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 =

	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 Minus Ondansetron
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 ondansetron group. Higher rates were observed in the palonosetron 0.25 mg group compared to the 0.75 mg group The low confidence interval of the difference of each palonosetron dose versus ondansetron was above the pre-set threhsold of –15%, inferiority of palonosetron to ondansetron. Although the palonosetron seems to demonstrate some efficacy at 120 hours some be considered. The p-values were not adjusted for multiple endpoints. Since there were multiple secondary endpoints, there m with multiplicity. In addition, the comparator arm Ondansetron is not indicated for prevention of CINV at 120 hours. Thus, w 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

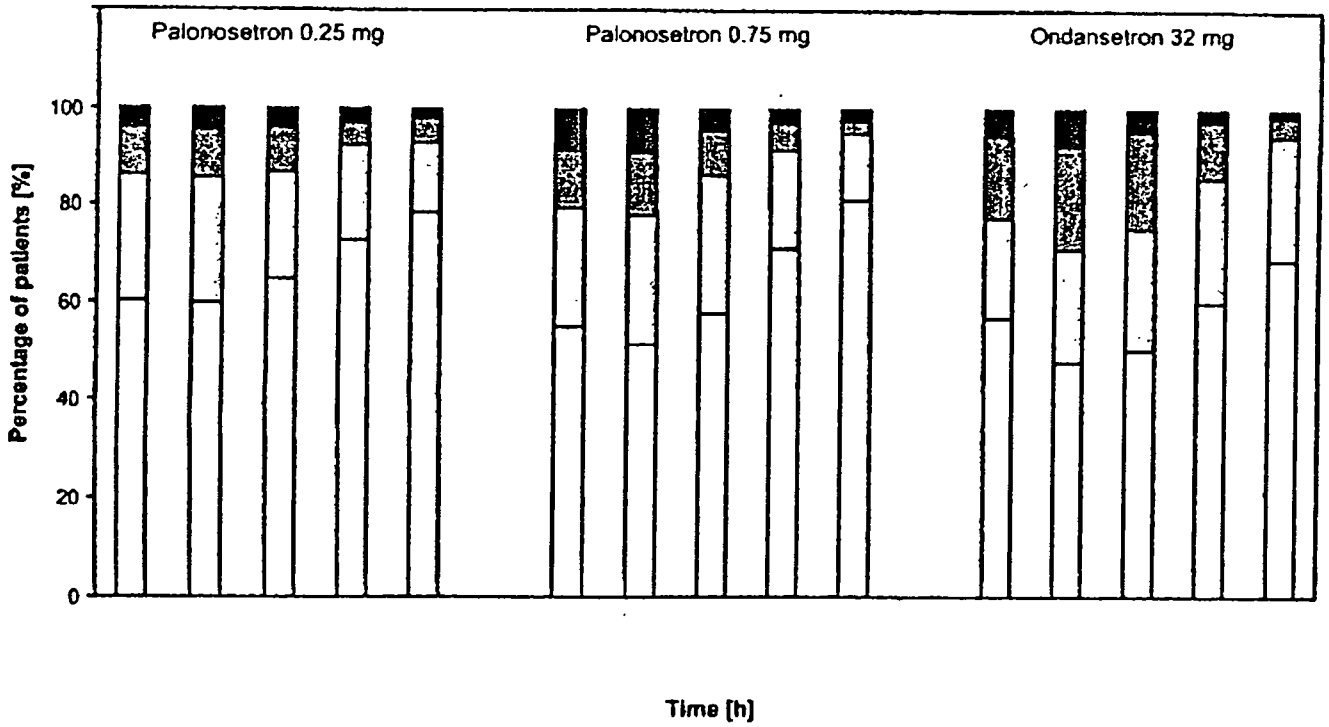
(Reference:Table 7.2.3-b, page 113, Volume 117)

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)



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