on gender.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Twenty three percent (316) of the 1374 adult cancer patients in clinical studies of palonosetron were over the age of 65 years. Review of this data reveals no overall differences in safety or effectiveness between these subjects and the younger subjects. There was a slightly increased incidence of selected cardiovascular AEs among older subjects than younger subjects but these AEs were not clearly related to the study drug. No alteration of the dose or special monitoring is required for geriatric patients.

The Phase 3 trials consisted of the following races:

- 65% Caucasian
- 31% Hispanic
- 1% Asian
- 3% Black
- 0.3% Other

No relevant differences in safety or effectiveness were seen based on race.

D. Comments on Data Available or Needed in Other Populations

The pivotal studies consisted of chemotherapy naïve and non-naïve subjects. There were no consistent differences seen in response rates between naïve and non-naïve subjects. In Study

PALO-99-03, naïve subjects generally had slightly greater complete response rates than non-naïve subjects during all time periods with few exceptions. However, in Study PALO-99-04, non-naïve subjects had slightly greater complete response rates than naïve subjects in all treatment groups during each time period. In naïve subjects, the response rates in both palonosetron groups were comparable and greater than in the dolasetron 100 mg group. In non-naïve subjects, differences in complete response rates between the treatment groups were comparable. In the highly emetogenic CINV trial, non-naïve subjects had a greater complete response than naïve subjects during the first 24 hours after chemotherapy with the exception of the palonosetron 0.75 mg group. When the data is taken as a whole, it appears chemotherapeutic history has no pronounced effect on complete response rate.

The applicant also performed sub-analysis based on corticosteroid use. The protocols were amended to allow corticosteroid use relatively late in subject recruitment. Thus for studies PALO-99-03, and PALO-99-04 there is not enough numbers to support meaningful comparisons. However for PALO-99-05, twice as many subjects received corticosteroids than subjects who did not. This use was balanced in all treatment arms. The results demonstrated in the palonosetron 0.25 mg group, the complete response rate during the first 24 hours after chemotherapy was greater in subjects with corticosteroid use compared to subjects without corticosteroid use. In contrast, in the palonosetron 0.75 mg group the response rate was greater in subjects without corticosteroid use. The complete response rates among subjects with corticosteroid use were greater in both palonosetron groups than in the ondansetron group.
Medical Officer Comments: *These results are somewhat surprising. Previous literature indicates that corticosteroid use is should improve complete response in all subjects. However, there may be a bias. The use of corticosteroids was at the discretion of the investigator. Thus, the corticosteroids could have been given to subjects with a greater risk of emesis.*

Additional data may be helpful for several other subgroups. Relative to the U.S. population there was a paucity of Black and Asian subjects. Additional PK, efficacy and safety data would be useful in these groups.

X. Conclusions and Recommendations

A. Conclusions

The applicant has demonstrated the efficacy of 0.25 mg palonosetron for the acute (0-24 hours) and delayed (24-120 hours) prevention of moderately emetogenic CINV. The data also supports the efficacy of 0.25 mg of palonosetron for acute prevention of highly emetogenic CINV, but not delayed prevention. This assessment of efficacy is based on three adequate and well-controlled pivotal Phase 3 efficacy trials, PALO-99-03, PALO-99-04 and PALO-99-05, that used standard, accepted efficacy and safety endpoints, and FDA-approved active comparators. The primary efficacy parameter was complete response within the first 24 hours after chemotherapy, which was, has been used as the basis for approval of other medications for this indication. The results demonstrated the non-inferiority of both palonosetron 0.25 mg and 0.75 mg when compared to ondansetron and dolasetron. The lower limit of the 97.5% confidence interval for the difference in complete response rates between the ondansetron and the palonosetron groups during the first 24 hours after chemotherapy was above the preset 15% delta.

However, these trials did not establish that palonosetron 0.25 mg was efficacious for delayed prevention (24-120 hours) in highly emetogenic chemotherapy. While the results did show non-

inferiority to the comparator arms, the comparator drug is not indicated for delayed prevention of CINV. Thus, in order to show efficacy the study drug should demonstrate superiority to the comparator drug. It did not do so. There was no statistically significant difference between palonosetron and ondansetron for delayed prevention of highly emetogenic CINV. The evidence the applicant has presented does not substantiate an efficacy claim for this indication

In regards to safety, review of this data demonstrates that palonosetron when given as single dose prior to chemotherapy was well tolerated. A wide dose range was studied (less than 0.25 mg to approximately 6 mg). No deaths occurred that were attributable to the study drug. An extensive review of cardiac safety was conducted which included analysis of ECG (performed in 2172 subjects) and Holter tracings (143 subjects) using high-resolution methods and a centralized review by a blinded cardiologist. No dose response on QTc interval was observed. The cardiac safety profile for palonosetron is similar to that of other drugs in this class. No signal for adverse effects of the study drug on laboratory or vital signs was detected. The most common adverse reactions seen with palonosetron ($\geq 2\%$) were constipation and headache. Incidences of these reactions were similar across all palonosetron dose groups and the active comparator 5-HT_3 receptor antagonists, ondansetron and dolasetron. All other adverse reactions were seen at incidences equal to or less than 1%. Constipation was mild in nearly all subjects, however, two subjects who took palonosetron in Phase 2 trials suffered from constipation that required treatment in a hospital. Both subjects symptoms resolved with treatment and neither needed surgical intervention.

B. Recommendations

From a medical standpoint, palonosetron is approvable for the indication of prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. It is also approvable for the indication of prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. The data provided does not support approval for the indication of delayed prevention of highly emetogenic CINV.

XI. Appendix

A. Other Relevant Materials - References

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B. Individual More Detailed Study Reviews (If performed)

Separate detailed reviews of Studies PALO-99-03, and PALO-99-04. These are filed separately in DFS.

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