- 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 Preferred term (MedDRA)	Palonosetron 0.25 mg (N = 193)			Palonosetron 0.75 mg (N = 195)			Dolasetron 100 mg (N =194)		
	N	%	n	N	%	n	N	%	n
Any 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

TABLE 31 – Serious Adverse Events by Body System and Preferred Term[1] (Cont'd)

System organ class Preferred term (MedDRA)	Palonosetron 0.25 mg (N = 193)			Palonosetron 0.75 mg (N = 195)			Dolasetron 100 mg (N =194)		
	N	%	n	N	%	n	N	%	n
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.

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