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)

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)

	Number and Percentage (%) of Subjects with Complete Response			Difference in Complete Response Rates, 97.5% Confidence Intervals	
Time Period (Hours)	Palonosetron 0.25 mg (N = 189)	Palonosetron 0.75 mg (N = 189)	Ondansetron 32 mg (N = 185)	Palonosetron 0.25 mg Minus Ondansetron 32 mg	Palonosetron 0.75 mg Minus Ondansetron 32 mg
Acute[a]					
0–24	153 (81.0)	139 (73.5)	127 (68.6)	[1.8%, 22.8%]*	[-6.1%, 15.9%]
Delayed[b]					
24–48	154 (81.5)	132 (69.8)	122 (65.9)	[4.9%, 26.1%]*	[-7.5%, 15.2%]
48–72	161 (85.2)	147 (77.8)	124 (67.0)	[8.0%, 28.4%]*	[-0.1%, 21.6%]
72–96	168 (88.9)	161 (85.2)	145 (78.4)	[1.5%, 19.5%]*	[-2.6%, 16.3%]
96–120	175 (92.6)	169 (89.4)	161 (87.0)	[-2.0%, 13.1%]	[-5.6%, 10.4%]

[a] = Primary efficacy endpoint.
[b] = Secondary endpoint.
* = 97.5% CIs for the difference between palonosetron and active comparator (ondansetron or dolasetron)

Medical Officer Comments: *During all study days, complete response rates were higher in the 2 palonosetron groups than in the ondansetron 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 ondansetron was above the pre-set threhsold of –15%, indicating non-inferiority of palonosetron to ondansetron. 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 Ondansetron 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.*

Complete Control

Table 16 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 16 – 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)		Ondansetron 32 mg (N = 185)	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
0-24	144 (76.2)	[69.4%, 81.9%]	134 (70.9)	[63.8%, 77.1%]	121 (65.4)	[58.0%, 72.1%]
0–48	133 (70.4)	[63.2%, 76.7%]	109 (57.7)	[50.3%, 64.7%]	101(54.6)	[47.1%, 61.9%]
0–72	124 (65.6)	[58.3%, 72.3%]	105 (55.6)	[48.2%, 62.7%]	87 (47.0	[39.7%, 54.5%]
0–96	120 (63.5)	[56.2%, 70.3%]	102 (54.0)	[46.6%, 61.2%]	84 (45.4)	[38.1%, 52.9%]
0–120	119 (63.0)	[55.9%, 69.8%]	101 (53.4)	[46.1%, 60.7%]	83 (44.9)	[37.6%, 52.3%]

(Reference: Table 7.1.2.2-a, page 109, Volume 117)

Medical Officer Comments: *Both palonosetron groups demonstrated higher complete control rates at all time periods when compared to ondansetron. The palonosetron 0.25 mg group had a higher proportion of patients that had complete control than the 0.75 mg group. The differences between the three groups were statistically significant for the time period 0 top 48 hours (p=0.004), 0 to 72 hours (p=0.001), 0 to 96 hours (p=0.002) and 0 to 120 hours (p=0.002). There was no statistical difference in the 0 to 24 hour time period (p=0.072 using Chi-Square test)*

Number of Emetic Episodes

Table 17 shows the number of emetic episodes during the observation period.

TABLE 17 – Number of emetic episodes during the observation period

Time Period	Palonosetron 0.25 mg (N=189)		Palonosetron 0.75 mg (N=189)		Ondansetron 32 mg (N=185)	
	N	(%)	N	(%)	N	(%)
ACUTE						
0–24						
0 episodes	161	(85.2)	147	(77.8)	132	(71.4)
1 episode	4	(2.1)	13	(6.9)	20	(10.8)
2 episodes	6	(3.2)	9	(4.8)	12	(6.5)
≥3 episodes	18	(9.5)	20	(10.6)	21	(11.4)
DELAYED						
24–48						
0 episodes	166	(87.8)	143	(75.7)	129	(69.7)
1 episode	11	(5.8)	24	(12.7)	30	(16.2)
2 episodes	5	(2.6)	7	(3.7)	11	(5.9)
≥3 episodes	7	(3.7)	15	(7.9)	15	(8.1)
48–72						
0 episodes	170	(89.9)	159	(84.1)	138	(74.6)
1 episode	14	(7.4)	17	(9.0)	29	(15.7)
2 episodes	2	(1.1)	4	(2.1)	8	(4.3)
≥3 episodes	3	(1.6	9	(4.8)	10	(5.4)
72–96						
0 episodes	174	(92.1)	169	(89.4)	165	(89.2)
1 episode	10	(5.3)	9	(4.8)	13	(7.0)
2 episodes	3	(1.6)	4	(2.1)	6	(3.2)
≥3 episodes	2	(1.1)	7	(3.7)	1	(0.5)
96–120						
0 episodes	178	(94.2)	176	(93.1)	173	(93.5)
1 episode	6	(3.2)	7	(3.7)	7	(3.8)
2 episodes	2	(1.1)	2	(1.1)	3	(1.6)
≥3 episodes	3	(1.6)	4	(2.1)	2	(1.1)

(Reference:Table 7.1.2.3-a, from page 112, Volume 117)

Medical Officer Comments: *The palonosetron 0.25 mg group had fewer emetic episodes than the other groups for days 1,2,and 3. There was no difference between the groups on day 4 and 5. On these days, most patients did not experience an episode of emesis. However, the palonosetron 0.75 mg group did have more patients who had 3 or more episodes of emesis on Days 4 and 5 than the other groups. It should be noted that 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 18 –Median Time to first emetic episode

Time Period	Palonosetron 0.25 mg (N=189)		Palonosetron 0.75 mg (N=189)		Ondansetron 32 mg (N=185)	
	Q1	Median	Q1	Median	Q1	Median
0-120 hours	115.1	>120	25.2	>120	20.5	>120

Q1= first quartile

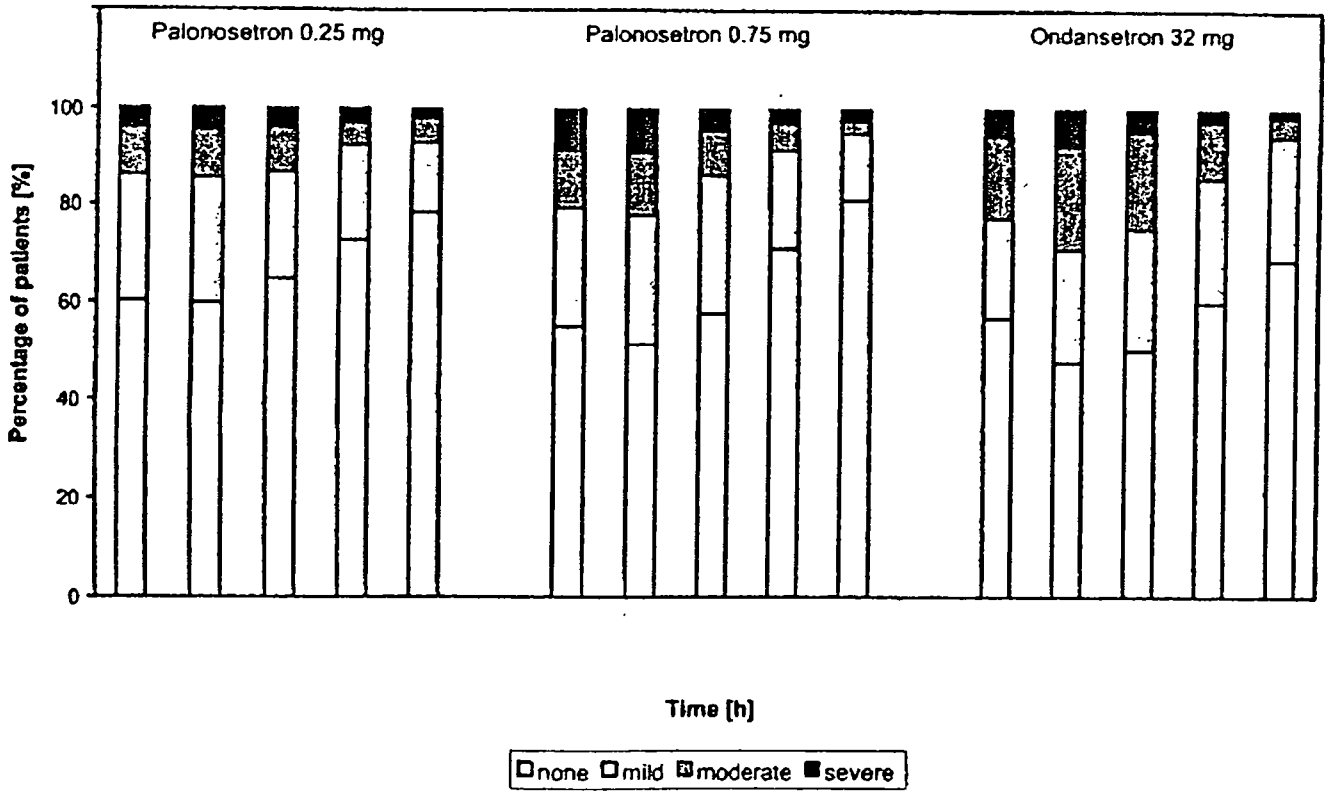
(Reference:Table 7.2.3-b, page 113, Volume 117)

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=563) (Scanned from figure 7.1.2.4-a, page 115, Volume 117)



Medical Officer Comments: *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.*

Time to Rescue Medication

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

TABLE 19 – Median Time to First Administration of Rescue Medication

Time Period	Palonosetron 0.25 mg (N=189)		Palonosetron 0.75 mg (N=189)		Ondansetron 32 mg (N=185)	
	Q1	Median	Q1	Median	Q1	Median
0-120 hours	>120	>120	>120	>120	72.1	>120

Q1= first quartile

(Reference: Tables 7.1.2.5-b, from page 118, Volume 117)

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 ondansetron 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.*

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

Time Period	Palonosetron 0.25 mg (N=189)		Palonosetron 0.75 mg (N=189)		Ondansetron 32 mg (N=185)	
	Q1	Median	Q1	Median	Q1	Median
0-120 hours	46.5	>120	21	>120	19.5	>120

Q1= first quartile

(Reference: Table 7.1.2.6-a, page 121 Volume 117).

Medical Officer Comments: *The median time to treatment failure was again greater than 120 hours for all groups. Analysis of the first quartile of patients found that the time to treatment failure was longest in the 0.25 mg Palonosetron group.*

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 21 – Quality of Life VAS scores for nausea and vomiting

Time Period (hours)	Palonosetron 0.25 mg (N=189) Median	Palonosetron 0.75 mg (N=189) Median	Ondansetron 32 mg (N=185) 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)

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 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)*

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.

TABLE 22 – 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)

***Medical Officer's Comments**: A statistical difference between treatment groups was found by Kruskal-Wallis testing for Day 3 (p=0.045) but not the other days (p=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.*

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.

TABLE 23– Statistical Analysis Results of Secondary Efficacy Endpoints

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
Complete Control (CC)					
0-24 hr	Chi-square	0.0720	--	--	--
24-48 hr	Chi-square	**0.0030**	**0.0010**	0.4870	**0.0100**
48-72 hr	Chi-square	**0.0010**	**0.0010**	**0.0040**	0.3960
72-96 hr	Chi-square	**0.0030**	**0.0030**	**0.0060**	0.7780
96-120 hr	Chi-square	0.2050	--	--	--
0-48 hr	Chi-square	**0.0040**	**0.0020**	0.5490	**0.0100**
0-72 hr	Chi-square	**0.0010**	**0.0010**	0.0990	**0.0460**
0-96 hr	Chi-square	**0.0020**	**0.0010**	0.0980	0.0600
0-120 hr	Chi-square	**0.0020**	**0.0010**	0.0970	0.0610
Number of Emetic Episodes (EE)					
0-24 hr	KW/Wilcoxon	**0.0166**	**0.0042**	0.2131	0.0983
24-48 hr	KW/Wilcoxon	**0.0001**	**0.0001**	0.2245	**0.0025**
48-72 hr	KW/Wilcoxon	**0.0004**	**0.0001**	**0.0300**	0.0786
72-96 hr	KW/Wilcoxon	0.5591	--	--	--
96-120 hr	KW/Wilcoxon	0.9116	--	--	--
0-120 hr	KW/Wilcoxon	**0.0004**	**0.0001**	0.0587	**0.0356**
Time to First EE	Log Rank	**0.0004**	**0.0001**	0.0789	**0.0306**
Severity of Nausea					
0-24 hr	KW/Wilcoxon	0.3183	--	--	--
24-48 hr	KW/Wilcoxon	**0.0117**	**0.0032**	0.3358	**0.0488**
48-72 hr	KW/Wilcoxon	**0.0094**	**0.0029**	0.0565	0.2328
72-96 hr	KW/Wilcoxon	**0.0157**	**0.0088**	**0.0242**	0.7148
96-120 hr	KW/Wilcoxon	**0.0253**	0.0616	**0.0097**	0.4988
Need of Rescue Medication					
0-24 hr	Chi-square	0.8380	--	--	--
24-48 hr	Chi-square	0.2740	--	--	--
48-72 hr	Chi-square	0.2030	--	--	--
72-96 hr	Chi-square	0.1890	--	--	--
96-120 hr	Chi-square	0.5300	--	--	--
0-120 hr	Chi-square	0.1430	--	--	--
Time to Rescue	Log Rank	0.1699	--	--	--
Subject Global Satisfaction					
0-24 hr	KW/Wilcoxon	0.7132	--	--	--
24-48 hr	KW/Wilcoxon	0.0703	--	--	--
48-72 hr	KW/Wilcoxon	**0.0452**	**0.0152**	0.2628	0.1393
72-96 hr	KW/Wilcoxon	0.1200	--	--	--
96-120 hr	KW/Wilcoxon	0.0768	--	--	--
Function Living Index-Emesis					
FLIE #1 Nausea	KW/Wilcoxon	0.4221	--	--	--
FLIE #1 Vomiting	KW/Wilcoxon	0.1520	--	--	--
FLIE #1 Total	KW/Wilcoxon	0.2794	--	--	--
FLIE #2 Nausea	KW/Wilcoxon	0.0953	--	--	--
FLIE #2 Vomiting	KW/Wilcoxon	0.0565	--	--	--
FLIE #2 Total	KW/Wilcoxon	0.0472	**0.0138**	0.1298	0.3687

PALO = Palonosetron; ONDA = Ondansetron;; 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.

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 24 – 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)			Ondansetron 32 mg (N = 185)		
	N	N*	%	N	N*	%	N	N*	%
Male	54	49	(90.7)	51	46	(90.2)	52	41	(78.8)
Female	135	104	(77)	138	93	(67.4)	133	86	(64.7)

N = number of female or male patients
N* = number of patients with response
(Reference: Table 7.2.1-a, page 129, Volume 117)

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. The lower limits of a 97.5% confidence interval for the difference in complete response rates between both palonosetron doses and ondansetron 32 mg were above the pre-set threshold of -15 % in male and female patients.*

Chemotherapeutic History

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

TABLE 25 - 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)			Ondansetron 32 mg (N = 185)		
	N	N*	%	N	N*	%	N	N*	%
Naïve	76	67	(88.2)	80	55	(68.8)	78	58	(74.4)
Non-naive	113	86	(76.1)	109	84	(77.1)	107	69	(64.5)

N = number of naïve or non-naive patients
N* = number of patients with response
(Reference: Table 7.3.1-a, page 144, Volume 117)

Medical Officer Comments: *The lower limits of the 97.5%confidence intervals for the difference between palonosetron 0.25 mg and ondansetron were above the preset threshold of –15% indicating non-inferiority of palonosetron 0.25 mg to ondansetron in regard to these subgroups. The palonosetron 0.75 mg dose was only able to demonstrate non-inferiority only in the non-naïve patients. 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. However, the results do not demonstrate such a bias. Naïve patients had a slightly higher complete response rates than non-naïve patients in all but the palonosetron 0.75 mg 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.

TABLE 26 – Treatment Emergent Adverse Events overview (Safety cohort, N=562)

Number of patients with AEs	Palonosetron 0.25 mg (N = 187)		Palonosetron 0.75 mg (N = 188)		Ondansetron 32 mg (N = 187)	
	N	%	N	%	N	%
All	114	61.0	125	66.5	120	64.2
Related[1]	30	16.0	30	16.0	26	13.9
By category						
All AEs/Non-Lab, Non-ECG	80	42.8	86	45.7	86	46.0
All AEs/Laboratory	65	34.8	61	32.4	62	33.2
All AEs/ECG	9	4.8	8	4.3	7	3.7
Related[1] AEs/Non-Lab, Non-ECG	22	11.8	26	13.8	23	12.3
Related[1] AEs/Laboratory	4	2.1	1	0.5	3	1.6
Related[1] AEs/ECG	6	3.2	5	2.7	2	1.1
Serious adverse events						
All SAEs	5	2.7	5	2.7	5	2.7
Related SAEs	1	0.5	0	0.0	0	0.0
Withdrawn due to AEs						
All	0	0.0	1	0.5	1	0.5
Related[1]	0	0.0	1	0.5	0	0.0

	N*	N	%	N*	N	%	N*	N	%
Subgroup: gender									
All AEs/male	54	30	55.6	51	29	56.9	52	33	63.5
All AEs/female	133	84	63.2	137	96	70.1	135	87	64.4
Related[1] AEs/male	54	5	9.3	51	6	11.8	52	5	9.6
Related[1] AEs/female	133	25	18.8	137	24	17.5	135	21	15.6
Subgroup: chemotherapeutic history									
All AEs/naive	75	45	60.0	80	52	65.0	79	49	62.0
All AEs/non-naive	112	69	61.6	108	73	67.6	108	71	65.7
Related[1] AEs/naive	75	12	16.0	80	19	23.8	79	11	13.9
Related[1] AEs/non-naive	112	18	16.1	108	11	10.2	108	15	13.9
Germany									
All AEs	42	24	57.1	40	28	70.0	40	27	67.5
Related[1] AEs	42	2	4.8	40	5	12.5	40	2	5.0

(continued)

TABLE 26 - Treatment Emergent Adverse Events (Cont'd)

Number of patients with AEs	Palonosetron 0.25 mg (N = 187)			Palonosetron 0.75 mg (N = 188)			Ondansetron 32 mg (N = 187)		
	N*	N	%	N*	N	%	N*	N	%
Italy									
All AEs	17	12	70.6	18	13	72.2	16	10	62.5
Related[1] AEs	17	5	29.4	18	5	27.8	16	3	18.8
United Kingdom/ The Netherlands									
All AEs	20	15	75.0	20	15	75.0	22	16	72.7
Related[1] AEs	20	4	20.0	20	5	25.0	22	8	36.4
Arkhangelsk									
All AEs	20	12	60.0	18	8	44.4	20	12	60.0
Related[1] AEs	20	8	40.0	18	2	11.1	20	5	25.0
Moscow									
All AEs	41	23	56.1	38	25	65.8	41	26	63.4
Related[1] AEs	41	7	17.1	38	6	15.8	41	6	14.6
St. Petersburg									
All AEs	47	28	59.6	54	36	66.7	48	29	60.4
Related[1] AEs	47	4	8.5	54	7	13.0	48	2	4.2

Source: Appendix B-1.3.1, Tables 1 and 3
[1] Adverse events which had a definite, possible, probable or unknown relationship to study medication
N = number of patients with events
N* = number of patients in the specific group
% = percentage of patients with events

(Scanned from Table 8.1.1, page 161-162, Volume 162)

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 equal in all groups. Female patients had a higher rate of adverse events versus males particularly in the palonosetron 0.25 mg arm. Chemotherapy naïve and non-naive patients had a similar rate of adverse events. The three Russian sites reported less adverse events than the other sites. The applicant does not offer an explanation for these differences.*

B. Adverse Events by Body System

The following table displays adverse events by body system.

TABLE 27 – Treatment Emergent Adverse events by body System and preferred term[1] (Safety Cohort, N=562)

System organ class[2] Preferred term[2] (MedDRA)	Palonosetron 0.25 mg (N = 187)			Palonosetron 0.75 mg (N = 188)			Ondansetron, 32 mg (N = 187)		
	N	%	n	N	%	n	N	%	n
Any adverse event	114	61.0	273	125	66.5	275	120	64.2	294
Blood and lymphatic system disorders	**47**	**25.1**	**73**	**45**	**23.9**	**63**	**45**	**24.1**	**69**
Lymphopenia	27	14.4	27	23	12.2	23	20	10.7	20
Leucopenia nos[3]	24	12.8	24	21	11.2	21	21	11.2	21
Neutropenia	15	8.0	15	8	4.3	8	15	8.0	15
Gastrointestinal disorders	**28**	**15.0**	**29**	**32**	**17.0**	**46**	**26**	**13.9**	**31**
Nervous system disorders	**28**	**15.0**	**30**	**28**	**14.9**	**34**	**37**	**19.8**	**48**
Headache nos[3]	19	10.2	20	23	12.2	26	28	15.0	33
General disorders and administration site conditions	**27**	**14.4**	**35**	**19**	**10.1**	**21**	**26**	**13.9**	**31**
Pyrexia	10	5.3	12	2	1.1	2	5	2.7	5
Metabolism and nutrition disorders	**23**	**12.3**	**26**	**18**	**9.6**	**20**	**24**	**12.8**	**24**
Investigations	**19**	**10.2**	**24**	**21**	**11.2**	**27**	**21**	**11.2**	**32**
Cardiac disorders	**10**	**5.3**	**10**	**8**	**4.3**	**13**	**12**	**6.4**	**12**
Skin & subcutaneous tissue disorders	**8**	**4.3**	**8**	**9**	**4.8**	**9**	**11**	**5.9**	**11**
Vascular disorders	**5**	**2.7**	**6**	**5**	**2.7**	**6**	**10**	**5.3**	**10**

Source: Appendix B-1.3.1, Table 4
MedDRA = Medical Dictionary for Regulatory Activities
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

(Scanned from Table 8.1.2.2-c, page 166, Volume 117)

Medical Officer Comment: *Adverse events of the blood and lymphatic system were most common in all treatment groups. These were equally spread out in all treatment groups and were secondary to chemotherapy. Following the blood and lymphatic disorders, headache was the most frequently reported adverse event. This also was balanced in all treatment arms. The percentage of patients with headache is less than the Phase I/II palonosetron studies where it occurred in 20% of the patients.*

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=187)		Palonosetron 0.75 mg (N=188)		Ondansetron 32 mg (N=187)	
	N	(%)	N	(%)	N	(%)
Mild	166	(60.8)	169	(61.5)	190	(64.6)
Moderate	95	(34.8)	90	(32.7)	97	(33)
Severe	12	(4.4)	16	(5.8)	7	(2.4)
TOTAL	273	100	275	100	294	100

(Reference: Table 8.1.2.2-a, page 167, Volume 117)

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 ondansetron group. The body system most frequently involved for severe adverse events was neutropenia (2/187, 1.1%) for the 0.25 mg palonosetron group and leukopenia (2/188, 1.1%) for the 0.75 mg palonosetron group.*

The following table displays the Number of displays by relationship to treatment.

TABLE 29 – Number of Adverse Events by Relationship to Treatment

	Palonosetron 0.25 mg (N=187)		Palonosetron 0.75 mg (N=188)		Ondansetron 32 mg (N=187)	
	N	(%)	N	(%)	N	(%)
Unrelated	153	(56)	157	(57.1)	156	(53.1)
Unlikely	80	(29.3)	73	(26.5)	88	(29.9)
Possible	24	(8.8)	32	(11.6)	34	(11.6)
Probable	9	(3.3)	7	(2.5)	12	(4.1)
Definite	0	(0)	0	(0.0)	1	(0.3)
Unknown	7	(2.6)	6	(2.2)	3	(1.0)
TOTAL	273	100	275	100	294	100

(Reference: Table 8.1.2.2-b, page 168, Volume 117)

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 related adverse events was slightly higher in the 0.75 mg palonosetron group than in the 0.25 mg group.*

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

TABLE 30 – Treatment Emergent Related Adverse Events by Body System and Preferred Term[2] (Safety cohort, N=562)

System organ class[3] Preferred term (MedDRA)	Palonosetron 0.25 mg (N = 187)			Palonosetron 0.75 mg (N = 188)			Ondansetron, 32 mg (N = 187)		
	N	%	n	N	%	n	N	%	n
Any related adverse event	30	16.0	40	30	16.0	45	26	13.9	50
Nervous system disorders	**13**	**7.0**	**13**	**11**	**5.9**	**13**	**15**	**8.0**	**19**
Headache nos[4]	9	4.8	9	10	5.3	12	10	5.3	11
Dizziness	1	0.5	1	0	0.0	0	6	3.2	6
Somnolence	3	1.6	3	1	0.5	1	0	0.0	0
Gastrointestinal disorders	**7**	**3.7**	**7**	**10**	**5.3**	**12**	**5**	**2.7**	**7**
Constipation	3	1.6	3	6	3.2	6	3	1.6	3
Metabolism and nutrition disorders	**6**	**3.2**	**7**	**1**	**0.5**	**1**	**3**	**1.6**	**3**
Metabolic disorders nos[4]	3	1.6	3	0	0.0	0	1	0.5	1
General disorders and administration site conditions	**5**	**2.7**	**5**	**6**	**3.2**	**6**	**2**	**1.1**	**2**
Cardiac disorders	**4**	**2.1**	**4**	**6**	**3.2**	**7**	**4**	**2.1**	**4**
Bradycardia nos[4]	3	1.6	3	0	0.0	0	2	1.1	2
Investigations	**1**	**0.5**	**2**	**3**	**1.6**	**3**	**3**	**1.6**	**5**
Skin & subcutaneous tissue disorders	**0**	**0.0**	**0**	**1**	**0.5**	**1**	**3**	**1.6**	**3**

Source: Appendix B-1.3.1, Table 9
MedDRA = Medical Dictionary for Regulatory Activities
N = number of patients
% = percentage of patients with adverse events
n = number of adverse events
[1] Adverse events which the investigator considered to have a definite, possible, probable or unknown relationship to study medication
[2] Multiple answers possible
[3] Incidence of at least 1.5% of patients in any treatment group
[4] Not otherwise specified

Scanned from Table 8.1.2.2.2-c, page 169, Volume 117

***Medical Officer Comments**: The rate of patients with related adverse events was higher in the 2 palonosetron groups than in the ondansetron group (16% vs. 13.9%) . 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. Metabolism and nutrition disorders occurred more often in the palonosetron 0.25 mg group (3.2% vs 1% and 1.6 %) . General disorders and administration site conditions occurred more in the palonosetron groups compared to the ondansetron group (2.7% and 3.2% versus 1.1%). Bradycardia was reported in 3 patents in the palonosetron 0.25 mg group and in 2 patients in the ondansetron 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.

- 19 (10.2%) of the 0.25 mg palonosetron group suffered headaches.
  - 9 (4.8%) were judged to be related to the study drug.
  - 13 (7%) were mild in intensity.
  - 6 (3.2%) were moderate in intensity.
- 23 (12.2%) of the 0.75 mg palonosetron group experienced headache.
  - 10 (5.3%) were judged to be related to the study drug.
  - 18 (9.6%) were mild in intensity.
  - 5 (2.7%) were moderate in intensity.

Four patients (3 in the 0.25 mg palonosetron group and 1 in the 0.75 mg palonosetron group) experienced somnolence. All were judged as related to the study drug. In one of the patients who received 0.25 mg of palonosetron, it was judged as moderate in severity. The others were reported as mild.

Medical Officer Comments: *The Phase I/II studies reported headache as occurring in 20.4% of subjects. It is unclear what criteria investigators in this study used to determine if a patients headache was related to the study drug but even counting all headache patients in this study as related to the study drug the percentage is much less (10.2%,12.2%) than seen in the Phase I/II studies.*

Gastrointestinal Disorders

Constipation was the most frequent adverse event in this category

- 4 (2.1%) of the 0.25 mg palonosetron group suffered constipation.
  - 3 (1.6%) were judged to be related to the study drug.
  - 2 (1.0%) were mild in intensity.
  - 2 (1.1%) were moderate in intensity.
- 7 (3.7) of the 0.75 mg palonosetron group experienced headache.
  - 6 (3.2%) were judged to be related to the study drug.
  - 3 (1.6%) were mild in intensity.
  - 3 (1.6%) were moderate in intensity.

Metabolic Disorders

The most common metabolic disorder was recorded as metabolic disorder not otherwise specified. 3 (1.6%) of the 0.25 mg palonosetron group experienced metabolic disorder not otherwise specified. All three were seen at the same investigative site in Arkhanglesk, Russia. They were all listed as having a worsening of metabolic pattern in the myocardium on ECG. This was judged as mild in intensity and of unknown or possibly related to the study drug. All recovered without treatment.

The remainder of patients consisted of 2 patients with hypocalcemia and 1 patient with hypokalemia. These were not considered severe adverse events and it is unclear if they are related to the study drug.

Cardiac Disorders

- Three patients in the palonosetron 0.25 mg group experienced bradycardia. Interestingly all three were seen at the same investigative site in Arkhanglesk, Russia.
  - Patient #1115 was a 40 year old female who was noted to have a heart rate of 47 of ECG on Visit 3. This was listed as probably related to the study drug. The adverse event was described as mild in intensity and resolved on without treatment. The pulse and blood pressure were normal when checked during vital signs screen at all visits.
  - Patient #`1240 was a 68 year old female with a history of hypertension and breast cancer. She was noted to have bradycardia on her ECG from Visit 3. The adverse event was listed as mild in intensity and resolved spontaneously. All vital signs were normal at all visits.
  - Patient #1248 was a 28-year-old male with Hodgkin's disease that was noted to have an ECG on visit 4 that showed a heart rate of 55. All other vital signs were normal and the patient recovered without treatment.
- Three patients had episodes of extra-systole in the palonosetron groups. The following 2 patients were rated as possible or of unknown relation to the study drug.
  - Patient #1137 was a 58 year old female with a history of breast and thyroid cancer. She received 0.25 mg of palonosetron. She was noted to have a single extrasystolic beat on her Visit 3 ECG. She had no further episodes and her vital signs remained normal. The investigator recorded this mild in intensity and unknown in terms of relation to the study drug.
  - Patient #1116 was a 64 year old male with a history of coronary artery disease, metastatic carcinoma of unknown primary and multiple other medical problems. He received 0.75 mg of palonosetron. He apparently underwent Holter monitor and was noted to have extra-systolic beats intermittently. The CRT does not clarify what exact arrhythmia he suffered but he did receive riboxinum, a cardiac medication not approved in the U.S. This adverse event was categorized as probably related to the study drug and mild in intensity.
- Two patients who received 0.75 mg palonosetron experienced first degree AV block. These were classified as possibly related to the study drug, however, both patients had this ECG finding prior to receiving the study drug.
- Patient #3138 was a 63 year old female with metastatic breast cancer. She received 0.75 mg of palonosetron. She suffered lower extremity edema that was judged to be mild in intensity and of unknown relationship to the study drug.
- Patient #1080 was a 63 year old female with metastatic ovarian cancer. She was noted to have tachycardia with a heart rate of 92 at Visit 3 and 4 that decreased to 80 at her final visit. This was judged mild in intensity and possibly related to the study drug.

Medical Officer Comments: *All cardiac adverse events were reviewed in the palonosetron group. The bradycardia episodes were mild in intensity and spontaneously*

resolved. Patient #1248 may not have had true bradycardia rather a physiologic slow heart rate due to relative young age. Patient #1116 had a pre-existing cardiac condition that may have contributed to his arrhythmia. Overall, all the cardiac adverse events in the palonosetron groups self resolved and were not severe in intensity.

E. Deaths

There were 4 deaths reported during the study. Three occurred in the palonosetron 0.75 mg group and 1 in the ondansetron group. All deaths were judged as either unlikely or unrelated to the study drug.

Patient # 3219 (palonosetron 0.75 mg group) was a 55 year old white female who had a history of disseminated gastric cancer with ascites, constipation, vomiting and depression. Two days after receiving the study medication, the patient suffered an intermittent severe obstruction of the gastric outlet. The patient underwent parenteral nutrition and received a gastric tube but died approximately 31/2 months after receiving the study drug. This was judged by the investigator as unlikely related to the palonosetron

Patient # 3145 (palonosetron 0.75 mg group) was a 63 year old white male with a history of gastric cancer, small cell lung cancer with wide spread metastasis. One week after receiving palonosetron he developed severe pneumonia with severe atelectasis and pleural effusion. He died three weeks later and the investigator judged his death unlikely to be related to the study drug.

Patient #1263 (palonosetron 0.75 mg group) was a 76 year old female with a history of breast cancer, hypertension, coronary artery disease and diabetes. She developed diabetic ketoacidosis 20 days after receiving the study drug. She was hospitalized and treated but expired 27 days after receiving palonosetron. Her death was judged unlikely to be related to the study drug.

Patient #3328 (ondansetron group) was a 66 year old white male who developed a pulmonary embolism 1 day after receiving ondansetron. He was intubated and placed on a ventilator but died one day later. This death was judged to unrelated to the study drug.

Medical Officer Comments: *All of the deaths were reviewed and were appropriately categorized by the investigator. There is no evidence to suggest a relation between the study drug and any of these deaths.*

F. Serious Adverse Events

The following table displays serious adverse events by body system.

TABLE 31 – Serious Adverse Events by Body System and Preferred Term[1]

System organ class Preferred term (MedDRA)	Palonosetron 0.25 mg (N = 187)			Palonosetron 0.75 mg (N = 188)			Ondansetron 32 mg (N = 187)		
	N	%	n	N	%	n	N	%	n
Any serious adverse event	5	2.7	5	5	2.7	8	5	2.7	5
Infection and infestations	**1**	**0.5**	**1**	**2**	**1.1**	**2**	**0**	**0.0**	**0**
Pneumonia nos[2]	1	0.5	1	1	0.5	1	0	0.0	0
Periodontitis	0	0.0	0	1	0.5	1	0	0.0	0
Injury and poisoning	**1**	**0.5**	**1**	**0**	**0.0**	**0**	**0**	**0.0**	**0**
Accident nos[2]	1	0.5	1	0	0.0	0	0	0.0	0
Neoplasms benign and malignant	**1**	**0.5**	**1**	**0**	**0.0**	**0**	**0**	**0.0**	**0**
Placental polyp	1	0.5	1	0	0.0	0	0	0.0	0
Psychiatric disorders	**1**	**0.5**	**1**	**0**	**0.0**	**0**	**0**	**0.0**	**0**
Acute psychosis	1	0.5	1	0	0.0	0	0	0.0	0
Renal and urinary disorders	**1**	**0.5**	**1**	**0**	**0.0**	**0**	**1**	**0.5**	**1**
Urinary retention	1	0.5	1	0	0.0	0	0	0.0	0
Urinary tract disorders nos[2]	0	0.0	0	0	0.0	0	1	0.5	1
Blood and lymphatic system disorders	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**2**	**1.1**	**2**
Thrombocytopenia	0	0.0	0	0	0.0	0	2	1.1	2
Gastrointestinal disorders	**0**	**0.0**	**0**	**1**	**0.5**	**1**	**0**	**0.0**	**0**
Gastrointestinal obstruction nos[2]	0	0.0	0	1	0.5	1	0	0.0	0
General disorders and administration site conditions	**0**	**0.0**	**0**	**1**	**0.5**	**1**	**0**	**0.0**	**0**
Condition aggravated	0	0.0	0	1	0.5	1	0	0.0	0
Metabolism and nutrition disorders	**0**	**0.0**	**0**	**1**	**0.5**	**1**	**0**	**0.0**	**0**
Diabetic ketoacidosis	0	0.0	0	1	0.5	1	0	0.0	0
Nervous system disorders	**0**	**0.0**	**0**	**1**	**0.5**	**1**	**0**	**0.0**	**0**
Convulsion nos[2]	0	0.0	0	1	0.5	1	0	0.0	0

(continued)

TABLE 31 – Serious Adverse Events by Body System and Preferred Term[1] (Safety cohort, N = 562)

System organ class Preferred term (MedDRA)	Palonosetron 0.25 mg (N = 187)			Palonosetron 0.75 mg (N = 188)			Ondansetron 32 mg (N = 187)		
	N	%	n	N	%	n	N	%	n
Respiratory, thoracic and mediastinal disorders	**0**	**0.0**	**0**	**1**	**0.5**	**2**	**0**	**0.0**	**0**
Atelectasis	0	0.0	0	1	0.5	1	0	0.0	0
Pleural Effusion	0	0.0	0	1	0.5	1	0	0.0	0
Vascular Disorders	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**2**	**1.1**	**2**
Collapse	0	0.0	0	0	0.0	0	1	0.5	1
Pulmonary embolism	0	0.0	0	0	0.0	0	1	0.5	1

Source: Appendix B-1.3.1, Table 10
MedDRA = Medical Dictionary for Regulatory Activities
N = number of patients
% = percentage of patients with adverse events
n = number of adverse events
[1] Multiple answers possible
[2] Not otherwise specified

Scanned from Table 8.1.4-a, page 172-171, Volume 117

***Medical Officer Comments**: The serious adverse events were evenly distributed in each treatment arm.*

The following table gives further detail about serious adverse events.

TABLE 31 – Serious Adverse Events by Patient

Patient No.	Age	Day of onset	Gender	Treatment group	Event [1]	Relationship [2]
3111	59	17	Male	Palonosetron 0.25 mg	Accident nos [3]	Unrelated
3313	62	23	Male	Palonosetron 0.25 mg	Pneumonia nos [3]	Unrelated
3232	74	8	Male	Palonosetron 0.25 mg	Urinary retention	Unknown/unassessable
3454	58	2	Male	Palonosetron 0.25 mg	Acute psychosis	Unlikely
1040	29	13	Female	Palonosetron 0.25 mg	Placental polyp	Unrelated
3114	52	20	Male	Palonosetron 0.75 mg	Periodontitis	Unrelated
3225	72	10	Male	Palonosetron 0.75 mg	Convulsions nos [3]	Unrelated
3145	63	8	Male	Palonosetron 0.75 mg	Atelectasis	Unrelated
					Pleural effusion	Unrelated
					Pneumonia nos [3]	Unrelated
3219	55	3	Female	Palonosetron 0.75 mg	Condition aggravated	Unlikely
					Gastrointestinal obstruction	Unlikely
1263	76	21	Female	Palonosetron 0.75 mg	Diabetic ketoacidosis	Unlikely
3112	63	15	Female	Ondansetron 32 mg	Thrombocytopenia	Unlikely
3339	62	13	Male	Ondansetron 32 mg	Thrombocytopenia	Unrelated
3328	66	2	Male	Ondansetron 32 mg	Pulmonary embolism	Unrelated
3203	49	1	Female	Ondansetron 32 mg	Collapse	Unrelated
3406	57	14	Female	Ondansetron 32 mg	Urinary tract disorder nos [3]	Unrelated

[1] Preferred term
[2] According to investigators assessment
[3] Not otherwise specified

Scanned from Table 8.1.4-b Page 174, Volume 117

Medical Officer Comments: *All the serious adverse events in the palonosetron group were judged to be unrelated or unlikely to be related to the study drug. One patient is not listed in this table. Patient # 3022 was in the 0.75 mg palonosetron arm. This patient was a 48 year old female who had to withdraw from the study due to debility. This adverse event was described as severe and the patient withdrew from the study. It was thought the adverse event was possibly related to the study drug.*

G. Laboratory Evaluation

Lab data was collected and analyzed for all patients. This consisted of hematology, chemistry and urinalysis as well as ECG and Holter Monitoring for some patients.The following table shows the hematology results. This table displays the changes in hematology parameters from below the reference range to within or above the reference range from Visit 1 to Visit 4.

TABLE 33 -Hematology values changing from normal to abnormal or abnormal to normal between Visit 1 and Visit 4

N = 562)

	Palonosetron 0.25 mg (N = 187)			Palonosetron 0.75 mg (N = 188)			Ondansetron 32 mg (N = 187)		
	Visit 1								
	N (%)			N (%)			N (%)		
Visit 4	-	=	+	-	=	+	-	=	+
Hematocrit									
-	33 (17.6)	29 (15.5)	0 (0.0)	37 (19.7)	15 (8.0)	1 (0.5)	35 (18.7)	27 (14.4)	0 (0.0)
=	5 (2.7)	97 (51.9)	10 (5.3)	9 (4.8)	110 (58.5)	7 (3.7)	8 (4.3)	98 (52.4)	11 (5.9)
+	0 (0.0)	0 (0.0)	3 (1.6)	0 (0.0)	1 (0.5)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Erythrocytes									
-	56 (29.9)	33 (17.6)	0 (0.0)	51 (27.1)	34 (18.1)	0 (0.0)	59 (31.6)	23 (12.3)	0 (0.0)
=	3 (1.6)	83 (44.4)	1 (0.5)	8 (4.3)	89 (47.3)	0 (0.0)	4 (2.1)	92 (49.2)	1 (0.5)
+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Monocytes									
-	3 (1.6)	83 (44.4)	0 (0.0)	3 (1.6)	76 (40.4)	0 (0.0)	4 (2.1)	65 (34.8)	0 (0.0)
=	3 (1.6)	85 (45.5)	2 (1.1)	7 (3.7)	93 (49.5)	2 (1.1)	5 (2.7)	103 (55.1)	2 (1.1)
+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eosinophils									
-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
=	0 (0.0)	159 (85.0)	7 (3.7)	0 (0.0)	169 (89.9)	8 (4.3)	0 (0.0)	173 (92.5)	3 (1.6)
+	0 (0.0)	5 (2.7)	5 (2.7)	0 (0.0)	2 (1.1)	3 (1.6)	0 (0.0)	1 (0.5)	2 (1.1)

(continued)

TABLE 33 -Hematology values changing from normal to abnormal or abnormal to normal between Visit 1 and Visit 4

	Palonosetron 0.25 mg (N = 187)			Palonosetron 0.75 mg (N = 188)			Ondansetron 32 mg (N = 187)		
	Visit 1								
	N (%)			N (%)			N (%)		
Visit 4	-	=	+	-	=	+	-	=	+
Basophils									
-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
=	0 (0.0)	176 (94.1)	0 (0.0)	0 (0.0)	182 (96.8)	0 (0.0)	0 (0.0)	178 (95.2)	1 (0.5)
+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Appendix B-1.3.2, Table 2
- = below reference range
= = within reference range
+ = above reference range
N = number of patients with changes
% = percentage of patients with changes
Visit 1 = screening, Visit 4 = Study Day 6-8

TABLE 33 -Hematology values changing from normal to abnormal or abnormal to normal between Visit 1 and Visit 4

	Palonosetron 0.25 mg (N = 187)			Palonosetron 0.75 mg (N = 188)			Ondansetron 32 mg (N = 187)		
	Visit 1								
	N (%)			N (%)			N (%)		
Visit 4	-	=	+	-	=	+	-	=	+
Basophils									
-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
=	0 (0.0)	176 (94.1)	0 (0.0)	0 (0.0)	182 (96.8)	0 (0.0)	0 (0.0)	178 (95.2)	1 (0.5)
+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Appendix B-1.3.2, Table 2
- = below reference range
= = within reference range
+ = above reference range
N = number of patients with changes
% = percentage of patients with changes
Visit 1 = screening, Visit 4 = Study Day 6-8

TABLE 33 Cont'd

Scanned from Table 8.2.1-b, page 180-181, Volume 117

Medical Officer Comments: *Most hematology parameters changed to below the reference range at Visit 4. This is likely secondary to chemotherapy. The changes in erythrocytes or monocytes from normal values to below normal were found slightly more frequently in the*

palonosetron groups compared to the ondansetron group. Also the palonosetron 0.25 mg group showed an increase in eosinophils more frequently when compared to other groups. Overall, these differences in all treatment groups are not likely clinically significant and more likely due to chemotherapy than the study drug.

The investigator rated each abnormal lab finding whether it was clinically relevant. The following table shows the number of clinically relevant abnormalities in hematology for each treatment arm.

TABLE 34 – Clinically relevant abnormalities in hematology according to the investigator.

	Palonosetron 0.25 mg (N = 187)		Palonosetron 0.75 mg (N = 188)		Ondansetron 32 mg (N = 187)	
	N	%	N	%	N	%
Hemoglobin						
Visit 1 (Screening)	15	8.0	16	8.5	12	6.4
Visit 3 (Study Day 2)	8	4.3	12	6.4	11	5.9
Visit 4 (Study Day 6-8)	9	4.8	9	4.8	8	4.3
Hematocrit						
Visit 1 (Screening)	6	3.2	9	4.8	8	4.3
Visit 3 (Study Day 2)	6	3.2	7	3.7	6	3.2
Visit 4 (Study Day 6-8)	5	2.7	5	2.7	5	2.7
Erythrocytes						
Visit 1 (Screening)	8	4.3	10	5.3	9	4.8
Visit 3 (Study Day 2)	5	2.7	7	3.7	6	3.2
Visit 4 (Study Day 6-8)	6	3.2	5	2.7	6	3.2
Leukocytes						
Visit 1 (Screening)	4	2.1	2	1.1	5	2.7
Visit 3 (Study Day 2)	3	1.6	0	0.0	5	2.7
Visit 4 (Study Day 6-8)	27	14.4	21	11.2	25	13.4
Lymphocytes						
Visit 1 (Screening)	5	2.7	5	2.7	3	1.6
Visit 3 (Study Day 2)	18	9.6	11	5.9	9	4.8
Visit 4 (Study Day 6-8)	22	11.8	22	11.7	16	8.6
Neutrophils						
Visit 1 (Screening)	3	1.6	2	1.1	4	2.1
Visit 3 (Study Day 2)	2	1.1	1	0.5	0	0.0
Visit 4 (Study Day 6-8)	16	8.6	9	4.8	20	10.7
Eosinophils						
Visit 1 (Screening)	0	0.0	0	0.0	1	0.5
Visit 3 (Study Day 2)	0	0.0	0	0.0	0	0.0
Visit 4 (Study Day 6-8)	0	0.0	0	0.0	0	0.0

(continued)

TABLE 34- Cont'd

	Palonosetron 0.25 mg (N = 187)		Palonosetron 0.75 mg (N = 188)		Ondansetron 32 mg (N = 187)	
	N	%	N	%	N	%
Monocytes						
Visit 1 (Screening)	0	0.0	0	0.0	0	0.0
Visit 3 (Study Day 2)	0	0.0	1	0.5	0	0.0
Visit 4 (Study Day 6-8)	1	0.5	1	0.5	1	0.5
Platelets						
Visit 1 (Screening)	1	0.5	0	0.0	2	1.1
Visit 3 (Study Day 2)	1	0.5	0	0.0	1	0.5
Visit 4 (Study Day 6-8)	3	1.6	2	1.1	3	1.6

Source: Appendix C-8, Listings
N = patients with abnormalities
% = percentage of patients with abnormalities

Scanned from page 183-184, Volume 117,

Medical Officer Comments: *The number of clinically relevant lab abnormalities was low in all treatment groups. An overall trend was noted that there were more clinically relevant abnormalities in Visit 4 and this is consistent with the effects of chemotherapy.*

Blood Chemistry values were also judged whether to be clinically relevant. The following table displays clinically relevant blood chemistry values from all three treatment arms.

TABLE 35 - Clinically Relevant Abnormalities in Blood Chemistry

	Palonosetron 0.25 mg (N = 187)		Palonosetron 0.75 mg (N = 188)		Ondansetron 32 mg (N = 187)	
	N	%	N	%	N	%
SGOT						
Visit 1 (Screening)	3	1.6	1	0.5	4	2.1
Visit 3 (Study Day 2)	1	0.5	0	0.0	3	1.6
Visit 4 (Study Day 6-8)	0	0.0	0	0.0	2	1.1
SGPT						
Visit 1 (Screening)	2	1.1	0	0.0	3	1.6
Visit 3 (Study Day 2)	1	0.5	0	0.0	2	1.1
Visit 4 (Study Day 6-8)	0	0.0	0	0.0	2	1.1
Alkaline phosphatase						
Visit 1 (Screening)	5	2.7	0	0.0	4	2.1
Visit 3 (Study Day 2)	3	1.6	0	0.0	4	2.1
Visit 4 (Study Day 6-8)	2	1.1	0	0.0	1	0.5
Total billrubin						
Visit 1 (Screening)	1	0.5	2	1.1	2	1.1
Visit 3 (Study Day 2)	1	0.5	3	1.6	2	1.1
Visit 4 (Study Day 6-8)	0	0.0	0	0.0	2	1.1
Calcium						
Visit 1 (Screening)	2	1.1	0	0.0	1	0.5
Visit 3 (Study Day 2)	9	4.8	3	1.6	4	2.1
Visit 4 (Study Day 6-8)	3	1.6	2	1.1	1	0.5
Glucose						
Visit 1 (Screening)	5	2.7	2	1.1	8	4.3
Visit 3 (Study Day 2)	4	2.1	4	2.1	4	2.1
Visit 4 (Study Day 6-8)	3	1.6	5	2.7	4	2.1
Bicarbonate						
Visit 1 (Screening)	0	0.0	0	0.0	0	0.0
Visit 3 (Study Day 2)	2	1.1	1	0.5	1	0.5
Visit 4 (Study Day 6-8)	0	0.0	1	0.5	0	0.0

(continued)

TABLE 36 -Cont'd

	Palonosetron 0.25 mg (N = 187)		Palonosetron 0.75 mg (N = 188)		Ondansetron 32 mg (N = 187)	
	N	%	N	%	N	%
Creatinine						
Visit 1 (Screening)	0	0.0	0	0.0	2	1.1
Visit 3 (Study Day 2)	0	0.0	0	0.0	1	0.5
Visit 4 (Study Day 6-8)	2	1.1	0	0.0	1	0.5
Blood urea nitrogen						
Visit 1 (Screening)	0	0.0	0	0.0	4	2.1
Visit 3 (Study Day 2)	0	0.0	0	0.0	2	1.1
Visit 4 (Study Day 6-8)	2	1.1	0	0.0	3	1.6
Potassium						
Visit 1 (Screening)	1	0.5	1	0.5	2	1.1
Visit 3 (Study Day 2)	8	4.3	7	3.7	3	1.6
Visit 4 (Study Day 6-8)	6	3.2	5	2.7	5	2.7
Sodium						
Visit 1 (Screening)	0	0.0	0	0.0	0	0.0
Visit 3 (Study Day 2)	1	0.5	0	0.0	0	0.0
Visit 4 (Study Day 6-8)	0	0.0	2	1.1	0	0.0
Chloride						
Visit 1 (Screening)	0	0.0	0	0.0	0	0.0
Visit 3 (Study Day 2)	0	0.0	0	0.0	0	0.0
Visit 4 (Study Day 6-8)	0	0.0	1	0.5	0	0.0

Source: Appendix C-8, Listing 3
N = patients with abnormalities
% = percentage of patients with abnormalities
[1] no clinically relevant abnormalities were seen for albumin

Scanned from Table 8.2.2c, pg. 195-196, Volume 117

Medical Officer Comments: *There were few differences between the groups for blood chemistries. There were no clinically relevant values of AST and ALT in the palonosetron group at Visit 4.*

The following table displays vital sign information.

TABLE 37 - Difference in Vital Signs between the visits

	Palonosetron 0.25 mg (N = 187)			Palonosetron 0.75 mg (N = 188)			Ondansetron 32 mg (N = 187)		
	N	Min	Mean Max	N	Min	Mean Max	N	Min	Mean Max
Weight [kg]									
Visit 1	187		71.6	188		69.4	187		71.1
Changes from									
Visit 1[1] to Visit 3[2]	181		-0.1	186		0.1	184		-0.1
Visit 1[1] to Visit 4[3]	178		-0.3	183		-0.1	180		-0.3
Visit 1[1] to Visit 5[4]	97		-0.3	90		-0.1	86		-0.2
Systolic blood pressure [mmHg]									
Visit 1	185		130.0	188		128.5	187		128.5
Changes from									
Visit 1[1] to Visit 3[2]	185		-0.9	187		- 2.4	187		-1.7
Visit 1[1] to Visit 4[3]	180		-1.1	185		- 1.5	184		-2.5
Visit 1[1] to Visit 5[4]	96		-2.3	91		-1.5	86		-1.0
Diastolic blood pressure [mmHg]									
Visit 1	185		79.2	188		79.1	187		79.0
Changes from									
Visit 1[1] to Visit 3[2]	185		-0.9	187		- 1.6	187		-1.4
Visit 1[1] to Visit 4[3]	180		-0.1	185		- 2.2	184		-1.2
Visit 1[1] to Visit 5[4]	96		-1.2	91		-1.8	86		-0.8

(continued)

TABLE 37- Cont'd

	Palonosetron 0.25 mg (N = 187)				Palonosetron 0.75 mg (N = 188)				Ondansetron 32 mg (N = 187)			
	N	Min	Mean	Max	N	Min	Mean	Max	N	Min	Mean	Max
Respiratory rate [breaths/min]												
Visit 1	176		16.5		176		16.6		175		16.6	
Changes from												
Visit 1[1] to Visit 3[2]	174		0.0		172		0.1		169		0.1	
Visit 1[1] to Visit 4[3]	171		0.1		172		0.0		168		-0.1	
Visit 1[1] to Visit 5[4]	88		-0.2		80		-0.2		82		0.3	
Heart rate [beats/min]												
Visit 1	185		75.0		188		77.4		187		77.2	
Changes from												
Visit 1[1] to Visit 3[2]	185		0.6		187		-0.7		187		0.8	
Visit 1[1] to Visit 4[3]	182		1.9		183		-0.6		182		1.3	
Visit 1[1] to Visit 5[4]	96		2.1		91		-0.8		86		1.2	

Source: Appendix B-1.3.3, Table 1
N = number of patients with data
SD = standard deviation
[1] screening
[2] Study Day 2
[3] Study Day 6-8
[4] Study Day 15-28

Scanned from Table 8.3.1-a , page 204. Volume 117

Medical Officer Comments: There was no significant change or trend seen in vital signs from visits 1 to 4.

H. ECG Evaluation

A 12 lead ECG was performed for all patients at Visit 1 (screening), Visit 3 and Visit 4. The interpretation of the ECG's was performed by a cardiologist at a central location who was blinded to the patient's treatment. In addition the investigator also interpreted the ECG.

A subset of patients were randomized to receive a Holter monitor. The numbers are listed in the following table.

TABLE 38 – Number of Patients who underwent Holter Monitor

	Palonosetron 0.25 mg (N=192)		Palonosetron 0.75 mg (N=190)		Ondansetron 32 mg (N=188)	
	N	(%)	N	(%)	N	(%)
Holter Patients[1]	20	(10.4)	15	(7.91)	14	(7.4)

(Reference: Table 6.3-d, page 77, Volume 117)

[1]Patients with data available: palonosetron 0.25 mg :19, palonosetron 0.75 mg: 14, ondansetron :12

At Visit 1 the majority of patients had normal ECG (palonosetron 0.25 mg group: 80%, palonosetron 0.75 mg group: 75%, ondansetron 32 mg group: 70%) .The following table displays Changes in ECG findings between the visits.

TABLE 39 – Changes in ECG findings between the visits

Changes from	Palonosetron 0.25 mg (N = 187) N	%	Palonosetron 0.75 mg (N = 188) N	%	Ondansetron 32 mg (N = 187) N	%
Visit 1 to 2 (screening to Study Day 1) Holter patients only[1]						
No change	16	80.0	10	66.7	8	57.1
Improved	0	0.0	2	13.3	1	7.1
Deteriorated	2	10.0	0	0.0	2	14.3
Missing	2	10.0	3	20.0	3	21.4
Normal to normal	14	70.0	6	40.0	6	42.9
Normal to abnormal	2	10.0	0	0.0	1	7.1
Visit 1 to 3 (screening to Study Day 2)						
No change	157	84.0	155	82.4	146	78.1
Improved	8	4.3	7	3.7	15	8.0
Deteriorated	6	3.2	14	7.4	9	4.8
Missing	12	6.4	10	5.3	12	6.4
Normal to normal	138	73.8	126	67.0	120	64.2
Normal to abnormal	5	2.7	9	4.8	8	4.3
Visit 1 to 4 (screening to Study Day 6-8)						
No change	149	79.7	154	81.9	143	76.5
Improved	8	4.3	9	4.8	16	8.6
Deteriorated	7	3.7	8	4.3	8	4.3
Missing	22	11.8	12	6.4	15	8.0
Normal to normal	130	69.5	126	67.0	122	65.2
Normal to abnormal	7	3.7	5	2.7	3	1.6

Source: Appendix B-1.3.3, Tables 2 and 3
N = number of patients in the specific group
[1] Calculation of percentages based on N_{Hol} (palonosetron 0.25 mg N_{Hol} = 20, palonosetron 0.75 mg N_{Hol} = 15 ondansetron 32 mg N_{Hol} = 14)

Scanned from Table 8.3.2-a: page 207, Volume 117

Medical Officer Comments: *The majority of patients had no change in ECG. Between Visit 1 and 3, a higher proportion of the 0.75 mg palonosetron group had worsening ECG as rated by the reading cardiologist. The designation of deteriorated ECG was based on the subjective opinion of the blinded cardiologist. The 0.25 mg palonosetron group had the least number of patients with worsening ECG's.*

The QT interval was evaluated also for any change after receiving treatment. The following table shows the changes in QT and QTc.

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TABLE 40 – Changes in QT and QTc at Visits

	Palonosetron 0.25 mg (N = 187)				Palonosetron 0.75 mg (N = 188)				Ondansetron 32 mg (N = 187)			
	N	Mean	Min	Max	N	Mean	Min	Max	N	Mean	Min	Max
QT												
Visit 1[1]	179	365			183	364			178	360		
Visit 2[2]	18	384			12	376			12	375		
Visit 3[3]	176	370			176	368			176	364		
Visit 4[4]	165	368			176	365			173	364		
Visit 2, 3 and 4	179	369			181	366			181	364		
Changes from												
Visit 1 to 2	18	5			12	1			12	4		
Visit 1 to 3	174	5			174	4			171	5		
Visit 1 to 4	164	2			174	1			169	4		
Visit 1 to 2, 3, 4	177	3			179	2			176	5		
Maximum change	177	12.6			179	12.1			176	13.4		
QTc by Bazett												
Visit 1[1]	179	407			183	406			178	405		
Visit 2[2]	18	417			12	410			12	420		
Visit 3[3]	176	408			176	409			176	408		
Visit 4[4]	165	406			176	407			173	411		
Visit 2, 3 and 4	179	407			181	408			181	410		

(continued)

TABLE 40 – cont'd

Changes from	Palonosetron 0.25 mg (N = 187) N	Mean	Min	Max	Palonosetron 0.75 mg (N = 188) N	Mean	Min	Max	Ondansetron 32 mg (N = 187) N	Mean	Min	Max
Changes from Visit 1 to 2	18	0			12	-5			12	10		
Visit 1 to 3	174	1			174	4			171	3		
Visit 1 to 4	164	-3			174	2			169	5		
Visit 1 to 2, 3, 4	177	-1			179	2			176	5		
Maximum change	177	6.6			179	10.4			176	12.6		
QTc by Fridericia												
Visit 1[1]	179	393			183	391			178	389		
Visit 2[2]	18	406			12	398			12	404		
Visit 3[3]	176	395			176	394			176	393		
Visit 4[4]	165	392			176	392			173	394		
Changes from Visit 2, 3 and 4	179	393			181	393			181	393		
Visit 1 to 2	18	1			12	-3			12	8		
Visit 1 to 3	174	2			174	4			171	4		
Visit 1 to 4	164	-1			174	1			169	5		
Visit 1 to 2, 3, 4	177	1			179	2			176	5		
Maximum change	177	7.5			179	9.3			176	11.6		

Source: Appendix B-1.3.3, Table 3
N = patients with changes, SD = standard deviation
[1] Visit 1 = screening, [2] Visit 2, Study Day 1, for Holter patient s only, calculation of percentages based on N_{Hol} (palonosetron 0.25 mg N_{Hol} = 20 palonosetron 0.75 mg N_{Hol} = 15, 32 mg N_{Hol} = 14)
[3] Visit 3 = Study Day 2, [4] Visit 4 = Study Day 6-8.

Scanned form Table 8.3.2-b, page 209-210, Volume 117

Medical Officer Comments: *There were no significant differences seen between treatment groups on QTc. The 0.25 palonosetron group showed a slight decrease in QTc in some intervals when corrected with Bazett's formula. Ondansetron arm had the highest QT/QTc mean maximum change in duration.*

When the QT and QTc intervals are averaged there can be regression to the mean. Thus, it can be more clinically relevant to examine the number of patients with critical changes for QT and QTc ECG findings. The following table displays this information.

TABLE 41 – Critical Changes for QT and QTc ECG findings at Visits

	Palonosetron 0.25 mg (N = 187)		Palonosetron 0.75 mg (N = 188)		Ondansetron, 32 mg (N = 187)	
Changes from	N	%	N	%	N	%
Visit 1[1] to Visit 2[2,3] (Holter patients only)						
QT 30 to 60 msec	2	10.0	0	0.0	2	14.3
QT > 60 msec	0	0.0	1	6.7	0	0.0
QTc by B 30 to 60 msec	1	5.0	0	0.0	3	21.4
QTc by B > 60 msec	0	0.0	0	0.0	0	0.0
QTc by F 30 to 60 msec	1	5.0	1	6.7	0	0.0
QTc by F > 60 msec	0	0.0	0	0.0	0	0.0
Visit 1[1] to Visit 3[4]						
QT 30 to 60 msec	26	13.9	15	8.0	16	8.6
QT > 60 msec	1	0.5	3	1.6	2	1.1
QTc by B 30 to 60 msec	6	3.2	12	6.4	11	5.9
QTc by B > 60 msec	1	0.5	2	1.1	1	0.5
QTc by F 30 to 60 msec	10	5.3	9	4.8	9	4.8
QTc by F > 60 msec	0	0.0	2	1.1	1	0.5

(continued)

TABLE 41 – cont'd

Changes from	Palonosetron 0.25 mg (N = 187) N	%	Palonosetron 0.75 mg (N = 188) N	%	Ondansetron 32 mg (N = 187) N	%
Visit 1[1] to Visit 4[5]						
QT 30 to 60 msec	9	4.8	13	6.9	19	10.2
QT > 60 msec	3	1.6	3	1.6	3	1.6
QTc by B 30 to 60 msec	7	3.7	16	8.5	16	8.6
QTc by B > 60 msec	0	0.0	0	0.0	2	1.1
QTc by F 30 to 60 msec	4	2.1	10	5.3	9	4.8
QTc by F > 60 msec	2	1.1	0	0.0	2	1.1

Source: Appendix B-1.3.3, Table 5
N = patients with changes
% = percentage of patients with changes
B = Bazett
F = Fridericia
[1] screening, [2] calculation of percentages based on N_{Hol} (palonosetron 0.25 mg N_{Hol} = 20, palonosetron 0.75 mg N_{Hol} = 15, ondansetron 32 mg N_{Hol} = 14), [3] Study Day 1 (15 minutes after study medication administration), [4] Study Day 2, [5] Study Day 6-8.

Medical Officer Comments: It is generally accepted that a change in QTc of greater than 60 msec is of concern and greater than 30 msec is potentially concerning. The 0.25 mg palonosetron group had the fewest number of patients in this group.

ECG's were rated by the cardiologist as to whether they had clinically relevant findings The following table displays the clinically relevant abnormalities for each treatment group.

TABLE 42 – Clinically relevant abnormalities detected by ECG assessed by cardiologist

	Palonosetron 0.25 mg (N = 187)		Palonosetron 0.75 mg (N = 188)		Ondansetron 32 mg (N = 187)	
	N	%	N	%	N	%
Visit 1 (Screening)	14	7.5	25	13.3	18	9.6
Visit 2 (Study Day 1)[1]	1	5.0	3	20.0	1	7.1
Visit 3 (Study Day 2)	12	6.4	28	14.9	17	9.1
Visit 4 (Study Day 6-8)	13	7.0	23	12.2	15	8.0

Source: Appendix B-1.3.3, Table 2
N = patients with abnormalities
% = percentage of patients with abnormalities
[1] Visit 2, Study Day 1, for Holter patients only, calculation of percentages based on N_{Hol} (palonosetron 0.25 mg N_{Hol} = 20, palonosetron 0.75 mg N_{Hol} = 15, ondansetron 32 mg N_{Hol} = 14)

Medical Officer Comments: *None of the groups showed an increase in the frequency of clinically relevant ECG findings during the study. The 0.25 mg palonosetron group showed the lowest number of ECG findings.*

A subset of patients underwent Holter monitoring from 2 hours prior to receiving the medication to 22 hours after getting the study drug. The results of this were analyzed by a cardiologist at a central location. The cardiologist assessed whether the findings were abnormal or normal and if they were clinically relevant. The results are displayed in the following table.

TABLE 43 – Summary of Global Information for Holter Monitoring (N=49)[1]

	Palonosetron 0.25 mg (N=20)		Palonosetron 0.75 mg (N=15)		Ondansetron 32 mg (N=14)	
	N	(%)	N	(%)	N	(%)
Holter Interpretation						
Normal	16	(80)	14	(93.3)	10	(71.4)
Abnormal	3	(15.0)	0	(0.0)	2	(14.3)
Clinical Relevance						
Relevant	3	(15.0)	0	(0.0)	2	(14.3)
Irrelevant	0	(0.0)	0	(0.0)	0	(0.0)
Equivocal	0	(0.0)	0	(0.0)	0	(0.0)

[1] Patients with data available: Palonosetron 0.25 mg =19, palonosetron 0.75 mg =14, ondansetron = 12
(Reference: Table 8.3.3-a, page 215, Volume 117)

The following are details about the patients with abnormal Holter monitor results in the palonosetron 0.25 mg group.

- Patient #1122 was a 46 year old female with breast cancer. She had a second-degree heart block 18.5 hours after receiving the study drug. She had no cardiac history.

- Patient #1125 was a 66 year old female with metastatic breast cancer. She had a history of coronary artery disease and angina. She had second and third degree heart block noted about 21.5 hours after administration of the study drug.

- Patient #1189 was a 54 year old male with a history lung cancer. He had a history of hypertension and anemia. On his Visit 4, he had a worsening ECG that showed subendocardial ischemia in the antero-septal zone. The change in ECG was thought to be secondary to anemia (hemoglobin was 6 mMol/L). He had a single run of non-sustained ventricular tachycardia of 3 beats 17.5 hours after getting the study medication.

Two patients had abnormal Holter monitors in the control group. One patient had second degree heart block and another had atrial fibrillation.

Medical Officer Comments: *It is likely that Patients #1125, and #1189 had abnormal Holter monitor readings due to underlying medical conditions unrelated to the study drug. This is less certain for Patient #1122. It should however be noted that in the ondansetron group, two patients also had abnormal Holter monitor readings.*

VII. Conclusion

The primary objective of the study PALO-99-03 was to compare the efficacy of single IV doses of palonosetron 0.25 mg or 0.75 mg, to ondansetron 32 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 ondansetron. In addition, the effect of anti-emetic control with palonosetron or ondansetron on the quality of life of patients receiving moderately emetogenic chemotherapy was evaluated. The study achieved these objectives

A. Efficacy

The primary efficacy parameter was complete response within the first 24 hours after chemotherapy. The results demonstrated the non-inferiority of both palonosetron 0.25 mg and 0.75 mg when compared to ondansetron. 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. There were multiple secondary endpoints. Pairwise testing between palonosetron 0.25 mg and ondansetron revealed differences in favor of ondansetron in the following parameters:

- Complete control for all time periods except Study Days 1 and 5
- Number of emetic episodes for all time periods except for Study Days 1,2,3 and the time period 0-120 hours
- Time to first emetic episode
- Time to First EE
- Severity of Nausea except for Study Day 1 and Study Day 5

Pairwise testing did not show any deference for the following secondary endpoints

- Need of rescue medication
- Time to rescue medications
- Global satisfaction except for Study Day 3 which palonosetron was better
- Function of Living Index-Emesis except for Study Day 5

Palonosetron 0.75 mg dose showed better efficacy when compared to ondansetron only for complete control on Study Days 3 an 4 as well as severity of nausea on Study Days 4 and 5. For all other secondary endpoints, there was no statistically significant difference between palonosetron 0.75 mg and ondansetron. These analyses were not adjusted for multiplicity.

In subgroup analysis, male patients had a higher complete response rate than female patients. However, the lower limits of a 97.5% confidence interval for the difference in complete response rates between both palonosetron doses and ondansetron 32 mg were above the pre-set threshold of -15 % in male and female patients. Naïve patients had a slightly higher complete response rate than non-naïve patients in all but the palonosetron 0.75 mg group. The lower limits of the 97.55 confidence intervals for the difference between palonosetron 0.25 mg and ondansetron were above the preset threshold of –15% indicating non-inferiority of palonosetron 0.25 mg to ondansetron in regard to these subgroups. The palonosetron 0.75 mg dose was only able to demonstrate non-inferiority in the non-naïve patients.