- 47 (24.1%) of the 0.75 mg palonosetron group experienced headache.
  - ➢ 30 (15.4%) were judged to be related to the study drug

  Of those judged to be related to the study drug:
  - ➢ 20 (10.3%) were mild in intensity.
  - ➢ 9 (4.6%) were moderate in intensity.
  - ➢ 1 (0.5%) was severe in intensity.

***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.*

Gastrointestinal Disorders

Constipation was the most frequent adverse event in this category

- 23 (11.9%) of the 0.25 mg palonosetron group suffered constipation.
  - ➢ 14 (7.3%) were judged to be related to the study drug.

  Of those judged to be related:
  - ➢ 12 (6.2%) were mild in intensity.
  - ➢ 2 (1.1%) were moderate in intensity.
- 29 (14.9%) of the 0.75 mg palonosetron group experienced constipation.
  - ➢ 18 (9.2%) were judged to be related to the study drug.

  Of those judged to be related :
  - ➢ 13 (6.7%) were mild in intensity.
  - ➢ 5 (2.6%) were moderate in intensity.

Cardiac Disorders

- Six patients in the palonosetron 0.25 mg group experienced cardiac disorders.
  - ➢ Patient #4140 was a 53 year old female who self reported a brief 15 second episode of tachycardia 2 days after receiving the study drug. No ECG was obtained at the time of the event. This was listed as possibly 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 # 2204 was a 54 year old female with a history of breast cancer. She was reported to have tachycardia on Visit 3. The adverse event was listed as mild in intensity and resolved spontaneously. All vital signs were normal at all visits. No further details were given
  - ➢ Patient # 2084 was a 62-year-old male with ovarian cancer that was noted to have a heart rate of 98 on Visit 3. ECG showed no clinically relevant abnormalities. All other vital signs were normal and the patient recovered without treatment.
  - ➢ Patient # 2185 was a 73 year old female with a history of breast cancer, anemia, and hypertension. She was found to have a heart rate of 124 on Visit 3. The adverse event was listed as moderate in intensity and not related to the study drug. It resolved without treatment. ECG was unremarkable
  - ➢ Patient # 4280 was a 83 year old male with a history of lung cancer, prostate cancer, and a history of PVC's and arrhythmia. Two days after receiving the study drug, he experienced atrial fibrillation for 5 days. This was judged as mild in intensity and was thought to be unrelated to the study drug.

- Patient # 4464 was a 83 year old male with history of esophageal cancer, prostate cancer, hypertension and myocardial infarction. He experienced occasional skipped heartbeats for 5 days after receiving the study drug. This was rated as mild in intensity and unrelated to the study drug.

- Six patients had arrhythmias in the palonosetron 0.75 mg group.
  - Patient # 4030 was a 80 year old female with a history of breast cancer. She was noted to have first degree heart block the day after receiving the study drug. This adverse event was categorized as possibly related to the study drug and mild in intensity.
  - Patient # 2252 was a 32 year old female with breast cancer. She tachycardia. At baseline prior to receiving medication, her heart rate was 96. At Visit 3 it was 116, and at Visit 4 it was 98. This was judged mild in intensity and probably related to the study drug.
  - Patient #2079 was a 47 year old male with nasopharyngeal cancer.He was noted to have tachycardia at Visits 4 and 5 with a heart rate of 96 and 104 respectively. ECG was otherwise unremarkable. This was judged mild in intensity and probably related to the study drug.
  - Patient # 4433 was a 79 year old female with breast cancer. She was noted to have a 1st degree heart block the day after receiving the study drug. This adverse event was categorized as not related to the study drug, and mild in intensity.
  - Patient #2082 was a 59 year old female with breast cancer. She was noted on Visit 4 to have tachycardia with a heart rate of 120. All other vital signs were normal. At Visit 5 her heart rate was 92. This was judged as moderate in intensity and probably related to the study drug.
  - Patient #2154 was a 49 year old female with breast cancer. She was noted to have a supraventricular arrhythmia on ECG during Visit 4. There apparently was some disagreement about interpretation between the investigators. Vital signs remained normal and this adverse event was rated as mild in intensity and unrelated to the study drug.

***Medical Officer Comments:*** *All cardiac adverse events were reviewed in the palonosetron group. There were no incidences of torsades de pointes or any other life threatening arrhythmia. Overall, all the cardiac adverse events in the palonosetron groups self resolved and were not severe in intensity.*

**E. Deaths**

There were 3 deaths reported during the study. All occurred in the palonosetron group. All deaths were judged as either unlikely or unrelated to the study drug.

Patient # 4343 (palonosetron 0.25 mg group) was a 75 year old white female who had a history of bilateral lung cancer. Two days after receiving the study medication, the patient developed urosepsis and mild dehydration. She died 14 days after receiving the study drug. This was judged by the investigator as unrelated to the palonosetron.

Patient # 4007 (palonosetron 0.75 mg group) was a 71 year old Hispanic male with a history of gastric and pancreatic cancer. Two days after receiving the study drug, he

died of a gastrointestinal bleed. The investigator judged his death unlikely to be related to the study drug.

Patient #2228 (palonosetron 0.75 mg group) was a 68 year old female with a history of non-Hodgkin's lymphoma. She developed sepsis and septic shock on the day of administration of the study medication. She died 8 days later. Her death was judged unlikely to be related 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<br>Preferred term<br>(MedDRA) | Palonosetron 0.25 mg (N = 193) | | | Palonosetron 0.75 mg (N = 195) | | | Dolasetron 100 mg (N =194) | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | % | n | N | % | n | N | % | n |
| Any serious adverse event | 4 | 2.1 | 8 | 13 | 6.7 | 21 | 9 | 4.6 | 12 |
| **Infection and infestations** | **2** | **1.0** | **2** | **2** | **1.0** | **3** | **3** | **1.5** | **3** |
| Pneumonia nos[2] | 1 | 0.5 | 1 | 1 | 0.5 | 1 | 1 | 0.5 | 1 |
| Urosepsis | 1 | 0.5 | 1 | 0 | 0.0 | 0 | 0 | 0.0 | 0 |
| Neutropenic sepsis | 0 | 0.0 | 0 | 0 | 0.0 | 0 | 1 | 0.5 | 1 |
| Sepsis nos[2] | 0 | 0.0 | 0 | 1 | 0.5 | 1 | 1 | 0.5 | 1 |
| Septic shock | 0 | 0.0 | 0 | 1 | 0.5 | 1 | 0 | 0.0 | 0 |
| **Metabolism and nutrition disorders** | **2** | **1.0** | **2** | **1** | **0.5** | **1** | **0** | **0.0** | **0** |
| Dehydration | 2 | 1.0 | 2 | 0 | 0.0 | 0 | 0 | 0.0 | 0 |
| Hyponatremia | 0 | 0.0 | 0 | 1 | 0.5 | 1 | 0 | 0.0 | 0 |
| **Gastrointestinal disorders** | **1** | **0.5** | **1** | **3** | **1.5** | **3** | **1** | **0.5** | **1** |
| Abdominal pain upper | 1 | 0.5 | 1 | 0 | 0.0 | 0 | 0 | 0.0 | 0 |
| Diarrhea nos[2] | 0 | 0.0 | 0 | 1 | 0.5 | 1 | 0 | 0.0 | 0 |
| Gastrointestinal hemorrhage nos[2] | 0 | 0.0 | 0 | 1 | 0.5 | 1 | 0 | 0.0 | 0 |
| Small intestinal obstruction nos[2] | 0 | 0.0 | 0 | 1 | 0.5 | 1 | 0 | 0.0 | 0 |
| Vomiting nos[2] | 0 | 0.0 | 0 | 0 | 0.0 | 0 | 1 | 0.5 | 1 |
| **General disorders and administration site conditions** | **0** | **0.0** | **0** | **1** | **0.5** | **1** | **2** | **1.0** | **2** |
| Chest pain nec[2] | 0 | 0.0 | 0 | 1 | 0.5 | 1 | 0 | 0.0 | 0 |
| Pyrexia | 0 | 0.0 | 0 | 0 | 0.0 | 0 | 1 | 0.5 | 1 |
| Rigors | 0 | 0.0 | 0 | 0 | 0.0 | 0 | 1 | 0.5 | 1 |
| **Neoplasm benign and malignant** | **1** | **0.5** | **1** | **1** | **0.5** | **1** | **0** | **0.0** | **0** |
| Lung cancer stage unspecified | 1 | 0.5 | 1 | 0 | 0.0 | 0 | 0 | 0.0 | 0 |
| Non Hodgkin's lymphoma nos | 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] (Cont'd)**

| System organ class<br>Preferred term<br>(MedDRA) | Palonosetron 0.25 mg (N = 193) | | | Palonosetron 0.75 mg (N = 195) | | | Dolasetron 100 mg (N =194) | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | % | n | N | % | n | N | % | n |
| **Respiratory, thoracic and mediastinal disorders** | **1** | **0.5** | **1** | **0** | **0.0** | **0** | **0** | **0.0** | **0** |
| Dyspnea nos[2] | 1 | 0.5 | 1 | 0 | 0.0 | 0 | 0 | 0.0 | 0 |
| **Blood and lymphatic system disorders** | **1** | **0.5** | **1** | **5** | **2.6** | **7** | **3** | **1.5** | **3** |
| Pancytopenia | 1 | 0.5 | 1 | 1 | 0.5 | 1 | 0 | 0.0 | 0 |
| Anemia nos[2] | 0 | 0.0 | 0 | 2 | 1.0 | 2 | 0 | 0.0 | 0 |
| Anemia nos[2] aggravated | 0 | 0.0 | 0 | 1 | 0.5 | 1 | 0 | 0.0 | 0 |
| Febrile neutropenia | 0 | 0.0 | 0 | 2 | 1.0 | 2 | 2 | 1.0 | 2 |
| Leucopenia nos[2] | 0 | 0.0 | 0 | 0 | 0.0 | 0 | 1 | 0.5 | 1 |
| Neutropenia | 0 | 0.0 | 0 | 1 | 0.5 | 1 | 0 | 0.0 | 0 |
| **Cardiac disorders** | **0** | **0.0** | **0** | **1** | **0.5** | **1** | **0** | **0.0** | **0** |
| Angina unstable | 0 | 0.0 | 0 | 1 | 0.5 | 1 | 0 | 0.0 | 0 |
| **Injury and poisoning** | **0** | **0.0** | **0** | **1** | **0.5** | **1** | **0** | **0.0** | **0** |
| Subdural hematoma | 0 | 0.0 | 0 | 1 | 0.5 | 1 | 0 | 0.0 | 0 |
| **Musculoskeletal, connective tissue and bone disorders** | **0** | **0.0** | **0** | **0** | **0.0** | **0** | **1** | **0.5** | **1** |
| Back pain | 0 | 0.0 | 0 | 0 | 0.0 | 0 | 1 | 0.5 | 1 |
| **Nervous system disorders** | **0** | **0.0** | **0** | **1** | **0.5** | **1** | **0** | **0.0** | **0** |
| Syncope | 0 | 0.0 | 0 | 1 | 0.5 | 1 | 0 | 0.0 | 0 |
| **Renal and urinary disorders** | **0** | **0.0** | **0** | **0** | **0.0** | **0** | **1** | **0.5** | **1** |
| Renal impairment nos[2] | 0 | 0.0 | 0 | 0 | 0.0 | 0 | 1 | 0.5 | 1 |
| **Vascular disorders** | **0** | **0.0** | **0** | **2** | **1.0** | **2** | **1** | **0.5** | **1** |
| Phlebitis nos[2] | 0 | 0.0 | 0 | 1 | 0.5 | 1 | 0 | 0.0 | 0 |
| Pulmonary embolism | 0 | 0.0 | 0 | 0 | 0.0 | 0 | 1 | 0.5 | 1 |
| Venous thrombosis deep limb | 0 | 0.0 | 0 | 1 | 0.5 | 1 | 0 | 0.0 | 0 |

Source: Appendix B-1.3.1, Table 10
N = number of patients
% = percentage of patients with adverse events
n = number of adverse events
[1] Multiple answers possible
[2] Not otherwise specified, not elsewhere classified

Scanned from Table 8.1.4-a, page 182-183, Volume 135

***Medical Officer Comments**: The palonosetron 0.75 mg group had the highest percentage of adverse events and the 0.25 mg group had the lowest percentage.*

The following table gives further detail about serious adverse events.

**TABLE 31 – Serious Adverse Events by Patient**

| Patient No. | Age | Gender | Treatment group | Event[1] | Day of onset | Relationship[2] |
|---|---|---|---|---|---|---|
| 4280 | 82 | Male | Palonosetron 0.25 mg | Pneumonia nos[3] | 2 | Unrelated |
| 4059 | 52 | Female | Palonosetron 0.25 mg | Abdominal pain upper | 8 | Unlikely |
| 4343 | 75 | Female | Palonosetron 0.25 mg | Dehydration | 3 | Unrelated |
| | | | | Dyspnea nos[3] | 3 | Unrelated |
| | | | | Lung cancer stage unspecified (exc. metastatic tumors to lung) | 4 | Unrelated |
| | | | | Urosepsis | 3 | Unrelated |
| 4348 | 29 | Female | Palonosetron 0.25 mg | Dehydration | 2 | Unrelated |
| | | | | Pancytopenia | 10 | Unrelated |
| 4002 | 68 | Male | Palonosetron 0.75 mg | Angina unstable | 21 | Unrelated |
| 4007 | 71 | Male | Palonosetron 0.75 mg | Anemia nos[3] | 2 | Unlikely |
| | | | | Gastrointestinal hemorrhage nos[3] | 2 | Unlikely |
| 4010 | 79 | Female | Palonosetron 0.75 mg | Diarrhea nos[3] | 10 | Unrelated |
| | | | | Febrile neutropenia | 13 | Unrelated |
| 4247 | 51 | Female | Palonosetron 0.75 mg | Pneumonia nos[3] | 7 | Unrelated |
| 4396 | 67 | Male | Palonosetron 0.75 mg | Small intestinal obstruction nos[3] | 14 | Unrelated |
| 4374 | 46 | Female | Palonosetron 0.75 mg | Anemia nos[3] aggravated | 2 | Unrelated |
| | | | | Neutropenia | 13 | Unrelated |
| | | | | Syncope | 13 | Unrelated |
| 4210 | 70 | Female | Palonosetron 0.75 mg | Venous thrombosis deep limb | 4 | Unrelated |
| 4262 | 54 | Male | Palonosetron 0.75 mg | Chest pain nec[3] | 18 | Unrelated |

(continued)

**TABLE 31 – Serious Adverse Events by Patient (Cont'd)**

| Patient No. | Age | Gender | Treatment group | Event[1] | Day of onset | Relationship[2] |
|---|---|---|---|---|---|---|
| 4267 | 78 | Male | Palonosetron 0.75 mg | Pancytopenia | 10 | Unrelated |
| 4164 | 74 | Female | Palonosetron 0.75 mg | Subdural hematoma | 7 | Unrelated |
| 4291 | 65 | Male | Palonosetron 0.75 mg | Anemia nos[3] | 10 | Unrelated |
| | | | | Febrile neutropenia | 10 | Unrelated |
| | | | | Hyponatremia | 10 | Unrelated |
| 2193 | 49 | Female | Palonosetron 0.75 mg | Phlebitis nos[3] | 21 | Unrelated |
| 2228 | 68 | Female | Palonosetron 0.75 mg | Non Hodgkin's Lymphoma nos[3] | 1 | Unrelated |
| | | | | Sepsis nos[3] | 1 | Unrelated |
| | | | | Septic shock | 1 | Unrelated |
| 4008 | 50 | Male | Dolasetron 100 mg | Back pain | 13 | Unrelated |
| 4044 | 65 | Female | Dolasetron 100 mg | Pyrexia | 14 | Unrelated |
| | | | | Sepsis nos[3] | 14 | Unrelated |
| 4402 | 42 | Female | Dolasetron 100 mg | Febrile neutropenia | 11 | Unrelated |
| 4399 | 58 | Female | Dolasetron 100 mg | Vomiting nos[3] | 22 | Unlikely |
| 4242 | 46 | Female | Dolasetron 100 mg | Febrile neutropenia | 18 | Unrelated |
| 4258 | 55 | Male | Dolasetron 100 mg | Pneumonia nos[3] | 2 | Unrelated |
| 4435 | 69 | Female | Dolasetron 100 mg | Leucopenia nos[3] | 6 | Unrelated |
| | | | | Neutropenic sepsis | 10 | Unrelated |
| | | | | Rigors | 10 | Unrelated |

(continued)

**TABLE 31- Serious Adverse Events (Cont'd)**

| Patient No. | Age | Gender | Treatment group | Event[1] | Day of onset | Relationship[2] |
|---|---|---|---|---|---|---|
| 4485 | 60 | Male | Dolasetron 100 mg | Pulmonary embolism | 21 | Unrelated |
| 2237 | 50 | Female | Dolasetron 100 mg | Renal impairment nos[3] | 28 | Unlikely |

[1] Preferred term
[2] According to investigators assessment
[3] Not otherwise specified, not elsewhere classified

Scanned from Table 8.1.4-b Page 174, Volume 135
***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. No clear pattern of serious adverse events is noted.*

**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**

| | Palonosetron 0.25 mg (N = 193) | | | Palonosetron 0.75 mg (N = 195) | | | Dolasetron 100 mg (N = 194) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 N (%) | | | Visit 1 N (%) | | | Visit 1 N (%) | | |
| Visit 4 | - | = | + | - | = | + | - | = | + |
| Hematocrit | | | | | | | | | |
| - | 18 (9.3) | 17 (8.8) | 0 (0.0) | 18 (9.2) | 22 (11.3) | 0 (0.0) | 27 (13.9) | 15 (7.7) | 0 (0.0) |
| = | 2 (1.0) | 78 (40.4) | 11 (5.7) | 0 (0.0) | 74 (37.9) | 9 (4.6) | 1 (0.5) | 74 (38.1) | 11 (5.7) |
| + | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (2.1) | 1 (0.5) | 0 (0.0) | 3 (1.5) |
| Erythrocytes | | | | | | | | | |
| - | 28 (14.5) | 16 (8.3) | 0 (0.0) | 21 (10.8) | 24 (12.3) | 0 (0.0) | 32 (16.5) | 21 (10.8) | 0 (0.0) |
| = | 2 (1.0) | 77 (39.9) | 2 (1.0) | 4 (2.1) | 73 (37.4) | 3 (1.5) | 1 (0.5) | 76 (39.2) | 1 (0.5) |
| + | 0 (0.0) | 0 (0.0) | 1 (0.5) | 0 (0.0) | 0 (0.0) | 2 (1.0) | 0 (0.0) | 0 (0.0) | 1 (0.5) |
| Monocytes | | | | | | | | | |
| - | 4 (2.1) | 74 (38.3) | 0 (0.0) | 0 (0.0) | 62 (31.8) | 0 (0.0) | 3 (1.5) | 86 (44.3) | 1 (0.5) |
| = | 1 (0.5) | 46 (23.8) | 1 (0.5) | 2 (1.0) | 61 (31.3) | 2 (1.0) | 1 (0.5) | 39 (20.1) | 2 (1.0) |
| + | 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) |
| 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) | 120 (62.2) | 4 (2.1) | 0 (0.0) | 124 (63.6) | 2 (1.0) | 0 (0.0) | 129 (66.5) | 1 (0.5) |
| + | 0 (0.0) | 2 (1.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.5) | 0 (0.0) | 1 (0.5) | 1 (0.5) |

(continued)

**TABLE 33 -Hematology values changing from normal to abnormal or abnormal to normal between Visit 1 and Visit 4 (Cont'd)**

| | Palonosetron 0.25 mg (N = 193) | | | Palonosetron 0.75 mg (N = 196) | | | Dolasetron 100 mg (N = 194) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 N (%) | | | Visit 1 N (%) | | | Visit 1 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) | 125 (64.8) | 1 (0.5) | 0 (0.0) | 127 (65.1) | 0 (0.0) | 0 (0.0) | 132 (68.0) | 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 (0.0) |

Source: Appendix 8-1 3 2, Table 3
- = 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 5-8

Scanned from Table 8.2.1-b, page 188-189, Volume 135

***Medical Officer Comments:*** *Most hematology parameters changed to below the reference range at Visit 4. This is likely secondary to chemotherapy. Overall, 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. This was based on whether the value changed more than one toxicity grade (NCI criteria). 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 = 193) | | Palonosetron 0.75 mg (N = 195) | | Dolasetron 100 mg (N = 194) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| **Hemoglobin** | | | | | | |
| Visit 1 (Screening) | 4 | 2.1 | 7 | 3.6 | 7 | 3.6 |
| Visit 3 (Study Day 2) | 2 | 1.0 | 4 | 2.1 | 4 | 2.1 |
| Visit 4 (Study Day 6-8) | 6 | 3.1 | 3 | 1.5 | 5 | 2.6 |
| **Hematocrit** | | | | | | |
| Visit 1 (Screening) | 0 | 0.0 | 6 | 3.1 | 5 | 2.6 |
| Visit 3 (Study Day 2) | 1 | 0.5 | 3 | 1.5 | 2 | 1.0 |
| Visit 4 (Study Day 6-8) | 2 | 1.0 | 3 | 1.5 | 2 | 1.0 |
| **Erythrocytes** | | | | | | |
| Visit 1 (Screening) | 0 | 0.0 | 6 | 3.1 | 4 | 2.1 |
| Visit 3 (Study Day 2) | 0 | 0.0 | 2 | 1.0 | 2 | 1.0 |
| Visit 4 (Study Day 6-8) | 3 | 1.6 | 1 | 0.5 | 2 | 1.0 |
| **Leukocytes** | | | | | | |
| Visit 1 (Screening) | 2 | 1.0 | 1 | 0.5 | 4 | 2.1 |
| Visit 3 (Study Day 2) | 4 | 2.1 | 2 | 1.0 | 2 | 1.0 |
| Visit 4 (Study Day 6-8) | 27 | 14.0 | 20 | 10.3 | 31 | 16.0 |
| **Lymphocytes** | | | | | | |
| Visit 1 (Screening) | 1 | 0.5 | 1 | 0.5 | 2 | 1.0 |
| Visit 3 (Study Day 2) | 5 | 2.6 | 10 | 5.1 | 4 | 2.1 |
| Visit 4 (Study Day 6-8) | 16 | 8.3 | 18 | 9.2 | 15 | 7.7 |
| **Neutrophils** | | | | | | |
| Visit 1 (Screening) | 1 | 0.5 | 1 | 0.5 | 2 | 1.0 |
| Visit 3 (Study Day 2) | 4 | 2.1 | 2 | 1.0 | 1 | 0.5 |
| Visit 4 (Study Day 6-8) | 15 | 7.8 | 11 | 5.6 | 20 | 10.3 |
| **Eosinophils** | | | | | | |
| 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) | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

(continued)

**TABLE 34- Cont'd**

| | Palonosetron 0.25 mg (N = 193) | | Palonosetron 0.75 mg (N = 195) | | Dolasetron 100 mg (N = 194) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| **Basophils** | | | | | | |
| 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 | 0 | 0.0 | 0 | 0.0 |
| **Platelets** | | | | | | |
| Visit 1 (Screening) | 1 | 0.5 | 0 | 0.0 | 1 | 0.5 |
| Visit 3 (Study Day 2) | 0 | 0.0 | 1 | 0.5 | 1 | 0.5 |
| Visit 4 (Study Day 6-8) | 2 | 1.0 | 3 | 1.5 | 3 | 1.5 |

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

Scanned from page 195-196, Volume 135,

***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 = 193) | | Palonosetron 0.75 mg (N = 195) | | Dolasetron 100 mg (N = 194) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| **SGOT** | | | | | | |
| Visit 1 (Screening) | 0 | 0.0 | 0 | 0.0 | 4 | 2.1 |
| Visit 3 (Study Day 2) | 0 | 0.0 | 0 | 0.0 | 1 | 0.5 |
| Visit 4 (Study Day 6-8) | 0 | 0.0 | 3 | 1.5 | 0 | 0.0 |
| **SGPT** | | | | | | |
| Visit 1 (Screening) | 0 | 0.0 | 0 | 0.0 | 4 | 2.1 |
| Visit 3 (Study Day 2) | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Visit 4 (Study Day 6-8) | 1 | 0.5 | 2 | 1.0 | 0 | 0.0 |
| **Alkaline phosphatase** | | | | | | |
| Visit 1 (Screening) | 0 | 0.0 | 1 | 0.5 | 1 | 0.5 |
| Visit 3 (Study Day 2) | 0 | 0.0 | 0 | 0.0 | 1 | 0.5 |
| Visit 4 (Study Day 6-8) | 0 | 0.0 | 0 | 0.0 | 1 | 0.5 |
| **Total bilirubin** | | | | | | |
| Visit 1 (Screening) | 0 | 0.0 | 1 | 0.5 | 0 | 0.0 |
| Visit 3 (Study Day 2) | 0 | 0.0 | 1 | 0.5 | 0 | 0.0 |
| Visit 4 (Study Day 6-8) | 0 | 0.0 | 1 | 0.5 | 1 | 0.5 |
| **Calcium** | | | | | | |
| Visit 1 (Screening) | 2 | 1.0 | 0 | 0.0 | 0 | 0.0 |
| Visit 3 (Study Day 2) | 1 | 0.5 | 2 | 1.0 | 1 | 0.5 |
| Visit 4 (Study Day 6-8) | 0 | 0.0 | 1 | 0.5 | 1 | 0.5 |
| **Albumin** | | | | | | |
| Visit 1 (Screening) | 4 | 2.1 | 1 | 0.5 | 1 | 0.5 |
| Visit 3 (Study Day 2) | 2 | 1.0 | 1 | 0.5 | 0 | 0.0 |
| Visit 4 (Study Day 6-8) | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Glucose** | | | | | | |
| Visit 1 (Screening) | 1 | 0.5 | 5 | 2.6 | 2 | 1.0 |
| Visit 3 (Study Day 2) | 2 | 1.0 | 8 | 4.1 | 1 | 0.5 |
| Visit 4 (Study Day 6-8) | 4 | 2.1 | 5 | 2.6 | 2 | 1.0 |

(continued)

**TABLE 36 -Cont'd**

| | Palonosetron 0.25 mg (N = 193) | | Palonosetron 0.75 mg (N = 195) | | Dolasetron 100 mg (N = 194) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| **Bicarbonate** | | | | | | |
| Visit 1 (Screening) | 1 | 0.5 | 1 | 0.5 | 0 | 0.0 |
| Visit 3 (Study Day 2) | 0 | 0.0 | 0 | 0.0 | 1 | 0.5 |
| Visit 4 (Study Day 6-8) | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Creatinine** | | | | | | |
| Visit 1 (Screening) | 0 | 0.0 | 1 | 0.5 | 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 | 0 | 0.0 | 0 | 0.0 |
| **Blood urea nitrogen** | | | | | | |
| 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 | 0 | 0.0 | 1 | 0.5 |
| **Potassium** | | | | | | |
| Visit 1 (Screening) | 0 | 0.0 | 0 | 0.0 | 1 | 0.5 |
| Visit 3 (Study Day 2) | 1 | 0.5 | 1 | 0.5 | 0 | 0.0 |
| Visit 4 (Study Day 6-8) | 2 | 1.0 | 1 | 0.5 | 2 | 1.0 |
| **Sodium** | | | | | | |
| Visit 1 (Screening) | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Visit 3 (Study Day 2) | 1 | 0.5 | 1 | 0.5 | 4 | 2.1 |
| Visit 4 (Study Day 6-8) | 1 | 0.5 | 2 | 1.0 | 0 | 0.0 |

Source. Appendix C-8, Listing 3
N = patients with abnormalities
% = percentage of patients with abnormalities

Scanned from Table 8.2.2c, pg. 195-196, Volume 135

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

The following table displays vital sign information.

**TABLE 37- Cont'd**

| Changes from | Palonosetron 0.25 mg (N = 193) N | Min | Mean | Max | Palonosetron 0.75 mg (N = 195) N | Min | Mean | Max | Dolasetron 100 mg (N = 194) N | Min | Mean | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Respiratory rate [breaths/min]** | | | | | | | | | | | | |
| Visit 1 | 185 | | 18.9 | | 186 | | 19.2 | | 181 | | 19.0 | |
| Changes from | | | | | | | | | | | | |
| Visit 1[1] to Visit 3[2] | 177 | | 0.0 | | 174 | | -0.2 | | 175 | | 0.1 | |
| Visit 1 to Visit 4[3] | 179 | | -0.0 | | 176 | | -0.0 | | 178 | | 0.1 | |
| Visit 1 to Visit 5[4] | 103 | | 0.2 | | 103 | | -0.1 | | 103 | | -0.2 | |
| **Heart rate [beats/min]** | | | | | | | | | | | | |
| Visit 1 | 192 | | 79.9 | | 194 | | 79.9 | | 191 | | 79.9 | |
| Changes from | | | | | | | | | | | | |
| Visit 1[1] to Visit 3[2] | 185 | | 0.8 | | 187 | | -1.5 | | 186 | | -1.5 | |
| Visit 1 to Visit 4[3] | 190 | | -0.7 | | 187 | | -1.1 | | 190 | | -0.1 | |
| Visit 1 to Visit 5[4] | 109 | | 0.1 | | 112 | | -1.1 | | 110 | | -1.2 | |

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

Scanned from Table 8.3.1-a , page 216-217. Volume 135

*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=201) | | Palonosetron 0.75 mg (N=197) | | Dolasetron 100 mg (N=194) | |
|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) |
| Holter Patients | 12 | (6.0) | 12 | (6.1) | 6 | (3.1) |

(Reference: Table 6.3-d, page 78, Volume 135)

At Visit 1 the majority of patients had normal ECG (range 65.6% to 74.2%).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 = 193) N | % | Palonosetron 0.75 mg (N = 195) N | % | Dolasetron 100 mg (N = 194) N | % |
|---|---|---|---|---|---|---|
| **Visit 1 to 2 (screening to Study Day 1) Holter patients only[1]** | | | | | | |
| No change | 10 | 83.3 | 7 | 58.3 | 4 | 66.7 |
| Improved | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Deteriorated | 0 | 0.0 | 1 | 8.3 | 0 | 0.0 |
| Missing | 2 | 16.7 | 4 | 33.3 | 2 | 33.3 |
| Normal to normal | 6 | 50.0 | 6 | 50.0 | 3 | 50.0 |
| Normal to abnormal | 0 | 0.0 | 1 | 8.3 | 0 | 0.0 |
| **Visit 1 to 3 (screening to Study Day 2)** | | | | | | |
| No change | 159 | 82.4 | 158 | 81.0 | 170 | 87.6 |
| Improved | 4 | 2.1 | 6 | 3.1 | 2 | 1.0 |
| Deteriorated | 15 | 7.8 | 15 | 7.7 | 12 | 6.2 |
| Missing | 10 | 5.2 | 14 | 7.2 | 7 | 3.6 |
| Normal to normal | 116 | 60.1 | 115 | 59.0 | 133 | 68.6 |
| Normal to abnormal | 10 | 5.2 | 6 | 3.1 | 7 | 3.6 |
| **Visit 1 to 4 (screening to Study Day 6-8)** | | | | | | |
| No change | 149 | 77.2 | 147 | 75.4 | 155 | 79.9 |
| Improved | 7 | 3.6 | 10 | 5.1 | 5 | 2.6 |
| Deteriorated | 11 | 5.7 | 6 | 3.1 | 7 | 3.6 |
| Missing | 24 | 12.4 | 28 | 14.4 | 25 | 12.9 |
| Normal to normal | 110 | 57.0 | 113 | 57.9 | 127 | 65.5 |
| Normal to abnormal | 9 | 4.7 | 3 | 1.5 | 2 | 1.0 |

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 $N_{Hol}$ = 12, palonosetron, 0.75 mg $N_{Hol}$ = 12, dolasetron 100 mg $N_{Hol}$ = 6).

Scanned from Table 8.3.2-a: page 207, Volume 135

***Medical Officer Comments:*** *The majority of patients had no change in ECG. Between Visit 1 and 3, a higher proportion of the 0.25 mg palonosetron group had worsening ECG as rated by the reading cardiologist. The differences were relatively small and no distinct pattern could be delineated.*

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 = 193) | | | | Palonosetron 0.75 mg (N = 195) | | | | Dolasetron 100 mg (N = 194) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | Min | Max | N | Mean | Min | Max | N | Mean | Min | Max |
| **QT** | | | | | | | | | | | | |
| Visit 1[1] | 178 | 368 | | | 180 | 367 | | | 182 | 365 | | |
| Visit 2[2] | 10 | 386 | | | 8 | 364 | | | 4 | 381 | | |
| Visit 3[3] | 183 | 373 | | | 181 | 370 | | | 187 | 373 | | |
| Visit 4[4] | 169 | 369 | | | 167 | 370 | | | 169 | 370 | | |
| Visit 2, 3 and 4 | 188 | 371 | | | 187 | 370 | | | 191 | 372 | | |
| Changes from | | | | | | | | | | | | |
| Visit 1 to 2 | 10 | 9.3 | | | 8 | -4.3 | | | 4 | 16.8 | | |
| Visit 1 to 3 | 169 | 5.8 | | | 172 | 4.2 | | | 177 | 6.9 | | |
| Visit 1 to 4 | 157 | 0.7 | | | 157 | 4.3 | | | 160 | 4.3 | | |
| Visit 1 to 2, 3, 4 | 174 | 3.4 | | | 176 | 4.1 | | | 181 | 5.7 | | |
| Maximum change | 174 | 12.2 | | | 176 | 11.9 | | | 181 | 14.6 | | |
| **QTc by Bazett** | | | | | | | | | | | | |
| Visit 1[1] | 178 | 414 | | | 180 | 409 | | | 182 | 408 | | |
| Visit 2[2] | 10 | 419 | | | 8 | 405 | | | 4 | 422 | | |
| Visit 3[3] | 183 | 419 | | | 181 | 414 | | | 187 | 416 | | |
| Visit 4[4] | 169 | 414 | | | 167 | 409 | | | 169 | 412 | | |
| Visit 2, 3 and 4 | 188 | 417 | | | 187 | 412 | | | 191 | 414 | | |
| Changes from | | | | | | | | | | | | |
| Visit 1 to 2 | 10 | -5.6 | | | 8 | -2.8 | | | 4 | 20.8 | | |
| Visit 1 to 3 | 169 | 5.5 | | | 172 | 4.8 | | | 177 | 7.7 | | |
| Visit 1 to 4 | 157 | 1.2 | | | 157 | 0.0 | | | 160 | 3.0 | | |

(continued)

**TABLE 40 – cont'd**

| | Palonosetron 0.25 mg (N = 193) | | | | Palonosetron 0.75 mg (N = 195) | | | | Dolasetron 100 mg (N = 194) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | Min | Max | N | Mean | Min | Max | N | Mean | Min | Max |
| Visit 1 to 2, 3, 4 | 174 | 3.3 | | | 176 | 2.7 | | | 181 | 5.3 | | |
| Maximum change | 174 | 10.3 | | | 176 | 10.1 | | | 181 | 12.9 | | |
| **QTc by Fridericia** | | | | | | | | | | | | |
| Visit 1[1] | 178 | 398 | | | 180 | 394 | | | 182 | 393 | | |
| Visit 2[2] | 10 | 407 | | | 8 | 391 | | | 4 | 408 | | |
| Visit 3[3] | 183 | 403 | | | 181 | 398 | | | 187 | 401 | | |
| Visit 4[4] | 169 | 398 | | | 167 | 395 | | | 169 | 397 | | |
| Visit 2, 3 and 4 | 188 | 401 | | | 187 | 397 | | | 191 | 399 | | |
| Changes from | | | | | | | | | | | | |
| Visit 1 to 2 | 10 | -0.6 | | | 8 | -3.5 | | | 4 | 19.3 | | |
| Visit 1 to 3 | 169 | 5.6 | | | 172 | 4.6 | | | 177 | 7.4 | | |
| Visit 1 to 4 | 157 | 1.1 | | | 157 | 1.5 | | | 160 | 3.5 | | |
| Visit 1 to 2, 3, 4 | 174 | 3.4 | | | 176 | 3.2 | | | 181 | 5.4 | | |
| Maximum change | 174 | 9.7 | | | 176 | 9.9 | | | 181 | 12.3 | | |

Source: Appendix B-1.3.3, Table 4
N = patients with changes
[1] Visit 1 = screening
[2] Visit 2, Study Day 1 (15 minutes after study medication administration) for Holter patients only, calculation of percentages based on $N_{Hol}$ (palonosetron 0.25 mg $N_{Hol}$ = 12, palonosetron 0.75 mg $N_{Hol}$ = 12, dolasetron 100 mg $N_{Hol}$ = 6)
[3] Visit 3 = Study Day 2
[4] Visit 4 = Study Day 6-8

Scanned form Table 8.3.2-b, page 220-221, Volume 135

***Medical Officer Comments:*** *There were no relevant differences seen between treatment groups for the mean duration of QTc. The 0.25 palonosetron group showed a mean change in QTc interval that was less than was seen in the dolasetron arm. However, the maximal change in QTc was highest in the palonosetron 0.25 mg arm, although the mean change was lower than the dolasetron arm.*

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 = 193) | | Palonosetron 0.75 mg (N = 195) | | Dolasetron 100 mg (N = 194) | |
|---|---|---|---|---|---|---|
| Changes from | N | % | N | % | N | % |
| **Visit 1[1] to Visit 2[2,3] (Holter patients only)** | | | | | | |
| QT 30 to 60 msec | 2 | 16.7 | 0 | 0.0 | 1 | 16.7 |
| QT > 60 msec | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| QTc by B 30 to 60 msec | 1 | 8.3 | 0 | 0.0 | 1 | 16.7 |
| QTc by B > 60 msec | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| QTc by F 30 to 60 msec | 1 | 8.3 | 0 | 0.0 | 1 | 16.7 |
| 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 | 24 | 12.4 | 23 | 11.8 | 21 | 10.8 |
| QT > 60 msec | 2 | 1.0 | 1 | 0 5 | 2 | 1.0 |
| QTc by B 30 to 60 msec | 17 | 8.8 | 14 | 7.2 | 17 | 8 8 |
| QTc by B > 60 msec | 2 | 1.0 | 1 | 0.5 | 3 | 1.5 |
| QTc by F 30 to 60 msec | 11 | 5.7 | 15 | 7.7 | 20 | 10.3 |
| QTc by F > 60 msec | 1 | 0.5 | 0 | 0.0 | 1 | 0.5 |
| **Visit 1[1] to Visit 4[5]** | | | | | | |
| QT 30 to 60 msec | 15 | 7.8 | 17 | 8.7 | 22 | 11.3 |
| QT > 60 msec | 1 | 0.5 | 2 | 1.0 | 2 | 1.0 |
| QTc by B 30 to 60 msec | 10 | 5.2 | 11 | 5.6 | 13 | 6.7 |
| QTc by B > 60 msec | 1 | 0.5 | 0 | 0.0 | 2 | 1.0 |
| QTc by F 30 to 60 msec | 7 | 3.6 | 7 | 3.6 | 10 | 5.2 |
| QTc by F > 60 msec | 1 | 0.5 | 0 | 0.0 | 1 | 0.5 |

Source: Appendix B-1.3.3, Table 7
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 $N_{Hol}$ = 12, palonosetron 0.75 mg $N_{Hol}$ = 12, dolasetron 100 mg $N_{Hol}$ = 6)
[3] Study Day 1 (15 minutes after study medication administration)
[4] Study Day 2
[5] Study Day 6-8

Scanned from Table 8.3.2-c, page 224, Volume 135,

***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 fewer patient or equal number of patients in this group. Only one patient in the palonosetron group had a change in QTc from ≤500 msec to >500 msec. Three patients in the dolasetron group had such a change.*

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 = 193) | | Palonosetron 0.75 mg (N = 195) | | Dolasetron 100 mg (N = 194) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Visit 1 (screening) | 14 | 7.3 | 10 | 5.1 | 8 | 4.1 |
| Visit 2 (Study Day 1)[1] | 3 | 25.0 | 1 | 8.3 | 0 | 0.0 |
| Visit 3 (Study Day 2) | 15 | 7.8 | 12 | 6.2 | 10 | 5.2 |
| Visit 4 (Study Day 6-8) | 11 | 5.7 | 7 | 3.6 | 7 | 3.6 |

Source: Appendix B-1.3.3, Table 3
N = patients with abnormalities
% = percentage of patients with abnormalities
[1] Calculation of percentages based on $N_{Hol}$ (palonosetron 0.25 mg $N_{Hol}$ = 12, palonosetron 0.75 mg $N_{Hol}$ = 12, dolasetron 100 mg $N_{Hol}$ = 6)

***Medical Officer Comments:*** *A slightly higher percentage of the palonosetron 0.25 mg group had ECG findings which were assessed to be clinically relevant. The judgement of clinical relevance was based on the subjective opinion of a blinded cardiologist. There were a relatively small number of patients who had ECG's available for Visit 2 (30 patients). Thus the percentage with abnormalities is high in the 0.25 mg palonosetron group despite only 3 patients having abnormal ECG's.*

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 blinded 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) | | Dolasetron 100 mg (N=14) | |
|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) |
| **Holter Interpretation** | | | | | | |
| Normal | 8 | (66.7) | 10 | (83.3) | 5 | (83.3) |
| Abnormal | 4 | (33.3) | 2 | (16.7) | 2 | (16.7) |
| **Clinical Relevance** | | | | | | |
| Relevant | 3 | (25.0) | 1 | (8.3) | 2 | (0.0) |
| Irrelevant | 1 | (8.3) | 1 | (8.3) | 0 | (16.7) |

[1] Patients with data available: Palonosetron 0.25 mg =19, palonosetron 0.75 mg =14, dolasetron = 12
(Reference: Table 8.3.3-a, page 227,Volume 135)

The following are details about the patients with abnormal Holter monitor results that were judged to be clinically relevant in the palonosetron group.

- Patient #4026 (palonosetron group 0.25 mg) was a 46 year old female with breast cancer. She had non-sustained ventricular tachycardia note on Study Day 3 with a heart rate of 73. She had no cardiac history.

- Patient #4174 (palonosetron group 0.25 mg) was a 62 year old female with breast cancer. She had a history of hypothyroidism. She had transient second degree heart block on Study Day 3.

- Patient #4464 (palonosetron group 0.25 mg) was a 86 year old male with a history esophageal and prostate cancer. lung cancer. He had a history of myocardial infarction in the past.. On Study Day 2, he had a non-sustained ventricular tachycardia with a heart rate of 82

- Patient #4267 (palonosetron group 0.75 mg) was a 79 year old male with a history of congestive heart failure, coronary artery disease, and hypertension. He experienced non-sustained ventricular tachycardia on Study Day 2 (prior to receiving the study drug) and at Study Day 3.

Two patients had abnormal a Holter monitor in the control group. This was judged as clinically relevant by the reviewing cardiologists.

***Medical Officer Comments:*** *It is likely that Patients #4464 and #4267 had abnormal Holter monitor readings due to underlying medical conditions unrelated to the study drug. This is less certain for Patients #4026 and #4174. However, both these abnormalities were self-limiting and apparently did not result in clinical symptoms.*

## VII. Conclusion

The primary objective of the study PALO-99-04 was to compare the efficacy of single IV doses of palonosetron 0.25 mg or 0.75 mg, to dolasetron 100 mg IV in preventing moderately emetogenic CINV. The secondary objectives were to evaluate the safety and tolerability of palonosetron and its relative safety in comparison with dolasetron. In addition, the effect of anti-emetic control with palonosetron or dolasetron on the quality of life of patients receiving moderately emetogenic chemotherapy was evaluated. 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 dolasetron. The lower limit of the 97.5% confidence interval for the difference in complete response rates between the dolasetron 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 dolasetron revealed differences in favor of palonosetron 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 Day 4 and 5. (Dolasetron had statistically less number of emetic episodes for Day 5.)
- Time to first emetic episode
- Severity of Nausea except for Study Day 1 and Study Day 5
- Function of Living Index-Emesis total score for the 24-96 hour time interval.

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

- Need of rescue medication
- Time to rescue medications
- Global satisfaction except for Study Day 3 which dolasetron was better
- Function of Living Index-Emesis except for 24-96 hours nausea scores where dolasetron was better.

The palonosetron 0.75 mg dose showed better efficacy when compared to dolasetron for complete control on Study Days 3 and 4, as well as severity of nausea on Study Day 4. This dose also had a fewer number of emetic episodes than dolasetron group for Study Day 3. All other secondary endpoint results were in favor of the dolasetron or showed no statistically significant difference between palonosetron 0.75 mg and dolasetron. However, the p-values for 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 the 0.25 mg palonosetron dose and dolasetron 100 mg was above the pre-set threshold of -15 % in male and female patients. For the palonosetron 0.75 mg group the confidence interval's lower limit was –28.4% for males and –8.2% for the females. This result for the palonosetron 0.75 mg dose in the males does not meet the pre-set threshold.

Naïve patients had a slightly higher complete response rate than non-naïve patients in all but the palonosetron 0.75 mg group. In naïve patients, the lower limits of the 97.5% confidence intervals for the difference between both palonosetron doses and dolasetron were above the preset threshold of –15% (-0.7%, -5.4% respectively). This indicates non-inferiority of palonosetron 0.25 mg to dolasetron in the naïve patients. However, in non-naïve patients the lower limits of the 97.5% confidence intervals for the difference in complete response rates were below the pre-set -15% threshold (-17.5% for the 0.25 mg dose, -25.9% for the 0.75 mg dose). This study failed to establish non-inferiority of palonosetron for non-naïve subjects.

There were some weaknesses in the study. 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. If a site only had one drug available, the patient was automatically enrolled in that treatment arm. This does not reflect true randomization. Although the palonosetron seems to demonstrate some efficacy at 120 hours, some factors need to be considered. The p-values were not adjusted for multiple endpoints. Since there were multiple secondary endpoints, there may be issues with multiplicity. In addition, the comparator arm dolasetron is not indicated for prevention of CINV at 120 hours. Thus, what the results may be demonstrating is that the nausea from the chemotherapy is simply wearing off.

**B. Safety**

In general, the palonosetron was well tolerated in this study. 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. The number of serious adverse events was lowest in the 0.25 mg palonosetron group and highest in the dolasetron group. Nervous system disorders were the most common class of adverse events in all treatment groups. These were equally spread out in all treatment groups. Headache was the most frequently reported adverse event. This also was balanced in all treatment arms. The majority of adverse events in all treatment arms were of mild intensity. The rate of severe adverse events was highest in the 0.75 mg palonosetron group and lowest in the 0.25 mg group. The body system most frequently involved for severe adverse events was infection and infestation for all 3 treatment arms. All the serious adverse events in the palonosetron group were judged to be unrelated or unlikely to be related to the study drug. There were 3 deaths reported during the study. Two occurred in the palonosetron 0.25 mg group and 1 in the 0.75 mg group. All deaths were judged as either unlikely or unrelated to the study drug.

No significant safety issues were seen in vital signs, blood, or urine laboratory parameters. The majority of patients had no change in ECG. The 0.25 mg palonosetron group had the highest percentage of patients with worsening ECG's but the difference was slight (5.7% vs. 3.6% for dolasetron). There were no significant differences seen

between treatment groups in mean duration of QTc. The 0.25 palonosetron group showed a smaller mean QTc duration compared to the dolasetron. However, this group did have the highest QT/QTc maximum change in duration. A subset of patients had undergone Holter monitoring. Three patients had clinically relevant abnormalities noted on Holter monitor after receiving palonosetron. One of these patients had underlying pre-existing cardiac disease. There were no incidences of Torsades de pointe. It is unclear if the abnormalities are related to the study drug in the other two patients.



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# CLINICAL REVIEW STUDY 99-03
# PALONOSETRON

**Detailed Review Of Study PALO-99-03 – A Double Blind Clinical Study To Compare Single IV Dose Of Palonosetron, 0.25 Mg Or 0.75 Mg And Ondansetron, 32 Mg IV, In Prevention Of Moderately Emetogenic Chemotherapy-Induced Nausea And Vomiting**

## I. OBJECTIVES

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.

## II. STUDY DESIGN AND METHODOLOGY

This was a double-blind clinical study to compare single IV doses of palonosetron 0.25 mg or 0.75 mg, and ondansetron 32 mg IV, in the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. The comparator drug ondansetron is an FDA approved medication that is indicated for the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. The dose of ondansetron is the standard dose used in clinical practice. The table on the following page lists the study procedures.

**TABLE 1 : Study Flow Chart**

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

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

(Reference Table 5.5-a , Page 38, volume 117)

Screening Study Day -7 to 0 (Visit 1)
Patients signed an informed consent and then had their demographic information recorded. The investigator performed an initial history and physical examination. Eligibility criteria were examined and the patient underwent laboratory studies. This included 12 lead ECG, blood chemistry, complete blood count and urinalysis. A urine pregnancy test was done for females of childbearing potential as well. Patients were instructed on how to use the diaries to record nausea and episodes of emesis. If patients were randomized to get a Holter monitor, this was started 2 hours before the start of the study medication administration.
Study Day 1 (Visit 2)
Study Day 1 was defined as the day the patient received a single dose of a major chemotherapeutic agent that was considered the most emetogenic (as classified by Hesketh et al., The Oncologist 1999:4:191-196). The administration of this agent was not to extend greater than 4 hours.
Each patient was randomized to 1 of 3 treatment groups

- Palonosetron 0.25 mg given as a single dose over 30 seconds, 30 minutes prior to chemotherapy
- Palonosetron 0.75 mg given as a single dose over 30 seconds, 30 minutes prior to chemotherapy
- Ondansetron 32 mg given as IV infusion over 15 minutes, 30 minutes prior to chemotherapy

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

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

***Medical Officer Comments:*** *All study sites should have been provided with ample supplies of the study drug and the active control. This would have allowed true randomization. If a site only had one drug available, the patient was automatically enrolled in that treatment arm. This does not reflect true randomization. However, this only occurred in five patients (2 in each of the palonosetron arms, and 1 in the*

*ondansetron arm)and did not invalidate the data. In addition, the applicant should have considered sending each site an unlabeled kit containing the study drug, or active control medication. This would have allowed the research pharmacist to remain blinded, and permitted all personnel at each site to be blinded to the treatment.*

Study Day 2 (Visit 3)
Patients returned 24 hours after the study medication administration to the study site. They underwent a repeat physical examination, 12 lead ECG, laboratory evaluation and documentation of adverse events. For patients who were selected to have a Holter monitor it was removed 22 hours after the start of the study medication.
Study Day 5 (Telephone contact 1)
All patients were contacted by telephone for adverse events and concomitant medication recording.
Study Day 6 to 8 (Visit 4)
Patients underwent a repeat physical examination, 12 lead ECG, laboratory evaluation and documentation of adverse events. For patients who were selected to have a Holter monitor it was removed 22 hours after the start of the study medication. At this visit the 5-day patient diary was completed.
Study Day 15 (Telephone contact 2)
All patients were contacted by telephone, and adverse events and concomitant medication were recorded.

## III. ELIGIBILITY CRITERIA

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

- Chemotherapy naïve subjects with histologically or cytologically confirmed malignant disease
- Chemotherapy non-naïve subjects with histologically proven diagnosis of cancer
- Have a Karnofsky index of ≥ 50%.
- Scheduled to receive a single dose of at least one of the following agents administered on Day 1 of the study: any dose of carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan or mitoxantrone; or methotrexate > 250 mg/m$^2$; or cyclophosphamide <1500 mg/m$^2$ IV; doxorubicin > 25 mg/m$^2$ IV; or cisplatin ≤ 50 mg/m$^2$ IV (to be administered over 1-4 hours).[a]
- If a subject has a known hepatic, renal or cardiovascular impairment and is scheduled to receive the above-mentioned chemotherapeutic agents, he/she may be enrolled in this study at the discretion of the investigator.
- If a subject experienced no more than mild nausea following any previous chemotherapy regimen, he/she could have been enrolled at the discretion of the investigator.

The following are exclusion criteria:

- Unable to understand or cooperate with study procedure

- Received any investigational drug 30 days prior to study entry
- Received any drug or were scheduled to receive any drug with anti-emetic efficacy within 24 hours of the start of treatment until Day 5 of the study
- Enrollment in a previous study with palonosetron
- Seizure disorder requiring anticonvulsant medication unless clinically stable and free of seizure activity
- Experienced any vomiting, retching, or NCI Common Toxicity Criteria grade 2 or 3 nausea in the 24 hours preceding chemotherapy.
- Ongoing vomiting from any organic etiology
- Experienced nausea (moderate to severe or vomiting following any previous chemotherapy. At the discretion of the investigator , a patient who experienced at maximum mild nausea following any previous chemotherapy might not be excluded from this study)
- Scheduled to receive any dose of a chemotherapeutic agent with an emetogenicity level 5 according to Hesketh et al Classification (The Oncologist 1999; 4:191-196) or were scheduled to receive any chemotherapeutic agent with an emetogenicity level 3 or higher during Days 2-6
- Known contraindication to 5-$HT_3$ antagonist
- Scheduled to receive radiotherapy of the upper abdomen or cranium during Study Day 2

***Medical Officer Comments:*** *The inclusion criteria are adequate. These doses of chemotherapy are considered moderately emetogenic according to the classification by Hesketh, et al., The Oncologist 1999. The exclusion criteria are adequate with one exception. The protocol excludes patients who had previous nausea or vomiting with previous chemotherapy. This could introduce bias into the study. Patients who are not chemotherapy naïve and enter the study are subjects who tolerate chemotherapy well with respect to emetogenicity. This could make the results appear more favorable in this subset of patients. However, the agency did agree to these criteria in a Special Protocol Assessment dated December 1999. The results demonstrated that for the 0.25 mg dose naïve subjects had a better response rate than non-naïve subjects.*

## IV. STATISTICAL ANALYSIS

PALO-99-03 was an active comparator, non-inferiority analysis that employed a 15% delta. The primary efficacy parameter in these trials was the proportion of subjects considered to have achieved a complete response (CR) during the first 24 hours after administration of chemotherapy. CR is defined as no emesis and no rescue medication during the first 24 hours after chemotherapy.

The lower bound of 97.5% CI for the difference (palonosetron minus active comparator) between the proportion of subjects with a complete response during the first 24 hours after administration of chemotherapy was calculated and compared to the pre-set threshold (-15% difference) to demonstrate non-inferiority. To demonstrate that the two palonosetron doses were equal with respect to CR (0–24 hours), the bounds of the two-sided 95% CI of the difference between the proportions of CR (0–24 hours) were compared to the pre-set threshold (± 15%). The intent to treat (ITT) population was used

in the primary analysis. Table 2 displays the various statistical methods used for the secondary efficacy parameters at various time intervals.

**TABLE 2 – Statistical Test Utilized for Secondary Efficacy Parameters**

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

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

Validity was demonstrated if:

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

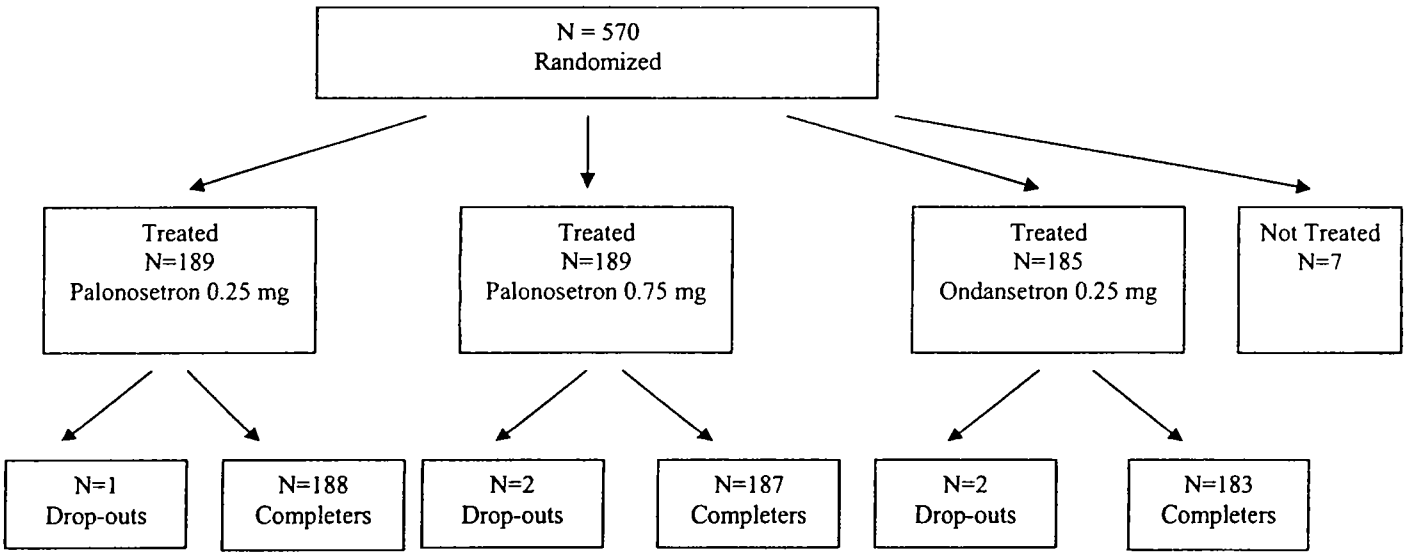
***Medical Officer Comments:*** *The Agency and the applicant agreed to this approach to validation in pre-NDA meetings and end of Phase II meetings held in spring of 1999.*

## V. RESULTS

### A. Demographics and Disposition of Patients

Fifty-Eight centers enrolled 571 patients. Of these, 570 were randomized to one of the three treatment groups (1 patient was not randomized and did not receive treatment). The following figure shows the disposition of patients.

**FIGURE 1 – Disposition of Patients**




From Figure 6.1-1, Volume 117, pg. 72

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

- 2 dropped out because of patient decision
- 1 dropped out due to non-serious adverse event (in the 0.75 mg group)

One patient dropped out due to patient decision and one patient dropped out due to adverse event in the ondansetron group.

The following table shows the number of patients by region. The United Kingdom had only seven patients so they were pooled with the Netherlands patients. Russia was divided into 3 regions: Arkhangelsk, Moscow, and St. Petersburg.

**TABLE 3 – List of Patients by Region**

| Country (Active centers) | Patients Randomized | Gender | | Chemotherapeutic History | | Holter Monitor Performed |
|---|---|---|---|---|---|---|
| | | Male | Female | Naïve | Non-Naïve | |
| Germany (16) | 124 | 69 | 55 | 30 | 94 | 3 |
| Italy (10) | 54 | 12 | 42 | 25 | 29 | 2 |
| U.K./Netherlands (9) | 64 | 3 | 61 | 34 | 30 | 3 |
| Arkahangelsk (2) | 58 | 33 | 25 | 28 | 30 | 8 |
| Moscow (10) | 121 | 7 | 114 | 57 | 64 | 11 |
| St. Petersburg (11) | 149 | 35 | 114 | 63 | 86 | 22 |
| Total (58) | 570 | 159 | 411 | 237 | 333 | 49 |

(Reference: Table 6.1-a, pg. 71, Volume 117)

St. Petersburg, Germany and Moscow were the regions that enrolled the largest number of patients.

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

**TABLE 4 - Gender/Chemotherapeutic History**

| | Palonosetron 0.25 mg (N=189) N (%) | Palonosetron 0.75 mg (N=189) N (%) | Ondansetron 32 mg (N=185) N (%) |
|---|---|---|---|
| **Gender** | | | |
| Male | 54 (28.6) | 51 (27) | 52 (28.1 |
| Female | 135 (71.4) | 138 (73) | 133 (71.9) |
| **Chemotherapeutic History** | | | |
| Naïve | 76 (40.2) | 80 (42.3) | 78 (42.2) |
| Non-naive | 113 (59.8) | 109 (57.7) | 107 (57.8) |

(Reference: Table 6.3-b, pg. 76, Volume 117)

***Medical Officer Comments:*** *The distribution of patients by gender and chemotherapeutic history is similar across treatment groups. The majority of patients were female and non-naïve. This is because moderate emetogenic chemotherapy is most frequently given for breast cancer.*

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

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

| Type of Cancer | Palonosetron 0.25 mg (N=189) N (%) | Palonosetron 0.75 mg (N=189) N (%) | Ondansetron 32 mg (N=185) N (%) |
|---|---|---|---|
| Breast Cancer female – nos | 114 (60.3) | 103 (54.3) | 105 (56.8) |
| Lung Cancer | 14 (7.4) | 11 (5.8) | 18 (9.7) |
| Colon cancer- nos | 11 (5.8) | 11 (5.8) | 3 (1.6) |
| Rectal Cancer- nos | 7 (3.7) | 2 (1.1) | 8 (4.3) |
| Small cell lung cancer stage unspecified | 7 (3.7) | 9 (4.8) | 3 (1.6) |
| Gastric cancer- nos | 6 (3.2) | 6 (3.2) | 6 (3.2) |
| Prostate cancer- nos | 6 (3.2) | 1 (0.5) | 3 (1.6) |
| Bladder cancer- nos | 5 (2.6) | 12 (6.3) | 12 (6.5) |
| Hodgkin's disease- nos | 3 (1.6) | 1 (0.5) | 2 (1.1) |
| Ovarian cancer- nos | 2 (1.1) | 4 (2.1) | 7 (3.8) |
| Bile duct cancer- nos | 0 (0.0) | 3 (1.6) | 1 (0.5) |

(Reference: Table 6.4.2-a, pg. 83, Volume 117)

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

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

**TABLE 6 – Demographic Data of Patients**

| | Palonosetron 0.25 mg (N=189) | | Palonosetron 0.75 mg (N=189) | | Ondansetron 32 mg (N=185) | |
|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) |
| **Gender** | | | | | | |
| Male | 54 | (28.6) | 51 | (27) | 52 | (28.1 |
| Female | 135 | (71.4) | 138 | (73) | 133 | (71.9) |
| **Ethnic Group** | | | | | | |
| White | 186 | (98.4) | 188 | (99.5) | 183 | (98.9) |
| Black | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Hispanic | 1 | (0.5) | 0 | (0.0) | 1 | (0.5) |
| Asian | 2 | (1.1) | 0 | (0.0) | 0 | (0.0) |
| Other | 0 | (0.0) | 1 | (0.5) | 1 | (0.5) |
| **Tobacco Use** | | | | | | |
| Non-smoker | 132 | (69.8) | 132 | (69.8) | 127 | (68.6) |
| Ex-smoker | 28 | (14.8) | 19 | (14.8) | 23 | (12.4) |
| Smoker | 28 | (14.8) | 38 | (20.1) | 35 | (18.9) |
| **Alcohol consumption** | | | | | | |
| No | 89 | (47.1) | 84 | (44.4) | 78 | (42.2) |
| Rarely | 75 | (39.7) | 71 | (37.6) | 72 | (39.5) |
| Occasionally | 15 | (7.9) | 27 | (14.3) | 23 | (12.4) |
| Regularly | 9 | (4.8) | 7 | (3.7) | 11 | (5.9) |

(Reference: Table 6.41-a, pg. 78, Volume 117)

***Medical Officer Comments:*** *Overall the treatment arms were balanced in regard to baseline demographic characteristics. Male patients were slightly older than female patients. In addition, more smoking and higher alcohol consumption were found in the male population as opposed to the female patients. Another notable fact* is *the lack of Black, Asian and Hispanic patients. This is not surprising given that the investigative sites were predominantly in Europe.*

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

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

| | Palonosetron 0.25 mg (N=189) | | Palonosetron 0.75 mg (N=189) | | Ondansetron 32 mg (N=185) | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| **Age (years)** | 56.1 | 11.7 | 54.8 | 10.1 | 55.3 | 10.8 |
| **Height (cm)** | 165 | 7.2 | 165.4 | 8.5 | 165.5 | 8.1 |
| **Weight (kg)** | 71.7 | 13.3 | 69.4 | 13.6 | 71.0 | 13.0 |
| **Karnofsky Index (%)** | 88.9 | 9.6 | 89.5 | 10.7 | 88.5 | 10.9 |

(Reference Table 6.4.1-a, pg. 78, Volume 117)

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

**TABLE 8 –Risk Factors for Patients**

| | Palonosetron 0.25 mg (N=189) | Palonosetron 0.75 mg (N=189) | Ondansetron 32 mg (N=185) |
|---|---|---|---|
| | N (%) | N (%) | N (%) |
| **Renal Impairment** | | | |
| Yes | 14 (7.4) | 19 (10.1) | 16 (9.2) |
| No | 175 (92.6) | 170 (89.9) | 168 (90.8) |
| **Hepatic Impairment** | | | |
| Yes | 27 (14.3) | 27 (14.3) | 24(13) |
| No | 162 (85.7) | 162 (85.7) | 161 (87.) |
| **Cardiac Impairment** | | | |
| Yes | 50 (26.5) | 47 (24.9) | 55(29.7) |
| No | 139 (73.5) | 142 (75.1) | 130(70.3) |

(Reference: Table 6.4.1-b, pg. 80, Vol. 117)

***Medical Officer Comments:*** *Most patients did not have any organ impairment but for those who did the most common organ impairment was cardiac.*

The protocol defined prior diseases as those starting before Visit 1 and not ongoing after Visit 1. Concomitant diseases were defined as those starting before Visit 1 and ongoing after Visit 1. The following table lists prior and concomitant diseases. Diseases are listed by the system organ class followed by preferred term according to MedDRA.

**TABLE 9 – Most Common Prior and Concomitant Diseases[1]**

| System Organ Class[2] Preferred Term[3] (MedDRA) | Palonosetron 0.25 mg (N=189) N (%) | Palonosetron 0.75 mg (N=189) N (%) | Ondansetron 32 mg (N=185) N (%) |
|---|---|---|---|
| **Any prior Disease** | 100 (52.9) | 93 (49.2) | 111 (60.0) |
| Infections and infestations | 31 (16.4) | 35 (18.5) | 34 (18.4) |
| Gastrointestinal disorders | 28 (14.8) | 19 (10.1) | 28 (15.1) |
| **Any concomitant diseases** | 151 (79.9) | 149 (78.8) | 148 (80.0) |
| Vascular disorders | 63 (33.3) | 51 (27.0) | 52 (28.1) |
| Hypertension nos (not otherwise specified) | 51 (27.0) | 39 (20.6) | 45 (24.3) |
| Cardiac disorders | 50 (26.5) | 37 (19.6) | 46 (24.9) |
| Myocardial ischemia | 25 (13.5). | 16 (8.5) | 18 (9.7) |
| Metabolism and nutrition disorders | 29 (15.3) | 18 (9.5) | 26 (14.1) |
| Infection and Infestations. | 28 (14.8) | 35 (18.5) | 27 (14.6) |
| Gastrointestinal disorders | 27 (14.3) | 32 (16.9) | 37 (20.0) |
| Neoplasm- benign and malignant | 27 (14.3) | 20 (10.6) | 15 (8.1) |
| Blood and lymphatic system | 24 (12.7) | 28 (14.8) | 24 (13.0) |
| Anemia | 20 (10.6) | 19 (10.1) | 19 (10.3) |

[1] Multiple answers possible
[2] Incidence at least 14% of patients in treatment group
[3] Incidence at least 10% of patients in treatment group
(Reference: Table 6.4.4-a, pg. 88, Vol. 117)

***Medical Officer Comments:*** *There was a slightly higher proportion of patients with gastrointestinal disorders in the ondansetron arm. (20% vs. 14.3% and 10.6%) If these patients were more prone to nausea, this may have led to a bias in favor of the study drug. However, since the difference is slight, it is unlikely to have contributed to a significant difference.*

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

TABLE 10 – Concomitant Medication[1]

| Concomitant Medication[2] | Palonosetron 0.25 mg (N=189) | | Palonosetron 0.75 mg (N=189) | | Ondansetron 32 mg (N=185) | |
|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) |
| Any concomitant medication | 129 | (68.3) | 124 | (65.6) | 125 | (67.6) |
| Analgesics | 41 | (21.7) | 39 | (20.6) | 36 | (19.5) |
| Other analgesics and antipyretics | 31 | (16.4) | 26 | (13.8) | 28 | (15.1) |
| Opioids | 17 | (9.0) | 15 | (7.9) | 20 | (10.8) |
| Antacids, drugs for treatment peptic ulcer | 30 | (15.9) | 38 | (20.1) | 31 | (16.8) |
| All other therapeutic products | 22 | (11.6) | 18 | (9.5) | 23 | (12.4) |
| Anti-inflammatory and anti-rheumatic products | 20 | (10.6) | 17 | (9.0) | 21 | (11.4) |
| Antibacterial for systemic use | 19 | (10.1) | 15 | (7.9) | 16 | (8.6) |
| Antithrombotic agents | 19 | (10.1) | 21 | (11.1) | 18 | (9.7) |
| Psycholeptics | 19 | (10.1) | 15 | (7.9) | 16 | (8.6) |

[1] Multiple answers possible

[2] Incidence at least 10% of patients in treatment group

(Reference: Table 6.4.5-a, pg. 90, Vol. 117)

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

Prior anti-emetic treatments were defined as intake within 12 months before randomization. By this criteria 84 (44%) patients of the 0.25 mg palonosetron group, 76 (40.2%) patients of the 0.75 mg palonosetron group, and 83 (44.9%) of the ondansetron group had prior anti-emetic treatment. Concomitant anti-emetic treatment included all medication taken after Study Day 5. Anti-emetic treatment taken between the administration of the study drug and Study Day 5 was considered rescue therapy and is included in the efficacy results. Concomitant anti-emetic treatment was seen in 29 (15.3%) patients of the 0.25 mg palonosetron group, 20 (10.6%) patients of the 0.75 mg palonosetron group, and 24 (13%) of the ondansetron group. Dexamethasone and metoclopromide were the two most common anti-emetic treatments received prior to the study and after Study Day 5. The use of these agents was balanced in all treatment arms.

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

**TABLE 11 - Chemotherapeutic treatment administered on Study Day 1[1]**

| Substance | Palonosetron 0.25 mg (N=189) | | Palonosetron 0.75 mg (N=189) | | Ondansetron 32 mg (N=185) | |
|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) |
| Cyclophosphamide | 119 | (63.0) | 120 | (63.5) | 117 | (63.2) |
| Doxorubicin | 97 | (51.3) | 87 | (46.0) | 87 | (47.0) |
| Cisplatin | 36 | (19.0) | 33 | (17.5) | 31 | (16.8) |
| Methotrexate | 23 | (12.2) | 32 | (16.9) | 36 | (19.5) |
| Carboplatin | 15 | (7.9) | 25 | (13.2) | 25 | (13.5) |
| Epirubicin | 13 | (6.9) | 17 | (9.0) | 14 | (7.6) |
| Irinotecan | 10 | (5.3) | 8 | (4.2) | 8 | (4.3) |
| Ifosfamide | 2 | (1.1) | 0 | (0.0) | 2 | (1.1) |
| Mitoxantrone | 1 | (0.5) | 1 | (0.5) | 3 | (1.6) |
| Idarubicin | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

[1] Multiple answers possible

(Reference: Table 6.4.3-a, pg. 85, Volume 117)

***Medical Officer Comment:*** *The treatment groups were similar in chemotherapy agents received. . The chemotherapy agents in the study groups are moderately emetogenic. Although cisplatin can be considered highly emetogenic, the dose used here ($\leq 50$ mg/m$^2$ IV ) is considered moderately emetogenic The palonosetron 0.25 mg dose group had fewer patients who received carboplatin compared to the other groups but this should not unduly influence the safety or efficacy data.*

**B. Protocol Deviations**

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

**TABLE 12 – Major Protocol Violations[1]**
**(All patients randomized, N=570)**

| Reason | Palonosetron 0.25 mg (N=192) | | Palonosetron 0.75 mg (N=190) | | Ondansetron 32 mg (N=188) | |
|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) |
| Never received any study drug | 3 | (1.6) | 1 | (0.5) | 3 | (1.6) |
| Intake of rescue medication before first episode on Day 1 | 11 | (5.7) | 10 | (5.3) | 6 | (3.2) |
| Received different kit number than randomized | 2 | (1.0) | 2 | (1.1) | 1 | (0.5) |
| Primary endpoint could not be calculated | 2 | (1.0) | 2 | (1.1) | 0 | (0.0) |
| Code broken | 0 | (0.0) | 0 | (0.0) | 2 | (2.2) |
| No diary card available | 0 | (0.0) | 1 | (0.5) | 1 | (0.5) |
| Emetic episode within 24 hours before chemotherapy | 1 | (0.5) | 1 | (0.5) | 0 | (0.0) |
| Forbidden chemotherapy on Day 1 | 1 | (0.5) | 0 | (0.0) | 1 | (0.5) |
| Forbidden anti-emetics on Day 0 | 0 | (0.0) | 0 | (0.0) | 2 | (1.1) |
| Forbidden anti-emetics on Day 1 | 0 | (0.0) | 0 | (0.0) | 2 | (1.1) |
| Ongoing prior anti-emetic medication. | 0 | (0.0) | 0 | (0.0) | 1 | (0.5) |
| **Total number of patients with major protocol violations** | 17 | (8.9) | 15 | (7.9) | 14 | (7.4) |

[1] Multiple answers possible

(Reference: Table 6.2-a, pg. 74, Volume 117)

***Medical Officer Comments:*** *The percentage of patients with major protocol violations was similar in all treatment arms. The most common protocol violation was the intake of rescue medication before the first emetic episode on Day 1. These patients should be considered treatment failures in the intent to treat analysis.*

The following table shows minor protocol violation for the study.

**TABLE 13 – Minor Protocol Violations[1]**
**(All patients randomized, N=570)**

| Reason | Palonosetron 0.25 mg (N=192) | | Palonosetron 0.75 mg (N=190) | | Ondansetron 32 mg (N=188) | |
|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) |
| Violation of Time window | 21 | (10.9) | 31 | (16.3) | 26 | (13.8 |
| Time between infusion and chemotherapy <25 or >45 minutes | 20 | (10.4) | 21 | (11.1) | 16 | (8.5) |
| Time between bolus and chemotherapy <25 or >45 minutes | 17 | (8.9) | 20 | (10.5) | 15 | (8.0) |
| Intake of rescue mediation before first episode after day 1 | 4 | (2.1) | 6 | (3.2) | 6 | (3.2) |
| Inclusion criterion mission | 1 | (0.5) | 1 | (0.5) | 0 | (0.0) |
| Start or end time of infusion missing | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Cisplatin given <60 minutes | 0 | (0.0) | 2 | (1.1) | 2 | (1.1) |
| Duration of chemotherapy >255 minutes | 1 | (0.5) | 1 | (0.5) | 0 | (0.0) |
| End time of chemotherapy missing | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Forbidden anti-emetics after day 1 | 1 | (0.5) | 0 | (0.0) | 0 | (0.0) |
| Ongoing prior anti-emetic PRN | 1 | (0.5) | 0 | (0.0) | 0 | (0.0) |
| **Total number of patients with minor protocol violations** | 49 | (25.5) | 49 | (25.5) | 49 | (25.5) |

[1] Multiple answers possible

(Reference: From Table 3, pg. 228, Volume 117)

***Medical Officer Comments:*** *The percentage of patients with minor protocol violations was similar in all treatment arms. Again, patients who had inappropriate intake of rescue medication should be considered treatment failures in the intent to treat analysis.*

## C. Efficacy Results

### 1. Primary Efficacy Parameter

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

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

**TABLE 14-Complete Response Rates During the First 24 Hours After Chemotherapy: Moderately Emetogenic CINV Studies PALO-99-03 (ITT Cohort; N = 663)**

| Treatment Group | Complete Response (CR) During the First 24 Hours | | | 97.5% CI for the Difference in CR Rates During the First 24 Hours Between Palonosetron and Active Comparator | |
|---|---|---|---|---|---|
| | N | n (%) | 95% CI | Palonosetron 0.25 mg Minus Active Comparator | Palonosetron 0.75 mg Minus Active Comparator |
| Palonosetron 0.25 mg | 189 | 153 (81.0) | [74.5%, 86.1%] | | |
| Palonosetron 0.75 mg | 189 | 139 (73.5) | [66.6%, 79.6%] | | |
| Ondansetron 32 mg | 185 | 127 (68.6) | [61.4%, 75.1%] | [1.8%, 22.8%]* | [-6.1%, 15.9%] |

CR = Complete Response (defined as no emetic episode and no rescue medication) during the first 24 hours after chemotherapy.
N = Number of subjects in treatment group.
n (%) = number and percentage of subjects with CR.
CI = Confidence Interval.
* = 97.5% CIs for the difference between palonosetron and active comparator (ondansetron ) indicating palonosetron superiority ($p < 0.05$).

***Medical Officer Comments:*** *The lower limit of the 97.5% confidence interval for the difference in complete response rates during the first 24 hours after chemotherapy was above the preset 15% delta. The comparator was adequate. The comparator drug ondansetron is an FDA approved medication that is indicated for the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. Based on this data, the non-inferiority of both palonosetron doses to ondansetron 32 mg was demonstrated for the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting during the first 24 hours after chemotherapy. The lower limit of the 97.5% CI for the comparison of palonosetron 0.25 mg to ondansetron was above zero. It is not clear why the higher dose of palonosetron seemed to have less efficacy.*