

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205718Orig1s000**

**MEDICAL REVIEW(S)**

## **Addendum to Medical Officer's Review**

**Application:** NDA 205718  
**Drug:** Akynzeo (Netupitant + Palonosetron Fixed Dose Combination)  
**Sponsor:** Helsinn Healthcare  
**Reviewer:** Nancy Snow, DO, MPH, Medical Officer  
**Team Leader:** Ruyi He, MD, Medical Team Leader  
**Date:** 9/5/14

### **Introduction:**

The purpose of this addendum is to make a correction to the Medical Officer Review, and to provide additional information not in the original review. The addendum will address four items:

1. An error in the Medical Officer review in which 5 deaths were said to occur in the test drug arm. The review should state that one death occurred in a patient in the test drug arm and 4 deaths occurred in patients in the control arms.
2. To provide additional information regarding protocol violations from clinical trial NETU-07-07.
3. To provide detail on 9 patients with possible drug induced liver injury from NETU-07-07 and PALO10-01.
4. Efficacy analyses for patients older than 65 years

Each of the four items will be discussed separately.

### **Item 1 – Deaths related to the chemotherapeutic agent docetaxel:**

Because of concerns about netupitant increasing the exposure to the chemotherapeutic agents cyclophosphamide, etoposide, ifosfamide and docetaxel the applicant was asked to provide a breakdown of SAEs by chemotherapeutic agent.

Page 91 of the Medical Officer's Review states:

*Of the 16 patients in the NETU+PALO arm who died, 4 (0.2%) received cyclophosphamide, 8 (2.6%) received etoposide and 5 (4.7%) received docetaxel.*

This statement is incorrect and the correct statement should be:

Of the 16 patients in the NETU+PALO arm who died, 2 received cyclophosphamide, 4 received etoposide and 1 received docetaxel as listed in my review on page 89-91.

**Item 2 - Protocol violations in clinical trial NETU-07-07**

Page 11 of the Medical Officer’s Review states:

An additional issue with NETU-07-07 was protocol violations found at clinical site 120 in Russia. The company performed a sensitivity analysis to determine the impact of the site on the overall efficacy results. The FDA statistical reviewer confirmed the sponsor’s re-analysis results and determined that the data of NETU-07-07 supported the efficacy of the study drug, i.e., palonosetron plus netupitant 300 mg, although not all of reanalysis results showed positive findings based on Holm-Bonferroni multiplicity adjustment method.

An FDA information request<sup>1</sup> was sent to the sponsor to obtain more detail on the protocol violations.

The sponsor provided the following tables showing protocol violation details for NETU-07-07, site 120, by treatment arm.

**Table 1 NETU-07-07 violations-site 120 Palonosetron**

Patient ID	Treatment	Category	Violation details	Impact Efficacy	Impact Safety	Comment
NETU-07-07/120/1472	PALONOSETRON 0.5 MG AND DEXAMETHASONE	Eligibility Criteria	Ondansetron	Major	NO	Ondansetron taken 14Jul2008 1 tab. Date of study drug administration 14Jul2008
		Eligibility Criteria	Dexamethasone	NO	NO	Dexamethasone 8 mg, IM, was given on 03Jul2008 i.e. earlier than 72 hours prior to Day 1 (date of study drug administration 14Jul2008).
NETU-07-07/120/1477	PALONOSETRON 0.5 MG AND DEXAMETHASONE	Eligibility Criteria	Ondansetron	Major	NO	Ondansetron taken 23Jul2008 1 tab sublingual. Date of study drug administration 23Jul2008
NETU-07-07/120/1529	PALONOSETRON 0.5 MG AND DEXAMETHASONE	Eligibility Criteria	Dexamethasone	NO	NO	Dexamethasone 8 mg, IM, was given on 07Aug2008 i.e. earlier than 72 hours prior to Day 1 (date of study drug administration 22Aug2008).
NETU-07-07/120/1563	PALONOSETRON 0.5 MG AND DEXAMETHASONE	Eligibility Criteria	Ondansetron	Major	NO	Ondansetron taken 22Aug2008 1 tab. Date of study drug administration 22Aug2008
		Eligibility Criteria	Dexamethasone	NO	NO	Dexamethasone 8 mg, IM, was given on 07Aug2008 i.e. earlier than 72 hours prior to Day 1 (date of study drug administration 22Aug2008).

Source: Sponsor’s table.

<sup>1</sup> NDA205718 Akynzeo (netupitant-palonosetron) Information Request Clinical. 8-26-14.

**Table 2 Netu-07-07-violations site 120- Netupitant 100 mg**

Patient ID	Treatment	Category	Violation details	Impact Efficacy	Impact Safety	Comment
NETU-07-07/120/1476	PALONOSETRON 0.5 MG AND NETUPITANT 100 MG AND DEXAMETHASONE	Eligibility Criteria	Ondansetron	Major	NO	Ondansetron taken 16Jul2008 1 tab. Date of study drug administration 16Jul2008
NETU-07-07/120/1580	PALONOSETRON 0.5 MG AND NETUPITANT 100 MG AND DEXAMETHASONE	Eligibility Criteria	Nausea and vomiting	Major	NO	Nausea and vomiting stop date 17Sep2008. Date of study drug administration 17Sep2008.
		Anti-emetic Concomitant Medication	Metoclopramide	Major	NO	Metoclopramide per os administered from 15Sep2008 to 19Sep2008. Date of study drug administration 17Sep2008.

Source: Sponsor's table.

**Table 3 Netu-07-07-violations-site 120 - Netupitant 200 mg**

Patient ID	Treatment	Category	Violation details	Impact Efficacy	Impact Safety	Comment
NETU-07-07/120/1213	PALONOSETRON 0.5 MG AND NETUPITANT 200 MG AND DEXAMETHASONE	Eligibility Criteria	Ondansetron	Major	NO	Ondansetron taken 21Jul2008 1 tab. Date of study drug administration 21Jul2008
NETU-07-07/120/1474	PALONOSETRON 0.5 MG AND NETUPITANT 200 MG AND DEXAMETHASONE	Eligibility Criteria	Ondansetron	Major	NO	Ondansetron taken 21Jul2008 1 tab sublingual. Date of study drug administration 21Jul2008
		Eligibility Criteria	Dexamethasone	NO	NO	Dexamethasone 8 mg, IM, was given on 08Jul2008 i.e. earlier than 72 hours prior to Day 1 (date of study drug administration 21Jul2008).
NETU-07-07/120/1479	PALONOSETRON 0.5 MG AND NETUPITANT 200 MG AND DEXAMETHASONE	Eligibility Criteria	Ondansetron	Major	NO	Ondansetron taken 16Jul2008 1 tab. Date of study drug administration 16Jul2008
NETU-07-07/120/1522	PALONOSETRON 0.5 MG AND NETUPITANT 200 MG AND DEXAMETHASONE	Eligibility Criteria	Ondansetron	Major	NO	Ondansetron taken 07Aug2008 1 tab. Date of study drug administration 07Aug2008
NETU-07-07/120/1530	PALONOSETRON 0.5 MG AND NETUPITANT 200 MG AND DEXAMETHASONE	Eligibility Criteria	Dexamethasone	NO	NO	Dexamethasone 8 mg BID, IM, was given from 28Jul2008 to 05Aug2008, i.e. earlier than 72 hours prior to Day 1 (date of study drug administration 11Aug2008).
NETU-07-07/120/1579	PALONOSETRON 0.5 MG AND NETUPITANT 200 MG AND DEXAMETHASONE	Eligibility Criteria	Metoclopramide	NO	NO	No violation of Eligibility criterion: Metoclopramide 2 mL administered on 01-Oct-2008 i.e. after date of study drug administration (30-Sep-2008). See below "Anti-emetic Concomitant Medication"
		Anti-emetic Concomitant Medication	Metoclopramide	Major	NO	Metoclopramide 2 mL administered on 01-Oct-2008. Date of study drug administration 30-Sep-2008.

Source: Sponsor's table.

**Table 4 Netu-07-07-violations-site 120- Netupitant 300 mg**

Patient ID	Treatment	Category	Violation details	Impact Efficacy	Impact Safety	Comment
NETU-07-07/120/1211	PALONOSETRON 0.5 MG AND NETUPITANT 300 MG AND DEXAMETHASONE	Eligibility Criteria	Ondansetron	Major	NO	Ondansetron taken 23Jul2008 1 tab sublingual. Date of study drug administration 23Jul2008.
		Eligibility Criteria	Dexamethasone	NO	NO	Dexamethasone 8 mg, IM, was given on 10Jul2008 i.e. earlier than 72 hours prior to Day 1 (date of study drug administration 23Jul2008).
NETU-07-07/120/1218	PALONOSETRON 0.5 MG AND NETUPITANT 300 MG AND DEXAMETHASONE	Eligibility Criteria	Dexamethasone	NO	NO	Dexamethasone 8 mg, IM, was given on 26Jun2008 i.e. earlier than 72 hours prior to Day 1 (date of study drug administration 09Jul2008).
NETU-07-07/120/1473	PALONOSETRON 0.5 MG AND NETUPITANT 300 MG AND DEXAMETHASONE	Eligibility Criteria	Ondansetron	Major	NO	Ondansetron taken 06Aug2008 1 tab sublingual. Date of study drug administration 06Aug2008
		Eligibility Criteria	Dexamethasone	NO	NO	Dexamethasone 8 mg, IM, was given on 25Jul2008 i.e. earlier than 72 hours prior to Day 1 (date of study drug administration 06Aug2008).
NETU-07-07/120/1478	PALONOSETRON 0.5 MG AND NETUPITANT 300 MG AND DEXAMETHASONE	Eligibility Criteria	Ondansetron	Major	NO	Ondansetron taken 17Jul2008 1 tab. Date of study drug administration 17Jul2008
		Eligibility Criteria	Dexamethasone	NO	NO	Dexamethasone 8 mg, IM, was given on 03Jul2008 i.e. earlier than 72 hours prior to Day 1 (date of study drug administration 17Jul2008).

Source: Sponsor's Table.

**Table 5 Netu-07-07-violations-site 120- Palonosetron+Aprepitant**

Patient ID	Treatment	Category	Violation details	Impact Efficacy	Impact Safety	Comment
NETU-07-07/120/1216	APREPITANT AND ONDANSETRON AND DEXAMETHASONE	Eligibility Criteria	Dexamethasone	NO	NO	Dexamethasone 8 mg, IM, was given on 19Jun2008 i.e. earlier than 72 hours prior to Day 1 (date of study drug administration 02Jul2008).
NETU-07-07/120/1480	APREPITANT AND ONDANSETRON AND DEXAMETHASONE	Eligibility Criteria	Dexamethasone	NO	NO	Dexamethasone 8 mg, IM, was given on 07Jul2008 i.e. earlier than 72 hours prior to Day 1 (date of study drug administration 16Jul2008).
NETU-07-07/120/1524	APREPITANT AND ONDANSETRON AND DEXAMETHASONE	Eligibility Criteria	Dexamethasone	NO	NO	Dexamethasone 8 mg, IM, was given on 16Jul2008 i.e. earlier than 72 hours prior to Day 1 (date of study drug administration 30Jul2008).

Source: Sponsor's Table.

The tables show:

- Three major violations (2 subjects) with impact on efficacy, one involving administration of ondansetron on the day of study drug, and two (same patient) involving presence of nausea and vomiting on day of study drug administration, and administration of metoclopramide before and during the period of study drug administration. Both patients were in the palonosetron 0.5 mg and netupitant 100 mg arm that have no impact on efficacy conclusion on the combination of netupitant 300 mg and palonosetron.

- Five major violations in patients receiving palonosetron 0.5 mg and netupitant 200 mg. Four violations involved administration of ondansetron on date of study drug administration and one involved administration of metoclopramide day after study drug administration that have no impact on efficacy conclusion on the combination of netupitant 300 mg and palonosetron.

Three major violations with impact on efficacy occurred in the palonosetron 0.5 mg and netupitant 300 mg arm, and involved administration of ondansetron on the date of study drug administration. Three major violations with impact on efficacy in the palonosetron 0.5 mg arm involved administration of ondansetron on the day of study drug administration. I do not believe these impact the final efficacy conclusion because equal numbers of violations occurred in both arms and any impact would be balanced between arms. In addition, ondansetron and palonosetron are the same class of drug, a serotonin-3 (5-HT3) receptor antagonist. Because both drugs act on the same receptor, using both drugs on the same day may not increase efficacy.

*Medical Officer's Comment:*

*None of the major violations involved safety. The FDA statistical reviewer confirmed the sponsor's re-analysis (treating patients with protocol violations as treatment failures or excluding them from analysis) and concluded that the data of NETU-07-07 is supportive of the efficacy of the study drug.<sup>2</sup> The clinical reviewer agrees with this assessment.*

### **Item 3 – Potential Hy's law cases**

Page 136 of the Medical Officer's Review states:

*Nine additional cases from NETU-07-07 and PALO-10-01 were reviewed by an independent expert, but none were regarded as potential Hy's Law cases.*

Additional details on these 9 cases were absent from the original Medical Officer Review and are, therefore, provided below. Table 6 provides information on each of the nine cases, Table 7 provides an overall summary of hepatic laboratory results for NETU-07-07, and Table 8 shows hepatic laboratory results for Phase 3 studies.

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<sup>2</sup> Chen, Yeh-Fong. Statistical Review and Evaluation. 7-2-14.

**Table 6 Patients with abnormal hepatic labs post chemo NETU-07-07 & PALO-10-01**

Pt ID	Treatment	Baseline labs	Day 2 post-dosing	Comment
1291503	Palo0.5/Netu100  Cisplatin cyclophosphamide	ALT 33 U/L (1.1 ULN),  AP 125 U/L (1.3 ULN),  AST nl., total bilirubin (TB) nl.	ALT 279 U/L (9.0 ULN), AST 323 U/L (10.1 ULN), AP 182 U/L (1.9 ULN),  TB 36 mmol/L (1.7 ULN), nl albumin. No workup was done to eliminate common causes of acute hepatitis.	Probable DILI possibly due to cisplatin, cyclophosphamide, netupitant and palonosetron
1131413	Palo0.5/Netu200  Cisplatin, fluorouracil	normal ranges for ALT, AST, AP, TB.	ALT 150 U/L (4.8 ULN), AST 115 U/L (3.6 ULN), AP 103 U/L (1.1 ULN), TB 23 mmol/L (1.1 ULN), albumin nl. No workup was done to eliminate common causes of acute hepatitis.	Probable DILI possibly due to cisplatin, fluorouracil, netupitant and palonosetron.
2102071	Palo0.5/Netu200  Cisplatin	normal ranges for ALT, AST, AP	ALT 399 U/L (12.9 ULN), AST 344 U/L (10.8 ULN), TB mmol/L (1.3 ULN) AP nl. No workup was done to eliminate common causes of acute hepatitis.	Probable DILI possibly due to cisplatin, netupitant and palonosetron.
1191128	Palo0.5/Netu300  Cisplatin, fluorouracil	normal ranges for ALT, AST, AP, albumin and TB.	ALT 780 U/L (25.1 ULN),AST 545 U/L (17.0ULN), AP 214 U/L (1.5 ULN), TB nl. No workup was done to eliminate common causes of acute hepatitis.	Probable DILI possibly due to cisplatin, fluorouracil, netupitant or palonosetron.
1321682	Palo0.5/Netu300  Cisplatin and etoposide	normal ranges for ALT, AST, AP  TB to 26 mmol/L (1.2 ULN).	ALT 39 U/L (1.3 ULN), AST, AP TB nl  Day 6 ALT 134 U/L (4.3 ULN), with TB 35 mmol/L (1.7ULN) AST, AP nl. No workup was done to eliminate common causes of acute hepatitis.	Possible DILI possibly due to cisplatin, etoposide, netupitant or palonosetron
1321643	Ondansetron + aprepitant  Cisplatin and etoposide	normal ranges for ALT, AST, AP, TB, and albumin	ALT 630 U/L (15.4 ULN), AST 428 U/L (11.3 ULN), AP 167 U/L (1.4 ULN), TB 26 mmol/L (1.2 ULN). No workup was done to eliminate common causes of acute hepatitis.	Probable DILI possibly due to cisplatin, etoposide, aprepitant, ondansetron.
1191130	Palo0.50 mg Cisplatin and etoposide	normal ranges for ALT, AST, AP, TB, and albumin	ALT 458 U/L (11.2 ULN), AST 295 U/L (8.1 ULN), AP 136 U/L (1.2 ULN) TB 26 mmol/L (1.2 ULN), No workup was done to eliminate common causes of acute hepatitis.	Probable DILI possibly due to cisplatin, etoposide and palonosetron
110503	Palo 0.25mg  cisplatin	normal ranges for ALT, AST, AP, TB, and albumin	Day 2 post dosing normal  Day 6 ALT 137 U/L (3.04 ULN), AST 78 U/L (1.9 ULN), TB 31 mmol/L (1.47	Possible role for palonosetron or cisplatin

			ULN), normal AP and albumin. No workup was done to eliminate common causes of acute hepatitis.	
520101	Palo 0.25 mg  Cisplatin, fluorouracil	normal AP and albumin	ALT 84 IU/L (1.8 ULN), AST 75 IU/L (1.8 ULN). Albumin, AP, TB normal  Day 6 ALT 84 IU/L (1.8 ULN), AST 75 IU/L (1.8 ULN), AP, albumin normal  No workup was done to eliminate common causes of acute hepatitis.	Possible DILI possibly due to cisplatin, fluorouracil and palonosetron

**Table 7 Abnormal hepatic Labs NETU-07-07 (Phase 2)**

	Netupitant / Palonosetron combination (100/0.50 mg) N= 135		Netupitant / Palonosetron combination (200/0.50 mg) N= 138		Netupitant / Palonosetron combination (300/0.50 mg) N= 136		Palonosetron (0.50 mg oral) N= 136		Aprepitant plus ondansetron N= 134		Total N= 679	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with at least a value >3*upper limit for AST	4	(3.0)	5	(3.6)	4	(2.9)	3	(2.2)	5	(3.7)	21	(3.1)
Patients with at least a value >5*upper limit for AST	3	(2.2)	1	(0.7)	0	(0.0)	3	(2.2)	3	(2.2)	10	(1.5)
Patients with at least a value >10*upper limit for AST	2	(1.5)	3	(2.2)	1	(0.7)	1	(0.7)	1	(0.7)	8	(1.2)
Patients with at least a value >3*upper limit for ALT	6	(4.4)	14	(10.1)	9	(6.6)	7	(5.1)	9	(6.7)	45	(6.6)
Patients with at least a value >5*upper limit for ALT	4	(3.0)	1	(0.7)	6	(4.4)	1	(0.7)	3	(2.2)	15	(2.2)
Patients with at least a value >10*upper limit for ALT	2	(1.5)	3	(2.2)	1	(0.7)	2	(1.5)	2	(1.5)	10	(1.5)
Patients with at least a value >3*upper limit for AST and >=2*upper limit for bilirubin	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Patients with at least a value >3*upper limit for ALT and >=2*upper limit for bilirubin	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

N= number of treated patients; n= number of patients with abnormal hepatic values  
Percentages are calculated on the number of treated patients

Source: (b) (4) Assessment of Potential Liver Toxicity Induced by a Fixed Oral Dose Combination of Netupitant and Palonosetron. 9 April 2013. NDA205719.

**Table 8 Abnormal hepatic lab Phase 3 studies**

	Netupitant / Palonosetron combination (100/0.50 mg) N= 135		Netupitant / Palonosetron combination (200/0.50 mg) N= 138		Netupitant / Palonosetron combination (300/0.50 mg) N= 136		Palonosetron (0.50 mg oral) N= 136		Aprepitant plus ondansetron N= 134		Total N= 679	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with at least a value >3*upper limit for AST	4	(3.0)	5	(3.6)	4	(2.9)	3	(2.2)	5	(3.7)	21	(3.1)
Patients with at least a value >5*upper limit for AST	3	(2.2)	1	(0.7)	0	(0.0)	3	(2.2)	3	(2.2)	10	(1.5)
Patients with at least a value >10*upper limit for AST	2	(1.5)	3	(2.2)	1	(0.7)	1	(0.7)	1	(0.7)	8	(1.2)
Patients with at least a value >3*upper limit for ALT	6	(4.4)	14	(10.1)	9	(6.6)	7	(5.1)	9	(6.7)	45	(6.6)
Patients with at least a value >5*upper limit for ALT	4	(3.0)	1	(0.7)	6	(4.4)	1	(0.7)	3	(2.2)	15	(2.2)
Patients with at least a value >10*upper limit for ALT	2	(1.5)	3	(2.2)	1	(0.7)	2	(1.5)	2	(1.5)	10	(1.5)
Patients with at least a value >3*upper limit for AST and >=2*upper limit for bilirubin	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Patients with at least a value >3*upper limit for ALT and >=2*upper limit for bilirubin	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

N= number of treated patients; n= number of patients with abnormal hepatic values  
Percentages are calculated on the number of treated patients

Source: (b) (4) NDA205718.

The FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation provides three criteria to apply when considering whether abnormal laboratory results post-dosing are Hy’s Law cases. These are:

- 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
- ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
- No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury<sup>3</sup>

None of the 9 cases listed above had TB >2x ULN and all patients were on chemotherapeutic agents. These cases do not meet the criteria for Hy’s law cases.

**Item 4 – Efficacy analysis by age with 65 years as cut-off**

The following tables provide complete response (CR) rates for patients < and > 65 years of age by study. The number of patients over 65 years was smaller in all studies compared to the number less than 65 years.

<sup>3</sup> FDA Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 2009.

**Table 9 NETU-07-07 CR 25-120 hours >65 years**

Complete Response Rate 25 - 120	Palo Alone (N=20)	PALO+100 NETU (N=23)	PALO+200 NETU (N=20)	PALO+300 NETU (N=20)	Aprepitant (N=25)
Count/Percent	18 (90.0%)	21 (91.3%)	19 (95.0%)	20 (100.0%)	22 (88.0%)
95% CI for CR	(76.9%, 100.0%)	(79.8%, 100.0%)	(85.4%, 100.0%)	(100.0%, 100.0%)	(75.3%, 100.0%)
Difference in CR from the Palonosetron alone with 95% CI		1.3% (-16.2%, 18.8%)	5.0% (-11.3%, 21.3%)	10.0% (-3.1%, 23.1%)	-2.0% (-20.3%, 16.3%)

**Table 10 NETU-07-07 CR 25-120 hours <65 years**

Complete Response Rate 25 - 120	Palo Alone (N=116)	PALO+100 NETU (N=112)	PALO+200 NETU (N=117)	PALO+300 NETU (N=115)	Aprepitant (N=109)
Count/Percent	91 (78.4%)	101 (90.2%)	106 (90.6%)	102 (88.7%)	97 (89.0%)
95% CI for CR	(71.0%, 85.9%)	(84.7%, 95.7%)	(85.3%, 95.9%)	(82.9%, 94.5%)	(83.1%, 94.9%)
Difference in CR from the Palonosetron alone with 95% CI		11.7% (2.4%, 21.0%)	12.2% (3.0%, 21.3%)	10.2% (0.8%, 19.7%)	10.5% (1.0%, 20.1%)

**Table 11 NETU-08-18 CR delayed >65 years**

Primary Efficacy Analysis: - >=65 Years	Netu/Palo FDC N=116 n (%)	Palo alone N=123 n (%)
Cycle 1 - Delayed Phase		
Responder [95% CI] (1)	94 ( 81.0) [ 73.0 ; 87.1]	99 ( 80.5) [ 72.6 ; 86.5]
Difference in response rate % (Netu/Palo FDC - Palo alone) [95% CI] (2)		0.5 [ -9.5 ; 10.5]
(1) 95% confidence interval using Wilson score method.		
(2) 95% confidence interval using Newcombe-Wilson's method.		

**Table 12 NETU-08-18 CR delayed age <65**

Primary Efficacy Analysis: - < 65 Years	Netu/Palo FDC N=608 n (%)	Palo alone N=602 n (%)
Cycle 1 - Delayed Phase		
Responder	463 ( 76.2)	405 ( 67.3)
CMH Test (1) odds ratio (Netu/Palo FDC vs. Palo alone) [95% CI] for CMH odds ratio		1.55 [ 1.20 ; 2.00]
CMH Test p-value		0.001
(1) Cochran-Mantel-Haenszel test, stratified by age class and region.		

**Table 13 NETU-10-29 CR delayed <65 years**

	Netu/Palo FDC N=231 n (%) [95% CI] (1)	Aprepitant/Palo N=77 n (%) [95% CI] (1)
Complete Response: - < 65 Years		
Cycle 1 - scheduled for treatment	231	77
Delayed Phase	194 ( 84.0) [ 78.7 ; 88.2]	58 ( 75.3) [ 64.6 ; 83.6]
Difference in response rate % (Netu/Palo FDC - Aprepitant/Palo) [95% CI] (2)		8.7 [ -1.2 ; 20.1]

(1) 95% confidence interval using Wilson score method.  
(2) 95% confidence interval using Newcombe-Wilson's method.

**Table 14 NETU-10-29 CR Delayed >65 years**

	Netu/Palo FDC N=78 n (%) [95% CI] (1)	Aprepitant/Palo N=26 n (%) [95% CI] (1)
Complete Response: - >=65 Years		
Cycle 1 - scheduled for treatment	78	26
Delayed Phase	63 ( 80.8) [ 70.7 ; 88.0]	22 ( 84.6) [ 66.5 ; 93.8]
Difference in response rate % (Netu/Palo FDC - Aprepitant/Palo) [95% CI] (2)		-3.8 [ -17.5 ; 15.7]

(1) 95% confidence interval using Wilson score method.  
(2) 95% confidence interval using Newcombe-Wilson's method.

**Table 15 PALO-10-01 CR acute <65 years**

	Oral Palo N=272 n (%)	IV Palo N=281 n (%)
< 65 Years		
Responder [95% CI] (1)	243 ( 89.3) [ 85.1 ; 92.5]	238 ( 84.7) [ 80.0 ; 88.4]
Difference in response rate % (Oral Palo - IV Palo) [95% CI] (2)		4.6 [ -1.0 ; 10.3]

(1) 95% confidence interval using Wilson score method.  
(2) 95% confidence interval using Newcombe-Wilson score method.

**Table 16 PALO-10-01 CR acute >65 years**

	Oral Palo N=97 n (%)	IV Palo N=88 n (%)
>=65 Years		
Responder [95% CI] (1)	87 ( 89.7) [ 82.1 ; 94.3]	80 ( 90.9) [ 83.1 ; 95.3]
Difference in response rate % (Oral Palo - IV Palo) [95% CI] (2)		-1.2 [ -10.0 ; 7.9]

(1) 95% confidence interval using Wilson score method.  
(2) 95% confidence interval using Newcombe-Wilson score method.

Although the number of patients over the age of 65 was smaller than the number under 65, patients on the Akynzeo FDC had better results in terms of complete response than patients on Palonosetron alone. Results were similar, or slightly better when compared to Aprepitant. Because the number of patients over 65 was small compared to the total number of cancer patients in the clinical studies conclusions about efficacy in geriatric patients cannot be made.

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NANCY C SNOW  
09/05/2014

RUYI HE  
09/06/2014

## CLINICAL REVIEW

Application Type NDA  
Application Number(s) 205718  
Priority or Standard S

Submit Date(s) 9/26/13  
Received Date(s) 9/27/13  
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Reviewer Name(s) Nancy Snow  
Review Completion Date 30-June-2014

Established Name netupitant +palonosetron  
(Proposed) Trade Name Akynzeo  
Therapeutic Class NK-1 and 5-HT3  
Applicant Helsinn

Formulation(s) Fixed Dose Capsule  
Dosing Regimen 1 tablet 1 hour before  
chemotherapy  
Indication(s) prevention of acute and  
delayed nausea and vomiting  
associated with initial and  
repeat courses of cancer

chemotherapy, including highly  
emetogenic chemotherapy.  
Intended Population(s) Adults  $\geq$  18 years old

Template Version: March 6, 2009

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

I recommend that NDA205718 for Akynzeo (netupitant and palonosetron fixed dose combination) capsule for oral use be approved for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including but not limited to highly emetogenic chemotherapy, in adult patients at a dose of one capsule administered approximately one hour prior to the start of chemotherapy.

### 1.2 Risk Benefit Assessment

Data from 4 Phase 2/3 trials, along with supportive data from early phase studies support the conclusion that the benefits of Akynzeo for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including but not limited to highly emetogenic chemotherapy, outweigh the risks.

Drugs of the 5-HT<sub>3</sub> receptor antagonist (5-HT<sub>3</sub> RA) class have been available for the prevention of chemotherapy induced nausea and vomiting (CINV) since the approval of Zofran in 1991. Emend was approved in 2005, and was the first NK-1 receptor antagonist (NK-1 RA) to gain marketing approval in the U.S. Akynzeo is now the first drug which combines a 5-HT<sub>3</sub> RA and an NK-1 RA into a single capsule, to be taken one hour before the administration of chemotherapy. Co-administration of a 5-HT<sub>3</sub> and an NK-1 has become standard practice to prevent nausea and vomiting that occur frequently with the administration of chemotherapeutic agents. Failure to prevent CINV may have negative consequences for cancer patients including suboptimal treatment.

Oral administration of AKYNZEO in combination with dexamethasone has been shown to prevent acute and delayed nausea and vomiting associated with initial and repeat courses of chemotherapy in two pivotal studies, NETU-07-07, and NETU-08-18. PALO-10-01 and NETU-10-29 also provide data to support efficacy.

Clinical trial **NETU07-07** was a multicenter, randomized, parallel, double-blind, controlled Phase II clinical study of 694 adult patients randomized in equal numbers and stratified by gender into five treatment groups. Patients participated in the trial for one chemotherapy cycle only. The purpose of the trial was to compare the efficacy and safety of three single oral doses of netupitant (100, 200, or 300 mg) combined with palonosetron, to palonosetron alone (0.5mg) in the prevention of CINV-HEC. Although all netupitant doses were superior to palonosetron alone for CR (complete response – no vomiting and no use of rescue medication) overall from 0 to 120 hours post-chemotherapy, the 300mg dose of netupitant in combination with palonosetron

performed better in the delayed (25-120 hours) and acute (0-24 hours) phases post-chemotherapy. Based on these results the sponsor chose the 300mg dose of netupitant to be used in combination with the 0.50 mg dose of oral palonosetron in the fixed dose combination.

Pursuant to interactions with the FDA NETU-07-07 was chosen to serve as the pivotal HEC trial. The primary efficacy endpoint of the original protocol was CR rate from 0 to 120 hours after administration of highly emetogenic chemotherapy.

The percent of patients with CR over 0-120 hours after cisplatin administration was 76.5% in the palonosetron alone group and 87.4%, 87.6%, and 89.6% in the netupitant 100 mg, 200 mg, and 300 mg groups, respectively. All doses of netupitant were statistically superior to palonosetron alone ( $p \leq 0.017$ ) for the protocol specified primary endpoint of CR overall. For the secondary endpoints CR acute and CR delayed the 300mg Netu/Palo dose performed better than the lower netupitant doses.

A post-hoc analysis was done to assess CR delayed as the primary endpoint. When the alternate Cochran-Mantel-Haenszel (CMH) test stratified for gender was applied to CR delayed phase, CR acute, and CR overall the sponsor confirmed that the results were the same as those obtained from the original analyses. The FDA statistical reviewer found the post hoc analysis acceptable.

An additional issue with NETU-07-07 was protocol violations found at clinical site 120 in Russia. The company performed a sensitivity analysis to determine the impact of the site on the overall efficacy results. The FDA statistical reviewer confirmed the sponsor's re-analysis results and determined that the data of NETU-07-07 supported the efficacy of the study drug, i.e., palonosetron plus netupitant 300 mg, although not all of re-analysis results showed positive findings based on Holm-Bonferroni multiplicity adjustment method.

**NETU-08-18** was a multicenter, randomized, parallel, double-blind, active controlled, superiority study, with a multiple cycle safety extension, in which the efficacy and safety of a single oral dose of Palonosetron 0.5mg +Netupitant 300mg was compared with a single oral dose of palonosetron 0.5 mg alone in cancer patients scheduled to receive the first cycle of an anthracycline and cyclophosphamide regimen for the treatment of a solid malignant tumor. All patients received a single oral dose of dexamethasone. At the time the trial was conducted coadministration of anthracycline and cyclophosphamide (AC) was considered to be moderately emetogenic cancer chemotherapy (MEC) and NETU-08-18 was the pivotal MEC trial for this application. In 2011 the American Society of Clinical Oncology reclassified AC as HEC.

In this trial a total of 1455 patients were randomized to either Akynzeo or palonosetron, and 1450 patients (Akynzeo n=725; palonosetron n=725) received study medication. Of these, 1438 patients (98.8 %) completed cycle 1 and 1286 patients (88.4 %) continued

treatment in the multiple-cycle extension. Most patients were treated with cyclophosphamide and all patients were additionally treated with either doxorubicin (68.0 %) or epirubicin (32.0 %).

The study demonstrated the superiority of the netupitant/palonosetron FDC over palonosetron alone with respect to the primary and key secondary endpoints: CR in the delayed (76.9% vs. 69.5%,  $p=0.001$ ), acute (88.4% vs. 85.0%,  $p=0.047$ ) and overall phases (74.3% vs. 66.6%,  $p=0.001$ ) in cancer patients receiving AC chemotherapy. The difference in efficacy between treatment groups in favor of the netupitant/palonosetron FDC was maintained across multiple treatment cycles although efficacy analysis for the multiple-cycle extension was exploratory only.

No major differences in safety data were observed between the two treatment groups and a similar pattern of results was maintained throughout all treatment cycles. The adverse event profile was as expected from cancer patients in a setting of cytotoxic chemotherapy. Many patients in both treatment groups experienced decreases in white cell populations and other events generally related to chemotherapy (bone marrow suppression, gastric disorders, and alopecia).

**PALO-10-01** was a multicenter, multinational, randomized, active-controlled, double-blind, double-dummy, parallel group, clinical non-inferiority study. The efficacy and safety of a single dose of oral palonosetron 0.50 mg was compared to I.V. palonosetron 0.25 mg in cancer patients scheduled to receive highly emetogenic cisplatin ( $\geq 70$  mg/m<sup>2</sup>) based chemotherapy. The purpose of this trial was to demonstrate that oral palonosetron 0.5 mg contributes to the efficacy of Akynzeo in the HEC setting. This was done because the 0.50-mg palonosetron oral capsule is approved in the U.S. for prevention of acute CINV-MEC but not CINV-HEC. Only the I.V. formulation is approved for HEC. Therefore in order to use oral palonosetron 0.50mg as part of the fixed-dose combination for HEC it was necessary to demonstrate its efficacy and safety in prevention of CINV-HEC. The sponsor sought to do this in PALO-10-01 by showing that 0.50mg oral palonosetron was not inferior to 0.25mg I.V. palonosetron.

The primary efficacy endpoint was complete response within 24 hours (acute phase) after the start of cisplatin-based chemotherapy administration. In the oral Palonosetron arm, 89.4% of patients had CR in the acute phase compared to 86.2% of patients in the I.V. Palonosetron arm, with a difference of 3.21% (99% CI: -2.74% to 9.17%). Non-inferiority of oral Palonosetron versus I.V. Palonosetron was demonstrated.

**NETU-10-29** was a multicycle study to compare the safety profile of Akynzeo to Aprepitant and Palonosetron in patients undergoing initial and repeat cycles of chemotherapy, including highly emetogenic chemotherapy. Because the trial was mainly to assess safety during repeat cycles of chemotherapy, efficacy assessments

were exploratory. Of the 413 patients randomized, approximately 25% of patients received HEC, and 75% MEC. More than 75% of patients continued on to cycle 4, and more than 40% of patients reached cycle 6. During their first chemotherapy cycle 83.2% of patients receiving Akynzeo had CR in the delayed phase, compared to 77.7% of patients receiving Aprepitant+PALO. In the acute phase the proportions were 92.9% to 94.2%. In the overall 120 hour time period 80.6% of patients receiving Akynzeo had CR, compared to 75.7% receiving Aprepitant+PALO.

During the clinical development for Akynzeo 1169 cancer patients received at least one dose of Akynzeo in the key Phase 2/3 trials. A total of 782 patients were exposed to Akynzeo for at least 4 chemotherapy cycles, and 321 patients were exposed for at least 6 chemotherapy cycles. In all studies, dexamethasone was co-administered with Akynzeo. The most common adverse reactions, assessed as treatment related and with an incidence  $\geq 2\%$ , were constipation (2.0% Akynzeo, 1.6% Palonosetron) and headache (2.4% Akynzeo, 2.1% Palonosetron).

Out of 3280 cancer patients in Phase 2/3 studies 39 (1.2%) patients died. Seventeen (1.2%) deaths occurred in patients randomized to one of the 3 Netupitant+palo dose groups, 21 (1.3%) deaths occurred in patients randomized to the oral or IV palonosetron alone arm, and 1 (0.4%) patient receiving aprepitant with palonosetron died. The most frequent causes of death were multi-organ failure, cardiopulmonary failure, progression of neoplasm, and pulmonary embolism. Because patients in these studies were gravely ill and exposed to cytotoxic chemotherapy deaths in this patient population were not unexpected.

Most serious adverse events (SAEs) occurred during cycle 1, and repeated treatment with Akynzeo in subsequent chemotherapy cycles did not seem to increase the frequency of SAEs. The most common SAEs seen through all cycles were febrile neutropenia (1.2%), neutropenia (0.7%), vomiting (0.4%), anemia (0.4%), and leukopenia (0.3%). In the netupitant-palonosetron and palonosetron groups, febrile neutropenia was the most frequently reported SAE (1.5% [16/1033] and 0.8% [6/725], respectively), while anemia was the most frequently reported SAE among patients in the aprepitant+palonosetron group (2.9%; 3/104).

Taking into account all patients who received at least one dose of netupitant and palonosetron, or one of its components, 834 of 4331 (19.3%) patients discontinued from a study. A total of 27 (2.3%) patients in the Netupitant-Palonosetron arm completed a cycle but did not continue into the next planned cycle due to an adverse event. The most frequent adverse event leading to discontinuation in patients receiving Akynzeo during cycle 1 was neutropenia. For patients receiving Palonosetron the main reason for discontinuation was nausea. Most AEs leading to discontinuation were experienced in only 1-2 subjects.

Palonosetron + netupitant were evaluated in a thorough QT study at the 200mg and 600mg Netupitant doses, compared against a positive control. The study was negative for clinically important effects on heart rate, PR and QRS interval duration, and cardiac morphology or repolarization. The 300mg dose of Netupitant is the dose in the fixed dose combination.

Based on concerns of cardiotoxicity seen in another drug of the NK-1 RA class, the sponsor was required to institute increased cardiovascular monitoring. In Phase 3 multicycle studies NETU-08-18 and NETU-10-29 cardiac troponin (cTnI) levels were obtained during screening for cycle 1, and on day 2 (24 hours after study drug administration) and on day 6 of each cycle. Patients with cTnI levels  $\geq 0.12$  ng/mL (but  $< 0.50$  ng/mL) had cardiovascular follow-up, either within the study or following discontinuation, but were permitted to continue in the study at the investigator's discretion. Patients with cTnI values  $\geq 0.50$  ng/mL also had cardiovascular follow-up for functional assessment, and were withdrawn from the study.

Of the 1033 patients in the NETU/PALO 300/0.50 mg arm 28 (2.7%) of patients had troponin  $\geq 0.12$  ng/mL and  $< 0.5$  ng/mL, compared to 17 (2.3%) patients receiving palonosetron alone (n=725), and 2 (1.9%) patients receiving Aprepitant + Palonosetron (n=104). Five (0.5%) patients in the NETU/PALO 300/0.50 mg arm, 5 (0.7%) patients in the palonosetron alone arm, and 1 (1.0%) patient receiving Aprepitant+Palonosetron had troponin levels  $\geq 0.5$ ng/mL.

As described above patients with elevated troponin entered into a cardiovascular follow-up study for assessment of LV function. Most patients with elevated troponin did not have significant changes in cardiac function (i.e. most had change in ejection fraction from baseline of  $< 10$ ). Four patients from NETU-08-18 receiving Netupitant/Palo 300/0.5 had changes in LVEF that ranged from -10 to -39. Two patients in the Palonosetron group had a decline in cardiac function ranging from -14 to -22. In NETU-10-29 one patient who received aprepitant + palonosetron had a change in cardiac function of -25. It is worth noting that patients in NETU-08-18 received the chemotherapy agent anthracycline, which is known to be cardiotoxic.

Given the complexity of the patient population and the cytotoxic chemotherapy regimens they received, it is difficult to draw conclusions from the safety results. Most deaths and non-fatal SAEs were associated with comorbidity due to their cancer diagnosis or the chemotherapy regimen. The elevations in troponin were not, for the most part, associated with a decline in cardiac function. In those few instances where there was decline in LVEF it was in conjunction with the administration of cardiotoxic chemotherapy.

In conclusion, the benefit of Akynzeo in providing increased protection from chemotherapy induced nausea and vomiting, and the lack of negative safety findings directly attributable to Akynzeo suggests an overall favorable risk/benefit associated with use of the drug combination.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

A postmarket risk evaluation and mitigation strategy is not recommended.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

The sponsor is required to conduct postmarketing studies in pediatric patients based on the Pediatric Research and Equity Act (PREA). Two studies will be required. The first is a PK/PD pediatric trial and the second a safety and efficacy trial. The sponsor will need to develop an oral or I.V. formulation of netupitant+palonosetron that is suitable for all ages. If an oral formulation of netupitant+palonosetron cannot be developed the sponsor may qualify for a waiver of pediatric studies for the populations for which an age-appropriate formulation of netupitant+palonosetron cannot be developed. Based on these contingencies, and the outcome of the pediatric PK/PD clinical study, a final (oral or I.V.) pediatric age appropriate formulation will be developed and used in pediatric clinical safety and efficacy study. The proposed pediatric study plan was presented to the Pediatric Review Committee (PeRC) and the committee agreed. The sponsor submitted revised timelines for the PREA studies.

The planned schedule for PK/PD Study #1 is:

- Protocol Submission to FDA: November 1, 2015
- Study Completion: April 30, 2018
- Study Report Submission to FDA: October 31, 2018

The planned schedule for safety and efficacy Study #2 is:

- Protocol Submission to FDA: April 30th, 2019
- Study Completion: December 31st, 2021
- Study Report Submission to FDA: April 30th, 2022

*Medical Officer's Comment:*

*These dates appear reasonable.*

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Akynzeo is a combination product containing 0.50mg of palonosetron and 300mg of netupitant combined in one hard gelatin capsule, to be given orally 1 hour before highly or moderately emetogenic chemotherapy. Palonosetron (Aloxi®) is a selective 5-HT<sub>3</sub> receptor antagonist (RA), and netupitant is an NK1 RA. The I.V. formulation of palonosetron (ALOXI 0.25 mg) was approved in the United States in 2003 for the following indications:

- Moderately emetogenic cancer chemotherapy (MEC) - prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
- Highly emetogenic cancer chemotherapy (HEC)- prevention of acute nausea and vomiting associated with initial and repeat courses

An oral formulation (ALOXI 0.50 mg) was approved in 2008 for:

- Moderately emetogenic cancer chemotherapy - prevention of acute nausea and vomiting associated with initial and repeat courses

Other approved 5-HT<sub>3</sub> antagonists include ondansetron (Zofran), granisetron (Kytril), dolasetron (Anzemet) and palonosetron (Aloxi).

Emend (Aprepitant/Fosaprepitant) is the only selective NK1 RA approved for CINV in the US, and is given in combination with other antiemetic agents. It is approved for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, and prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

Because each drug in the fixed dose combination product of netupitant + palonosetron works at different neuropathways (5-HT<sub>3</sub> receptors and NK1 receptors) each makes a contribution to the combination. The netupitant component of the combination product extends the half-life of the drug product to approximately 90 hours.

In the current submission the applicant has provided data to support their proposed indications of prevention of acute and delayed nausea and vomiting associated with initial and repeat cycles of highly and moderately emetogenic cancer chemotherapy. As will be discussed in further detail in this review, because of a reclassification of the anthracycline and cyclophosphamide regimen from moderately to highly emetogenic<sup>1</sup>, the division has decided to condense all chemotherapeutic agents with emetogenic potential into one category. The new indication will be prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including but not limited to highly emetogenic chemotherapy.

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<sup>1</sup> Antiemetics: ASCO Guidelines Update. [guidelines@asco.org](http://guidelines@asco.org)

The dosing regimen for adults is one Akynzeo capsule approximately one hour before the start of chemotherapy. The drug may be taken with or without food. Patients below the age of 18 have not been studied.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Drug	Class	Indication
Palonosetron	5-HT3 RA	Acute and Delayed MEC & HEC
Ondansetron	5-HT3 RA	Initial and repeat courses of MEC & HEC
Granisetron	5-HT3 RA	Initial and repeat courses emetogenic cancer chemotherapy, including high dose cisplatin
Dolasetron	5-HT3 RA	Initial and repeat MEC in patients $\geq 2$ years old
Aprepitant/Fosaprepitant	NK-1 RA	Acute and Delayed MEC & HEC

## 2.3 Availability of Proposed Active Ingredient in the United States

Akynzeo is a fixed dose combination of netupitant, a new molecular entity not currently marketed in the United States, and oral palonosetron marketed as Aloxi and approved for prevention of acute nausea and vomiting associated with moderately emetogenic chemotherapy.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Drugs of the 5-HT3 RA class are widely used and have generally been found to be safe and well-tolerated. Drugs of this class have the potential to affect the heart rate, PR interval, QRS interval duration and cardiac morphology. However a thorough QT study of palonosetron (PALO-03-11) conducted in healthy subjects did not demonstrate QT prolongation, even at supratherapeutic doses.

Experience with drugs of the NK-1 class is limited to Emend, whose current label lists the following contraindications:

- Hypersensitivity to any component of this medication
- Should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride, since inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.

The Warning and Precautions for Emend state:

- Co-administration of aprepitant with warfarin (a CYP2C9 substrate) may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time.
- The efficacy of hormonal contraceptives during and for 28 days following the last dose of EMEND may be reduced. Alternative or back-up methods of contraception should be used.

- EMEND is a dose-dependent inhibitor of CYP3A4, and should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4
- Caution should be exercised when administered in patients with severe hepatic impairment

*Medical Officer's Comment:*

*The Netupitant component of Akynzeo is a CYP3A4 inhibitor. The Akynzeo label will contain information on drug-drug interactions based on this enzyme. More details of metabolizing enzymes can be found in the Clinical Pharmacology review.*

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

The following is a chronological summary of important regulatory activity related to this application.

### Pre-IND meeting April 5, 2006 (written responses only)

- Netupitant monotherapy for HEC patients would provide inadequate antiemetic coverage in phase 2/3 trials
- Acute and delayed phase efficacy endpoint should be evaluated separately. A primary endpoint of CR for 0-24 hours for acute CINV, and 25-120 hours for delayed should be evaluated.
- Palonosetron dose (0.5mg) could be used in combination with Netupitant in phase 2/3 trials
- Available clinical experience supports use of 100mg to 450mg netupitant in combination with palonosetron in clinical studies
- Drug-drug-interaction studies with dexamethasone are necessary
- Thorough QT study should be done prior to Phase 3 trials
- Netupitant and metabolites block hERG K<sup>+</sup> channels in vitro and produce QT-prolongation in dog studies. Arrhythmogenic potential of netupitant and metabolites should be fully assessed with in vitro and in vivo cardiac EP studies.
- Chronic oral tox studies in rats and dogs are needed to assess consequences of phospholipidosis. Daily dosing should be used in 90-day combination toxicology studies. For netupitant a 6-month oral chronic toxicity study in rats and a 9-month oral chronic toxicity study are needed. Carcinogenicity studies of 2-years duration in rats and mice should be done.
- FDA agreed that gender (male vs. female) and chemotherapy history (naïve vs. non-naïve) as stratification factors for treatment assignment are acceptable.

### Teleconference June 14, 2006

- Complete response 0 to 120 hours acceptable as primary endpoint of efficacy. Evaluations of 0-24 hours (acute) and 25-120 hours (delayed) would be assessed as secondary efficacy endpoints.

- FDA and the Sponsor agreed on doses of netupitant and palonosetron and the dose ratio for the combination to be used in planned tox studies

IND submitted Sept. 14, 2006 (IND 73,493)

- Single-dose phase 1 netupitant + palonosetron PK drug-drug interaction study NETU-06-06 in healthy subjects

Inactivation of IND October 26, 2006

- PharmTox reviewer recommends clinical hold. The sponsor should conduct single oral dose toxicity studies and 2-week repeated oral dose toxicity studies with the combination product in rodent and non-rodent species.
- Sponsor should conduct cardiovascular pharmacology studies recommended in pre-IND meeting
- Although Netupitant monotherapy and palonosetron monotherapy toxicology and clinical data were submitted in the IND, toxicology data or clinical data for the combination were not available at that time and so were not included in the original IND submission. FDA agreed that the Sponsor could temporarily inactivate the IND until the Sponsor submitted tox and/or clinical safety data on the combination. Study NETU-06-06, other phase 1 trials, and phase 2 study NETU- 07-07 were performed outside the US as non-IND trials for non-US approval.

FDA Carcinogenicity Assessment Committee (CAC) recommendations July 2, 2008 & July 22, 2008

- Committee recommended netupitant doses and control groups for carcinogenicity study; hematology and clinical chemistry data not needed.
- Per CAC committee's recommendation DGIEP agreed that netupitant rat and mouse carcinogenicity studies not needed for CINV indication

End-of-Phase-2 Meeting July 20, 2009

- Discussion centered around difficulty in using oral palonosetron in phase 2 HEC trial NETU-07-07 since the treatment effect of oral palonosetron for HEC has not been established
- If a path forward cannot be found for the HEC indication two MEC studies will be needed
- FDA stated that NETU-07-07 established netupitant's efficacy to the combination, and a netupitant monotherapy arm is not needed to fulfill the combination rule
- FDA agreed with 300mg dose netupitant to use in combination capsule
- Due to accumulation of netupitant and metabolites in myocardium in 4-week dog tox study, safety information beyond 4 cycles, including troponin and other safety monitoring, is needed in phase 3 clinical studies
- The division agreed with drug-drug interaction study plan, planned food effect study, and plan to evaluate PK in cancer patients for inclusion of PK data in labeling. FDA recommended inclusion of elderly patients in trials, and inclusion of severe hepatic impairment patients in hepatic impairment PK trial

- FDA agreed it is acceptable to convey palonosetron monotherapy mutagenicity, reprotox and carcinogenicity data from I.V. and oral Aloxi labeling to combination capsule labeling in the planned NDA.
- Segment III reprotox study on netupitant should be included in NDA
- FDA requested data be submitted to IND on abuse potential of netupitant
- Company agreed to add troponin monitoring to phase 3 trials
- FDA agreed that MEC trial with anthracycline and HEC trial without anthracycline would be acceptable

SPA (no agreement) November 27, 2009 NETU-08-18 (MEC) and [REDACTED] (b) (4)

- Use of different palonosetron doses in the control [REDACTED] (b) (4) and treatment (0.50mg oral) arms will hamper assessment of the individual contribution of netupitant to efficacy
- Statistically significant successful outcomes for CR Acute and CR Delayed are necessary to support the acute and delayed phase indications in the labeling for the netupitant component of the fixed combination of an appropriately designed study. The proposed trial design is not adequate to establish the contribution of oral palonosetron to the primary endpoint (overall 0-120 hours) and the “key” secondary endpoint, delayed phase.
- Safety data beyond cycle 5 is needed
- Sponsor should use a standardized troponin assay. To assure consistency use a central laboratory for troponin (cTnI) assessment with proper handling, storage, shipment, and processing of specimens. For each cycle, obtain cTnI samples at 12 and 24 hours after dosing. Report all cTnI levels as the exact figure (e.g., report “0.026” rather than “< 0.04,” regardless of whether it is out-of-range).
- Assess left ventricular ejection fraction (LVEF) at baseline and end-of-study in subjects on cardiotoxic chemotherapy. Use the same LVEF assessment tool for both baseline and end of-study assessment.

SPA Meeting January 22, 2010

- FDA told sponsor of plan to seek guidance from Office of Medical Policy (OMP) before finalizing SPA
- Division stated that 0.5 mg palonosetron dose in the combination may be acceptable if PALO-10-01 (HEC) demonstrates in HEC patients that oral palonosetron 0.5 mg is non-inferior to the I.V. palonosetron 0.25 mg dose
- A 15% non-inferiority margin has been used in the past and is likely to be acceptable.
- Division stated that in NETU-08-18 the cleanest path is to use oral palonosetron 0.5mg as active comparator, and most appropriate efficacy endpoint CR delayed, followed by acute and overall. Final decision pending meeting with OMP.

March 8, 2010 letter to sponsor providing FDA/OMP feedback

- Sponsor told that PALO-10-01 (HEC; oral Aloxi 0.5 mg vs. I.V. Aloxi 0.25 mg) and NETU-07-07 (HEC) will be acceptable to support efficacy of the combination for the prevention of acute and delayed CINV-HEC, provided that FDA is able,

after their review of the NETU-07-07 data, to confirm its positive outcome, and if the outcome of PALO-10-01 is also positive.

- (b) (4) does not appear to be necessary
- For NETU-08-18 (MEC) an oral Aloxi 0.5 mg arm should be included in study design as a separate arm or by replacing the (b) (4) active comparator
- For NETU-08-18 the primary efficacy endpoint can be tested either as a co-primary endpoint consisting of acute and delayed phases, or tested hierarchically with delayed phase followed by acute and overall, to control Type I error.

March 17, 2010 letter clarifying (b) (4)

- The division stated that inclusion of repeat cycles and an adequate number of patients in MEC trial NETU-08-18 might be sufficient to support the safety database and inclusion of the words repeat cycle in the indication for CINV-HEC (b) (4)
- The division expressed concerns about relying on (b) (4)  
(b) (4) If the company has concerns that NETU-07-07 may not be supportive they should include (b) (4)

FDA NETU-08-18 (MEC) SPA resubmission letter May 14, 2010

- FDA stated no agreement
- FDA asked sponsor for clarification regarding plan to stratify randomization by region
- Non-key secondary endpoints supportive only (b) (4)
- FDA noted that in NETU-08-18, repeat cycle safety data would not be obtained beyond 4 cycles because the study would involve largely breast cancer patients who generally do not receive chemotherapy beyond 4 cycles. FDA indicated that additional safety data could be obtained in repeat dosing in HEC or MEC that extend beyond 4 cycles.
- Limiting population PK/PD to cycle 1 is acceptable but palonosetron PK, in addition to netupitant/metabolite PK, should be evaluated
- Troponin levels need to be reported as ng/mL rather than as a range.

PALO-10-01 SPA review letter June 18, 2010

- No agreement
- Substantial proportion of patients will have to be treated for  $\geq 6$  cycles
- To obtain "repeat courses" wording for HEC or MEC there needs to be additional safety data beyond cycle 4 for HEC or MEC patients
- NETU-07-07 will be acceptable as sole efficacy trial for combination product for acute and delayed HEC provided FDA reviews of NETU-07-07 and PALO-10-01 conclude data support efficacy and safety data beyond cycle 4.

- From an efficacy standpoint labeling in HEC will rely on observations in MEC. From safety standpoint, repeat cycle labeling claim will need to be obtained from HEC and/or MEC.

Meeting minutes Sept. 7, 2010 NETU-08-18 & PALO-10-01 SPA meeting (7/15/10)

Discussion of protocol NETU-08-18 (CINV-MEC)

- Randomized treatment assignments and maintenance of the blind will continue beyond cycle 1 in the NETU-08-18 multi-cycle extension
- Agency agreed that primary objective of NETU-08-18 is to demonstrate superiority of combination to oral Aloxi 0.5mg CR in the delayed phase (25-120h)
- Primary endpoint NETU-08-18 is CR delayed, key secondary CR acute and CR overall
- Sensitivity analyses should be performed and pre-specified
- FDA asked sponsor to capture repeat cycle safety data beyond cycle-4 for the Combination in phase 3 and emphasized the importance of having a control arm for the safety assessment
- Population PK assessment can be limited to cycle 1
- FDA recommended that palonosetron PK blood samples be obtained, in addition to those already planned for netupitant and netupitant metabolites M1, M2 and M3, in the population PK analysis. Sponsor agreed and FDA stated the proposed PK plan is acceptable.

Discussion of protocol PALO-10-01 (HEC)

- Agency agreed to primary and secondary endpoints, inclusion/exclusion criteria, safety measures
- Type I error controlled at 1% (2-sided) level
- 15% non-inferiority margin acceptable
- FDA agreed the proposed analysis populations (FAS, PP, Safety) are acceptable but should also include the ITT population (all randomized patients).

Discussion of protocol NETU-07-07

- NETU-07-07 acceptable as sole efficacy trial for fixed dose combination capsule in acute and delayed CINV-HEC prevention provided the reviews of NETU-07-07 and PALO-10-01 conclude the data support efficacy and there are sufficient data beyond cycle 4
- FDA stated that CR in the delayed phase was the primary analysis of interest even though overall phase CR was the pre-specified primary endpoint; a CMH test instead of the pre-specified logistic regression model should be the primary analysis
- FDA agreed that full analysis set (FAS) can serve as primary analysis but ITT should be performed as a sensitivity analysis
- For labeling for repeat cycles from an efficacy standpoint HEC will rely on MEC observations from study NETU-08-18. From safety standpoint repeat cycle labeling claims will need to be obtained from HEC and/or MEC.

NETU-08-18 (MEC) SPA agreement letter, Nov. 3, 2010

- FDA confirmed that if NETU-08-18 repeat cycle efficacy data are favorable for the Combination, these MEC repeat cycle efficacy results would be suitable to support inclusion of “repeat course” wording in both the target indications for MEC-CINV and HEC-CINV.
- FDA agreed that the proposed analysis populations (FAS as main efficacy analysis population) are acceptable. FDA stated that the results of ITT sensitivity analysis are expected to be consistent with FAS in order to support approval.

PALO-10-01 (HEC) SPA agreement letter, Nov. 3, 2010

- FDA agreed that the full analysis set (FAS) and per protocol (PP) populations are acceptable for primary efficacy analysis. However the ITT sensitivity analysis will be an important review component for assessing non-inferiority.

NETU-10-29 (HEC/MEC) advice letter, Nov. 19, 2010

- Patient population acceptable for obtaining repeat cycle safety data, but FDA recommends sponsor enroll patients who are receiving repeat dose anthracycline therapy.
- Active control (3-day Aprepitant regimen + 0.5mg oral palonosetron) is acceptable.
- FDA recommends stratify randomization by chemotherapy type (HEC or MEC) to achieve 3:1 balance within each stratum.

February 14, 2011 t-con

- Siemens' ADVIA Centaur Tnl-Ultra assay for troponin acceptable for use in phase 3 studies.

FDA/DMEPA letter, Dec. 8, 2011 regarding proprietary name

- Proprietary name Akynzeo acceptable. Request for proprietary name for Akynzeo should be submitted with NDA. If proposed product characteristics are altered prior to submission of the NDA the proprietary name should be resubmitted for review.

CMC t-con Feb. 29, 2012 regarding colorant

- Discussion of (b) (4). FDA agreed with submission of long-term stability data and 3 month accelerated data for caramel capsule but noted that this data may only support an (b) (4) month expiration period based on real time data. If an issue arises with 24-month stability data on (b) (4) capsule the sponsor may not be able to request 24-month or (b) (4) - month expiry period for the white/caramel capsule depending upon nature of issue.
- Company stated that the change in (b) (4) is not expected to have impact on the critical quality attributes of drug product. The company does not plan to use the caramel capsule in clinical trials. FDA agreed but said sponsor must demonstrate that caramel capsule conforms to all specifications, including dissolution specifications.

FDA letter May 31, 2012 regarding ISS, ISE, SC and Datasets

- FDA agreed with plan to not integrate results from phase 2/3 trials for efficacy analysis.
- FDA agreed with sponsor's plans to provide a Summary of Clinical Efficacy (SCE-CTD Module 2, section 2.7.3) outlining and discussing each of the three critical efficacy studies and providing other supporting efficacy information from the development program as appropriate. Since there is no proposed integrated efficacy analysis, the sponsor plans to provide only an overall demographic and disposition table for the four Phase 2 and 3 studies in CTD Module 5, section 5.3.5.3.
- Sponsor plans to pool phase 2/3 studies in cancer patients (NETU-07-07, NETU-08-18, NETU-10-29, and PALO-10-01) in integrated safety database and provide tabular presentations of number of patients exposed by dose, number of healthy volunteers exposed by dose in phase 1 trials, number of patients/volunteers exposed by dose in other (non-CINV) trials. All non-integrated safety data discussed as appropriate in SCS. FDA agreed.
- In repeat cycle trial sponsor will present AE analyses by number and percentage of patients with AEs in cycle 1 and throughout the study, number and percentage of cycles with AEs, subpopulation with at least 6 cycles, the number and percentage of patients with AEs by cycle. FDA agreed but stated that the sponsor should present an analysis of individual AEs that examines whether there is an increase in incidence rate with increase in number of exposures.
- Sponsor proposes to submit study data tabulations and not individual patient data listings; efficacy and safety data from NETU- 07-07, NETU-10-29, NETU-08-18, and PALO-10-01 following CDISC standards.
- For phase 1 studies the sponsor will provide both tabulations and analysis datasets for study NETU-07-20 (tQT study) and tabulation datasets for PK and safety data only for BE-formulation-bridging studies NETU-09-07 and NETU-11-02. FDA found proposal to submit study data tabulations and not individual patient data listings acceptable.
- For the population PK analysis NETU-10-02, FDA requested that (1) all model development and validation should be submitted as SAS transport files, (2) model codes or control streams and output listings should be provided for all major model building steps, (3) a model development decision tree and/or table with an overview of modeling steps should be provided, and (4) for the population analysis reports submit standard model diagnostic plots and individual plots for a representative number of subjects.

FDA correspondence August 31, 2012 repeat cycle safety data tables

- FDA agreed with sponsor's plan to evaluate whether there is an increase in incidence rate with increase in number of exposures.
- FDA agreed with sponsor's plan to not submit PK tabulation datasets for older PK studies conducted by Roche.

FDA telephone feedback regarding submission of Pediatric Study Plan Jan. 31, 2012 (not in DARRTS)

- If combination NDA submitted in 2013, PSP should be included in NDA.

FDA March 28, 2013 feedback regarding Controlled Substances staff review of preclinical abuse liability study

- CSS expressed need to determine if Netupitant is associated with abuse liability since Netupitant is a new molecular entity. FDA CSS reviewers review abuse liability study reports submitted to the IND in advance of the NDA to determine if additional preclinical or clinical abuse liability studies are required. In response, Sponsor emailed all abuse liability study reports to the FDA Project Manager and submitted the all reports to the IND.

Pre-NDA meeting April 16, 2013

- FDA noted that NETU-08-18 is the sole MEC pivotal efficacy trial using AC therapy, and AC chemotherapy recently reclassified as HEC. If approved, labeling will describe regimens studied. The division is moving beyond HEC and MEC classifications due to evolution of opinions in clinical medicine, particularly as new chemotherapy drugs are approved. The sponsor expressed concern about FDA changing definition of target indications since it can have substantial impact on drug use. The MEC and HEC indications were the basis for the phase 2/3 efficacy program, as agreed with FDA during the SPA process. FDA stated that the approved label will describe the chemo regimens studied, and wording of indications will be a review issue.
- FDA agreed with proposed Summary of Clinical Safety and Integrated Safety Summary.
- Sponsor agreed to perform in-vitro transporter interaction study on M2 to include in NDA.
- FDA asked sponsor to submit safety and PK data in cancer patients analyzed by kidney function. Sponsor indicated that less than 5% of oral Netupitant is excreted renally as unchanged drug or metabolites. As per discussion at End-of-Phase 2 meeting, no specific renal impairment PK studies were performed. Population PK/PD study NETU-10-02 will be performed on a sizable subset of about 500 cancer patients in MEC efficacy study NETU-08-18, and this analysis will evaluate the impact of calculated creatinine clearance on the PK of Netupitant and Netupitant metabolites M1, M2 and M3. Sponsor noted that in clinical practice renal impairment limits the use of cytotoxic chemotherapy and this was an exclusion criterion in all phase 3 studies. Therefore there may not be many patients with impaired renal function in the NDA safety database. FDA stated this will be a review issue. In order to provide appropriate labeling for renal impairment a postmarketing special population safety study may be required.
- FDA asked that a Clinical Pharmacology Summary written according to FDA Question and Answer template be completed. However this is not a replacement for modules 2.7.1 or 2.7.2. The Summary should be placed in module 2 as an appendix.

- Abuse Liability Studies – Sponsor should include all abuse liability study reports as part of pharm/tox studies in NDA. (b) (4) Justification for (b) (4) should be in the NDA and will be a review issue.
- Abuse Potential Assessment Section of NDA – Drug Abuse Potential Assessment Section of NDA should be a compilation of abuse liability studies and a summary of abuse-related AEs observed in clinical trials. FDA provided an outline of eCTD sections that need to include abuse potential information. The Abuse Potential Assessment section should provide a justification if a human abuse potential study was not conducted.
- CMC - Drug Product. FDA required evaluation of elemental impurities on drug product in accordance with USP <232>. A justification for omitting (b) (4) testing of the finished capsule will be required in the NDA. A complete description of the manufacturing and testing procedures for the novel excipient in the capsule in the NDA or in a DMF is needed. The capsule dissolution method and acceptance criteria were also discussed and the sponsor will have to prove the discriminating abilities of the dissolution methods for both the APIs present in the combination product.
- Pediatric Plan – Sponsor indicated that Pediatric Plan will be included in the NDA. An agreeable pediatric plan must be provided prior to the NDA PDFUA date. FDA comments on the pediatric plan will be communicated to the sponsor during the NDA review period.
- REMS – Based on review of safety data in pre-NDA meeting package a REMS is not anticipated.

## 2.6 Other Relevant Background Information

None.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

Six clinical sites and the sponsor headquarters were inspected by the Office of Scientific Investigations. Inspection sites were chosen to be representative of the four main safety and efficacy trials conducted in cancer patients. Due to political unrest in Russia and Ukraine only one Russian site was inspected. All clinical sites had the classification of no deviation from regulations (NAI) or deviation from regulations (VAI) with minor regulatory violation cites. The following is a listing of sites that were inspected, and results of these inspections.

**Table 1 Inspection Results (by site)**

Name, Address and Type of Inspected Entity	Protocol # Site # and # of Subjects	Inspection Date	Final Classification*
CI: Dr. Tibor Csozsi Tószegi út 21, H-5004 Szolnok Hungary	NETU-08-18/ Site 5403/ 47 Subjects  PALO-10-01/ Site 5405/ 45 Subjects	January 13 to 23, 2014	VAI
CI: Dr. Anna Lowczak ul. Kuracyjna 30 82-550 Prabuty, Poland	NETU-10-29/ Site 5607/ 30 Subjects	January 27 to 30, 2014	NAI
CI: Dr. Katarzyna Zajad ul. Roentgena 5 02-781 Warszawa, Poland Phone: +48.225.462.169	PALO-10-01/ Site 5602/ 37 subjects	January 20 to 24, 2014	VAI
CI: Dr. Anna V. Alyasova 2 Nizhne-Volzhsкая Nab. 603001 Nizhny Novgorod, Russia	NETU-07-07/ Site 101/ 37 subjects	December 9 to 13, 2013	VAI
CI: Dr. Mamillapalli Gopichand #33-25-33 Venkatakrishanayya Street Suryaraopet Vijayawada 520002, India	NETU-08-18/ Site 3102/ 55 Subjects	February 10 to 14, 2014	NAI
CI: Professor Narendra Khippal S.M.S. College and Hospital Shastri Nagar, Jaipur, India, 302016	NETU-10-29/ Site 4205/ 20 Subjects	February 3 to 7, 2014	NAI
Sponsor: Helsinn Healthcare SA Via Pian Scairolo 9 Pazzallo-Lugano Switzerland	NETU-07-07 NETU-08-18 NETU-10-29 PALO-10-01	March 24 to April 4, 2014	Pending* (preliminary NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

\*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

In addition to inspection results above, Phase 2 dose-ranging and HEC trial NETU-07-07 had an in-depth quality assurance auditing process by the sponsor after the FDA agreed that the trial could be used to support CINV-HEC. As outlined in the clinical study report, 55% of the records of patients enrolled in the study were audited. Site No. 120 in Russia (Principal Investigator Dr. Vadim Popov) was found to have multiple protocol violations. To further investigate the impact these protocol violations at Site 120 on the efficacy assessment for the trial the division asked the sponsor to perform additional analysis including and excluding patients from site 120.

*The statistical reviewer confirmed the sponsor's sensitivity analysis results and concluded that the impact of Site #120 on the efficacy of PALO+NETU in the three doses do not seem to be markedly severe and should not be a concern although not all the efficacy results shown for the PALO+NETU 300 mg are statistically significant.*

### **3.2 Compliance with Good Clinical Practices**

The studies were conducted according to the ethical principles expressed in the World Medical Association's Declaration of Helsinki, the ICH guideline for GCP (ICH E6), and applicable national and local laws and regulations for conducting clinical research and protecting privacy. Approval was obtained from the appropriate regulatory authorities before the study was initiated in participating countries. Informed consent was obtained for all patients participating in trials to support this application.

### **3.3 Financial Disclosures**

For Phase III studies PALO-10-01, NETU-08-18, and NETU-10-29 the sponsor has certified that they have not entered into any financial arrangement with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. NETU-07-07 was a Phase II study conducted earlier in the clinical development program. Later, after the FDA agreed that the trial could be used to demonstrate efficacy of the netupitant component, the company attempted to locate investigators to obtain financial disclosure information.

The sponsor has certified that they have acted with due diligence to obtain information required under 21 CFR 54.4. The company notes in the financial disclosure section of the NDA that, together with the CRO, the following methods were undertaken to obtain information with regard to financial interests of the investigators in the outcome of NETU-07-07:

- A list of PI and subinvestigators and their original mailing addresses and telephone numbers were prepared. A total of 195 primary investigators and subinvestigators were included.
- For investigators no longer at that site, an internet search, university and hospital websites, websites for physician professional organizations, and Human Resources of the hospital were used
- A list of current contact information was compiled.
- If investigators did not respond after multiple attempts at phone and email contact, continued internet research in conjunction with efforts from human resources at the hospital where investigators were previously employed were employed.

Ultimately, completed and signed financial disclosure forms were obtained for 181 investigators for Phase 2 trial NETU-07-07.

*Medical Officer's Comment:*

*The company exercised due diligence in their attempts to obtain financial disclosure from 100% of investigators and subinvestigators. Further, the company has outlined the*

*steps that were taken to obtain this information. This reviewer believes all possible measures were taken.*

#### 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

##### **4.1 Chemistry Manufacturing and Controls**

Reference is made to the CMC review.

##### **4.2 Clinical Microbiology**

Not applicable since not an intravenous formulation.

##### **4.3 Preclinical Pharmacology/Toxicology**

Reference is made to the PharmTox review

##### **4.4 Clinical Pharmacology**

###### **4.4.1 Mechanism of Action**

Palonosetron and netupitant exert their effects by means of different pathways. Netupitant acts at the NK-1 (neurokinin 1) receptor and blocks the action of Substance P. It has its greatest effect on delayed emesis. Palonosetron works at the 5-HT<sub>3</sub> (serotonin) receptor, and works primarily by blocking the emetic impulse in the first 24 hours post cytotoxic cancer chemotherapy.

###### **4.4.2 Pharmacodynamics**

Pharmacodynamic results are exploratory only. The NDA submission references results from a positron emission tomography (PET) study demonstrating that netupitant binds to NK1 receptors for a duration that covers the 120-hour period in CINV. At 6 hours post-dose, close to the expected C<sub>max</sub>, netupitant showed high NK1 receptor occupancy (90% or higher) for the occipital cortex and frontal cortex for all investigated doses (100, 300 and 450 mg), and for the striatum for the 300 mg and 450 mg netupitant doses. Based on these PK/PD parameter estimates, a netupitant plasma concentration of 225 µg/L corresponded to NK1 receptor occupancy of 90% in striatum [NETU-06-08]. These results suggested that an effective netupitant dose would be between 100 mg and 300 mg.

###### *Medical Officer's Comment:*

*Assessment of the PD marker of NK1 receptor occupancy by means of a PET study is not a clinical outcome measure. The above information is exploratory only.*

#### 4.4.3 Pharmacokinetics

Pharmacokinetic parameters for netupitant were obtained during the Akynzeo development program, whereas the clinical pharmacology of palonosetron was detailed during the clinical development of Aloxi. Plasma concentrations of netupitant follow a first order absorption with  $T_{max}$  ~ 5 hours. Females have a slightly higher exposure to netupitant than males. Three major metabolites (M1, M2, and M3) have been detected in human plasma at netupitant oral doses of 30mg and higher. All metabolites were shown to be pharmacologically active. The apparent median elimination half-life of netupitant in cancer patients was 88 hours after a single oral dose of the FDC.

Netupitant is metabolized via the CYP3A4 pathway. When given with a strong CYP3A4 inhibitor (e.g. ketoconazole) the peak plasma concentration of Akynzeo was increased by 25%, and the AUC was increased by 140%. When co-administered with rifampicin, a strong CYP3A4 inducer, the systemic exposure to netupitant was decreased by 82%. Thus when Akynzeo is given with medications that induce CYP3A4 activity the reduction in netupitant plasma concentrations could result in decreased efficacy.

Dexamethasone doses should be reduced when given with Akynzeo. Doses of chemotherapy agents metabolized by CYP3A4 were not adjusted in clinical trials, and mild increases in systemic exposure were shown for docetaxel and etoposide when co-administered with Akynzeo versus oral palonosetron alone. No clinically relevant interactions with oral contraceptives have been shown. The potential effects of increased plasma concentrations of midazolam or similar benzodiazepines metabolized via CYP3A4 should be considered by health care practitioners administering Akynzeo.

*Medical Officer's Comment:*

*The sponsor was sent an information request to address the issue of increases in systemic exposure of the chemotherapeutic agents docetaxel, etoposide, ifosfamide and cyclophosphamide when given in conjunction with Akynzeo. The sponsor responded to the IR by providing more detailed information on SAEs and certain TEAEs experienced by patients receiving these drugs. The overall conclusion of the sponsor is that there is no evidence of increased frequency in SAEs (including death) and TEAEs of interest in the FDC group compared to other treatment groups. The medical reviewer concurs with the sponsor's conclusions.*

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Table 2 lists the key safety and efficacy studies upon which this review is based.

**Table 2 Tabular Listing of Pivotal Studies**

Phase 2 Studies					
NETU-07-07	Pivotal evidence of FDC efficacy in HEC	Randomized (1:1:1:1), double-blind, active-controlled parallel group	Patients scheduled to receive HEC-based chemotherapy (cisplatin $\geq 70$ mg/m <sup>2</sup> ) for solid tumors	694 randomized 679 treated (77M, 59F) 19-77 yrs	Single-cycle Palonosetron PO, Palonosetron + Netupitant 100 mg, Palonosetron + Netupitant 200, Palonosetron + Netupitant 300, or Aprepitant +Ondansetron
Phase 3 Studies					
NETU-08-18	Pivotal evidence of FDC efficacy in MEC	Randomized (1:1), double-blind, active-controlled parallel group	Patients scheduled to receive the first course of an anthracycline and cyclophosphamide containing MEC regimen for malignant solid tumors	1455 randomized 1450 treated (28M, 1422F) 22-79 yrs	Single and Multiple cycle PO Netupitant/ palonosetron FDC 300/0.5 mg Palonosetron 0.5 mg
NETU-10-29	Safety and supportive efficacy of FDC in MEC and HEC	Double-blind, randomized (3:1) active-controlled parallel group	Patients receiving either HEC or MEC regimen for any malignant tumor	413 randomized 412 treated (206M, 206F) 21-80 yrs	Multiple cycle Netupitant/ palonosetron FDC 300/0.5 mg  Aprepitant + palonosetron oral
PALO-10-01	Efficacy of PO palonosetron alone in HEC	Randomized (1:1), double-blind, parallel group	HEC	743 randomized 739 treated (436M, 303F) 20-83 yrs	Single-dose Palonosetron oral 0.50 mg PalonosetronIV 0.25 mg

Ref: 5.2 Tabular Listing of All Clinical Studies, p. 11.

## 5.2 Review Strategy

The clinical review focuses on four main studies: Phase 3 studies NETU-08-18, NETU-10-29, and PALO-10-01, and Phase 2 study NETU-07-07. Each makes a unique contribution to the overall indications being sought by the sponsor.

## 5.3 Discussion of Individual Studies/Clinical Trials

***NETU-08-18 (MEC) “A phase III multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group study of the efficacy and safety of oral netupitant administered in combination with palonosetron and dexamethasone compared to oral palonosetron and dexamethasone for the prevention of nausea and vomiting in cancer patients receiving moderately emetogenic chemotherapy”***

The primary objective of this trial was to compare the efficacy of a single oral dose of a fixed combination of netupitant 300mg and palonosetron 0.50 mg given with oral dexamethasone, versus oral palonosetron 0.50 mg with oral dexamethasone in terms of complete response in the delayed phase (25-120 hours) at cycle 1 in MEC patients. The secondary objectives were to compare the efficacy, safety and tolerability of a single oral dose of netupitant/palonosetron with oral dexamethasone to oral palonosetron 0.50 mg with oral dexamethasone for the prevention of MEC induced nausea and vomiting in initial and repeat cycles. An additional objective was to assess the population PK and

PD of netupitant (and its metabolites M1, M2 and M3) and palonosetron in patients receiving the combination product.

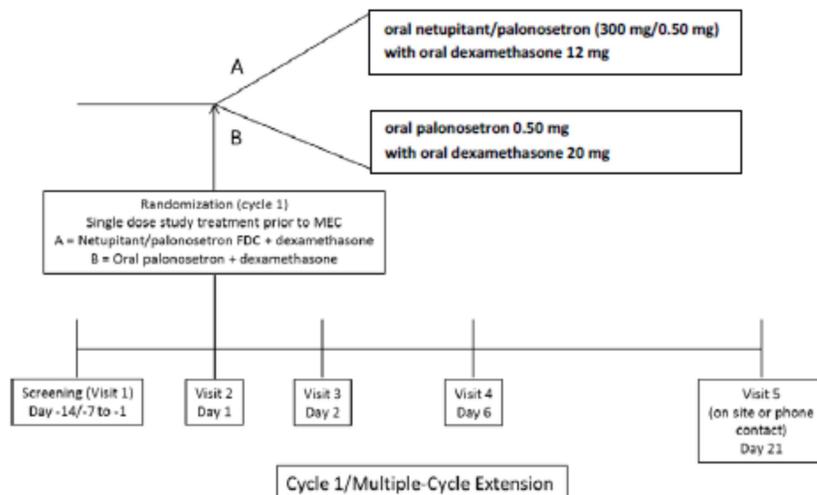
Patients were randomized to receive either oral netupitant/palonosetron (300mg/0.50mg) with 12 mg oral dexamethasone, or oral palonosetron 0.50mg with 20 mg oral dexamethasone before the administration of MEC on the first day of chemotherapy cycle 1. The dose of dexamethasone was reduced to 12 mg in the netupitant/palonosetron arm based on results of drug-drug interaction studies showing a clinically relevant increase in dexamethasone exposure when administered with netupitant. (See section 7.5.5 Drug Interactions)

The number of patients randomized in the study was planned to be 1460, equally distributed in two groups. For a two-sided test of difference using alpha equal to 0.050, a sample size of 661 evaluable patients per group was planned to ensure 90% power to detect a difference of 9% (assuming a CR rate in the delayed phase at cycle 1 of 60% in the fixed combination arm and 51% in the palonosetron arm). The target study population was adult chemotherapy naïve male or female patients with a malignant solid tumor requiring treatment with an anthracycline-based regimen on Day 1 of each cycle. (i.e. cyclophosphamide I.V. (500 to 1500 mg/m<sup>2</sup>) and I.V. doxorubicin (≥40 mg/m<sup>2</sup>) or cyclophosphamide I.V. (500 to 1500 mg/m<sup>2</sup>) and I.V. epirubicin (≥ 60 mg/m<sup>2</sup>)).

The total number of visits per patient/cycle was 5, and each patient could participate in multiple consecutive repeat cycles if they continued to fulfill the inclusion exclusion criteria. The total study duration per patient was to be approximately 5 weeks in cycle 1 and at least 4 weeks in each cycle of the Multiple-Cycle Extension. Figure 1 provides an overview of the study design.

Figure 1 Study Design and Plan

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Abbreviations: FDC=Fixed-Dose Combination; MEC=Moderately Emetogenic Chemotherapy.

NETU-08-18 Clinical Study Report p.30.

#### Inclusion Criteria – Major Inclusion criteria were:

- Male or female patients  $\geq 18$  years of age
- Scheduled to receive first course of an anthracycline and cyclophosphamide containing MEC regimen for the treatment of a solid malignant tumor: cyclophosphamide I.V. (500 to 1500 mg/m<sup>2</sup>) and I.V. doxorubicin ( $\geq 40$  mg/m<sup>2</sup>) or cyclophosphamide I.V. (500 to 1500 mg/m<sup>2</sup>) and I.V. epirubicin ( $\geq 60$  mg/m<sup>2</sup>).
- Female patients of non-childbearing potential or require a negative urine dipstick pregnancy test within 24-hours prior to day 1 and with acceptable contraceptive use (outlined in protocol)
- ECOG performance status of 0,1 or 2

#### Inclusion criteria for multiple-cycle extension

- Considered appropriate by investigator and does not pose unwarranted risk
- Satisfactory compliance in preceding cycle of chemotherapy
- Scheduled to receive same chemotherapy regimen as cycle 1
- Adequate hematologic and metabolic status

#### Exclusion criteria – Major Exclusion criteria

- Pregnant or lactating female
- Scheduled to receive HEC
- Any medication with known or potential antiemetic activity within 24 hours prior to day 1 of cycle 1
- CNS malignancy

#### Exclusion Criteria for Multiple-cycle extension

- If female, pregnant or lactating, (positive urine dipstick pregnancy test within 24 hours prior to Day 1)
- Active infection or uncontrolled disease except for malignancy
- Use of restricted medications
- Any vomiting, retching, or mild nausea (grade  $\geq 1$  as defined by National Cancer Institute) within 24 hours prior to Day 1

### **Efficacy Assessments**

Efficacy assessments started at the time of chemotherapy administration. Efficacy parameters were evaluated in the delayed phase (25 to 120 hours after the start of chemotherapy), acute phase (0 to 24 hours after the start of chemotherapy) and overall phase (0-120 hours after the start of chemotherapy).

### **Primary efficacy endpoint**

The primary efficacy endpoint is the proportion of patients with complete response (CR) (no emesis, no rescue medication) in the time interval 25-120 hours after the start of the MEC administration at cycle 1.

### **Secondary efficacy endpoints at cycle 1**

Key secondary efficacy endpoints are defined as the proportion of patients with:

- Complete response during the acute phase
- Complete response during the overall phase

#### *Medical Officer's Comments:*

*Primary endpoints and key secondary efficacy endpoints were agreed to by the Agency in a Special Protocol Assessment, and are suitable for inclusion in the product label.*

*The primary endpoint of CR delayed will isolate the effect of the Netupitant component in the delayed phase since palonosetron exerts its primary effect during the acute 0-24 hour time period.*

Other secondary efficacy endpoints are defined as the proportion of patients with:

- no emesis during the delayed, acute and overall phase
- no rescue medication during the delayed, acute and overall phase
- no significant nausea (maximum Visual Analogue Scale (VAS) $<25$  mm) during the delayed, acute and overall phase
- no nausea (maximum VAS $<5$  mm) during the delayed, acute and overall phase
- complete protection (no emetic episode, no rescue medication and no significant nausea), during the delayed, acute and overall phase
- total control (no emetic episode, no rescue medication and no nausea) during the delayed acute and overall phase

### **Other efficacy endpoints at cycle 1**

- proportion of patients with severity of nausea, defined as the maximum nausea on the VAS in the delayed, acute and overall phase
- time to first emetic episode, time to first rescue medication, time to treatment failure (based on time to the first emetic episode or time to the first rescue medication, whichever occurs first)
- impact on subjects' daily life activities for the first 120 hours following the administration of chemotherapy as assessed by the FLIE questionnaire

#### **Secondary efficacy endpoints evaluated during the Multiple-Cycle Extension**

- complete response during the delayed, acute and overall phase in each subsequent cycle of MEC
- no significant nausea during the delayed, acute and overall phase in each subsequent cycle of MEC

#### **Medical Officer's Comment:**

*The impact on subjects' daily life activities for the first 120 hours following the administration of chemotherapy as assessed by the Functional Living Index-Emesis (FLIE) questionnaire is exploratory only. The Study Endpoints and Labeling Development (SEALD) team reviewed*

(b) (4)

(b) (4)

(b) (4) *Non-key endpoints, including*

*FLIE, will be considered exploratory evidence, not confirmatory evidence of treatment efficacy. Furthermore, the sponsor did not submit any information to support development and validation (i.e., content validity, psychometric validation, translation and cultural adaptation) of the FLIE. At face value it is questionable whether patients can determine independent contributions of nausea and vomiting on their daily life when both of these symptoms are present. (Ref: Study Endpoint Consult Review, Dr. Paivi Miskala, 3/4/14)*

#### **Safety Assessments**

The following safety assessments were to be obtained in each cycle: physical examination (PE), vital signs, 12-lead electrocardiogram (ECG), cardiac troponin levels (cTnI), laboratory tests (hematology, blood chemistry, urinalysis), and adverse events (AEs) assessment. Left Ventricular Ejection Fraction (LVEF) will be assessed at screening cycle 1 and at the end of study.

Upon regulatory request, particular attention was paid to cardiac, CNS and psychiatric adverse events, defined as 'events of special interest', and identified based on pre-defined standard MedRA Queries (SMQs). The CNS SMQs were: anticholinergic

syndrome, convulsions, dementia, depression and suicide-self injury, extrapyramidal syndrome, hostility-aggression, neuroleptic malignant syndrome, non-infectious encephalitis, non-infectious encephalopathy delirium, non-infectious meningitis, psychosis and psychotic disorders. The Cardiac SMQs were: cardiac arrhythmias, cardiac failure, cardiomyopathy, embolic and thrombotic events, ischemic heart disease, and Torsade de pointes-QT prolongation. In addition 5 more MedDRA PTs were added as TEAEs of special interest: anxiety, insomnia, sleep disorders, euphoric mood and obsessive thoughts.

### **Study Results- Disposition**

A total of 1455 patients were randomized; 1450 received study medication. A total of 39 (2.7%) patients discontinued from the study after randomization and during one of the planned chemotherapy cycles. Most patients (1438 (98.8%)) completed cycle 1, and 1286 patients participated in the multicycle extension. The main reasons for discontinuation were “other”, inclusion/exclusion criteria not met for multiple cycle extension, and withdrawal of consent. Discontinuations for AEs were 1.4% in the Netu/Palo arm and 2.6% in the Palo arm. The category “other” was used when study closure occurred (i.e. when the last enrolled patient completed their last scheduled chemotherapy cycle), and was stipulated in the protocol. The primary analysis population was Full Analysis Set (FAS), defined as all patients who were randomized to treatment and received a MEC regimen and study drug. Table 3 shows patient disposition by ITT population.

**Table 3 Summary of Patient Disposition - ITT**

	NETU/PALO		PALO alone		Overall	
	n	(%)	n	(%)	n	(%)
Randomized	726	(100.0)	729	(100.0)	1455	(100.0)
Treated	724	(99.7)	726	(99.6)	1450	(99.7)
Completed Planned/Unplanned Chemotherapy Cycles	453	(62.4)	463	(63.5)	916	(63.0)
Completed Planned Chemotherapy Cycles but Discontinued During Additional Unplanned Cycle	2	(0.3)	0		2	(0.1)
Completed a Cycle But Not Continuing in the Next Planned Cycle	253	(34.8)	245	(33.6)	498	(34.2)
Discontinued After Randomization and During any Planned Chemotherapy Cycle	18	(2.5)	21	(2.9)	39	(2.7)
<b>Reason for Not Continuing or for Discontinuation</b>						
Inclusion/Exclusion Criteria not Met (Multiple-Cycle Extension)	55	(7.6)	66	(9.1)	121	(8.3)
Adverse event	10	(1.4)	19	(2.6)	29	(2.0)
Death	0		2	(0.3)	2	(0.1)
Protocol Violation	5	(0.7)	6	(0.8)	11	(0.8)
Lost to Follow-up	0		5	(0.7)	5	(0.3)
Withdrawal of Consent	65	(9.0)	42	(5.8)	107	(7.4)
Lack of Efficacy	1	(0.1)	3	(0.4)	4	(0.3)
Sponsor's Decision	0		0		0	
Other	136	(18.7)	123	(16.9)	259	(17.8)

Netu08-18 study report, Table 4, p.64.

NETU-08-18 was one of two Phase 3 studies submitted with this application that collected data on patients beyond cycle 1. A total of 1286 patients entered into cycle 2. By cycle 6 the number had fallen to 388, still more than the 100 patients needed for long term exposure. Table 4 shows patient disposition for additional cycles.

**Table 4 Patient Disposition by Cycle**

	NETU/PALO FDC (N=726)		PALO alone (N=729)		Overall (N=1455)	
	n	(%)	n	(%)	n	(%)
Scheduled for Treatment Cycle 2	635	(87.5)	651	(89.3)	1286	(88.4)
Treated Cycle 2	635	(87.5)	651	(89.3)	1286	(88.4)
Completed Cycle 2	630	(86.8)	645	(88.5)	1275	(87.6)
Scheduled for Treatment Cycle 3	598	(82.4)	606	(83.1)	1204	(82.7)
Treated Cycle 3	598	(82.4)	605	(83.0)	1203	(82.7)
Completed Cycle 3	596	(82.1)	603	(82.7)	1199	(82.4)
Scheduled for Treatment Cycle 4	551	(75.9)	560	(76.8)	1111	(76.4)
Treated Cycle 4	551	(75.9)	560	(76.8)	1111	(76.4)
Completed Cycle 4	548	(75.5)	559	(76.7)	1107	(76.1)
Scheduled for Treatment Cycle 5	272	(37.5)	249	(34.2)	521	(35.8)
Treated Cycle 5	271	(37.3)	249	(34.2)	520	(35.7)
Completed Cycle 5	268	(36.9)	248	(34.0)	516	(35.5)
Scheduled for Treatment Cycle 6	197	(27.1)	191	(26.2)	388	(26.7)
Treated Cycle 6	197	(27.1)	191	(26.2)	388	(26.7)
Completed Cycle 6	197	(27.1)	191	(26.2)	388	(26.7)
Scheduled for Treatment Cycle 7	3	(0.4)	3	(0.4)	6	(0.4)
Treated Cycle 7	3	(0.4)	3	(0.4)	6	(0.4)
Completed Cycle 7	3	(0.4)	3	(0.4)	6	(0.4)
Scheduled for Treatment Cycle 8	3	(0.4)	2	(0.3)	5	(0.3)
Treated Cycle 8	3	(0.4)	2	(0.3)	5	(0.3)
Completed Cycle 8	3	(0.4)	2	(0.3)	5	(0.3)

Ref: NETU08-18 Study Report, Table 5, p.65.

**Medical Officer's Comment:**

*Disposition and reasons for discontinuation appear balanced. The number of patients treated in subsequent cycles is similar between the Netupitant/Palonosetron and Palonosetron group.*

**Study Sites**

There were 177 study sites in 15 countries participating in the study. No study sites have been identified that should be excluded from the analysis. Most patients were randomized from India and Ukraine, with the United States contributing among the smallest number of patients. Participating countries are shown in Table 5.

**Table 5 Study Sites**

Region Country	Sites Activated for Recruitment	Sites Enrolling Patients	Patients Randomized
<b>Asia</b>			
India	14	13	200
<b>Commonwealth of Independent States</b>			
Belarus	6	6	81
Russian Federation	23	23	168
Ukraine	12	10	218
<b>Europe</b>			
Bulgaria	12	11	65
Croatia	9	9	89
Germany	11	8	37
Hungary	8	7	161
Italy	5	4	35
Poland	10	8	106
Romania	13	11	110
<b>Latin America</b>			
Argentina	9	6	28
Brazil	12	9	39
Mexico	5	3	51
United States	28	18	67
<b>Total</b>	<b>177</b>	<b>146</b>	<b>1455</b>

NETU08-18 CSR, Table 1, p.25.

### Demographics

Most patients were female, which is consistent with a breast cancer population receiving anthracycline+cyclophosphamide (AC) chemotherapy. Alcohol consumption was low, as was smoking. Most patients had an ECOG performance status of 0. Baseline characteristics are shown in Table 6.

**Table 6 Baseline Characteristics - Safety Population cycle 1**

Parameter	NETU/PALO FDC (N=725)		PALO alone (N=725)		Overall (N=1450)	
<b>Alcohol consumption, n (%)</b>						
No	577	(79.6)	584	(80.6)	1161	(80.1)
Occasionally	142	(19.6)	137	(18.9)	279	(19.2)
Regularly	5	(0.7)	4	(0.6)	9	(0.6)
Missing	1	(0.1)	0		1	(0.1)
<b>Tobacco consumption, n (%)</b>						
Non-smoker	605	(83.4)	599	(82.6)	1204	(83.0)
Ex-smoker	44	(6.1)	49	(6.8)	93	(6.4)
Smoker	76	(10.5)	77	(10.6)	153	(10.6)
<b>Smokers: number of cigarettes/cigars per day</b>						
N	75		77		152	
Mean (SD)	11.8	(6.50)	13.7	(8.63)	12.8	(7.69)
Median	10.0		10.0		10.0	
Min, max	1, 30		1, 40		1, 40	
<b>ECOG performance status, n (%)</b>						
Grade 0	504	(69.5)	502	(69.2)	1006	(69.4)
Grade 1	215	(29.7)	222	(30.6)	437	(30.1)
Grade 2	6	(0.8)	1	(0.1)	7	(0.5)

Ref: Netu0818, study report, table 9, p.72.

### Chemotherapy Regimen

All but one patient in each group received cyclophosphamide, and each cyclophosphamide-receiving patient also received an anthracycline (doxorubicin or epirubicin). Table 7 shows the breakdown by chemotherapy agent, by treatment group.

**Table 7 Chemotherapy in Cycle 1 - Safety Population**

<b>Parameter</b>	<b>NETU/PALO FDC (N=725)</b>		<b>PALO alone (N=725)</b>		<b>Overall (N=1450)</b>	
Cyclophosphamide, n (%)	724	(99.9)	724	(99.9)	1448	(99.9)
Cyclophosphamide: total dose (mg)						
N	724		724		1448	
Mean (SD)	989.28	(169.340)	988.16	(159.998)	988.72	(164.679)
Median	1000.00		1000.00		1000.00	
Min, max	590.0, 2400.0		600.0, 2200.0		590.0, 2400.0	
Doxorubicin, n (%)	493	(68.0)	461	(63.6)	954	(65.8)
Doxorubicin: total dose (mg)						
N	493		461		954	
Mean (SD)	97.88	(15.098)	98.22	(14.670)	98.04	(14.886)
Median	100.00		100.00		100.00	
Min, max	50.0, 150.0		50.0, 185.0		50.0, 185.0	
Epirubicin, n (%)	232	(32.0)	263	(36.3)	495	(34.1)
Epirubicin: total dose (mg)						
N	232		263		495	
Mean (SD)	132.09	(27.784)	130.25	(27.806)	131.11	(27.783)
Median	128.50		125.00		126.00	
Min, max	70.0, 200.0		70.0, 220.0		70.0, 220.0	

NETU-08-18 Study Report, p.75.

In addition to cyclophosphamide and doxorubicin or epirubicin about a third of patients received additional chemotherapeutic agents, shown in Table 8.

**Table 8 Concomitant Chemotherapy Cycles 1 - Safety Population**

Parameter	NETU/PALO FDC (N=725)		PALO alone (N=725)		Overall (N=1450)	
No concomitant chemotherapy, n (%)	490	(67.6)	494	(68.1)	984	(67.9)
Any concomitant chemotherapy, n (%)	235	(32.4)	231	(31.9)	466	(32.1)
<b>Time of concomitant chemotherapy, n (%)</b>						
Day 1 only	229	(31.6)	230	(31.7)	459	(31.7)
Days 1-5	10	(1.4)	4	(0.6)	14	(1.0)
Post 120 hours	1	(0.1)	1	(0.1)	2	(0.1)
<b>Type of chemotherapy, n (%)</b>						
<b>Anthracyclines and related substances</b>	1	(0.1)	0		1	(0.1)
Epirubicin	1	(0.1)	0		1	(0.1)
<b>Nitrogen mustard analogues</b>	1	(0.1)	0		1	(0.1)
Cyclophosphamide	1	(0.1)	0		1	(0.1)
<b>Podophyllotoxin derivatives</b>	5	(0.7)	3	(0.4)	8	(0.6)
Etoposide	5	(0.7)	3	(0.4)	8	(0.6)
<b>Pyrimidine analogues</b>	205	(28.3)	208	(28.7)	413	(28.5)
Fluorouracil	202	(27.9)	204	(28.1)	406	(28.0)
Fluorouracil sodium	3	(0.4)	4	(0.6)	7	(0.5)
<b>Taxanes</b>	21	(2.9)	12	(1.7)	33	(2.3)
Docetaxel	19	(2.6)	12	(1.7)	31	(2.1)
Paclitaxel	2	(0.3)	0		2	(0.1)
<b>Vinca alkaloids and analogues</b>	3	(0.4)	8	(1.1)	11	(0.8)
Vincristine	3	(0.4)	7	(1.0)	10	(0.7)
Vincristine sulfate	0		1	(0.1)	1	(0.1)

Ref: NETU0818 study report, Table 12, p.76.

## Efficacy

The primary efficacy endpoint was the proportion of patients with CR in the delayed time interval 25-120 hours after the start of MEC administration in cycle 1. The primary population of analysis was the FAS. The percentage of patients with CR delayed in cycle 1 was 7.4% higher in the netupitant/palonosetron group than the palonosetron group (76.9% vs. 69.5%). Superiority of the netupitant/palonosetron FDC compared to palonosetron was demonstrated using a two-sided Cochran-Maentel-Haenszel (CMH) test including treatment, age class (< 55 or ≥ 55 years old) and region (US, Latin America including Mexico, Europe, Commonwealth of Independent States and Asia) as strata.

The study results showed the superiority of netupitant/palonosetron (300mg/0.50mg) FDC over palonosetron not only with respect to the primary endpoint of CR in the delayed phase, but also key secondary endpoints, CR in the acute and overall phases. These results are shown in Table 9.

**Table 9 Complete Response delayed, acute and overall cycle 1 –Full Analysis Set**

	NETU/PALO FDC (N=724)	PALO alone (N=725)
<b>Delayed</b>		
Responder, n (%)	557 (76.9)	504 (69.5)
Difference from palonosetron alone, %	7.4	
CMH OR (95% CI)	1.48 (1.16; 1.87)	
p-value <sup>a</sup>	0.001	
<b>Acute</b>		
Responder, n (%)	640 (88.4)	616 (85.0)
Difference from palonosetron alone, %	3.4	
CMH OR (95% CI)	1.37 (1.00; 1.87)	
p-value <sup>a</sup>	0.047	
<b>Overall</b>		
Responder, n (%)	538 (74.3)	483 (66.6)
Difference from palonosetron alone, %	7.7	
CMH OR (95% CI)	1.47 (1.17; 1.85)	
p-value <sup>a</sup>	0.001	

(a) p-value from CMH test, stratified by age class and region.

NETU-08-18 Study Report p.6.

### Efficacy During Multiple Cycle Extension

Efficacy data from repeat cycles are exploratory. Exploratory efficacy analysis for the multiple-cycle extension study focuses on cycles 2 to 6 since the number of patients who continued in the study after cycle 6 was too low for evaluation. CR in the netupitant/palonosetron group was higher than in the palonosetron group in each cycle up to cycle 6. The difference in response rate in the delayed phase between netupitant/palonosetron and palonosetron groups ranged from 12.9% in cycle 2 to 5.6% in cycle 6. During the acute phase, the percentage of patients with CR in the netupitant/palonosetron group was higher than in the palonosetron group in each cycle up to cycle 6. The difference in response rate between netupitant/palonosetron and palonosetron groups ranged from 7.8% in cycle 3 to 3.0% in cycle 5. During the overall phase, the percentage of patients with CR in the netupitant/palonosetron group was higher than in the palonosetron group in each cycle up to cycle 6, ranging from 13.6% in cycle 2 to 5.2% in cycle 5.

Complete Response Delayed Cycles 2-6 [NETU-08-18]	
Cycle	Difference in Response Rate %(CR Delayed) Netu/Palo FDC – Palo alone
2	12.9
3	10.7
4	8.2
5	5.7
6	5.6

Reviewer's table

### **Safety Analysis**

The safety population was comprised of all patients who received study drugs, and consisted of 1450 patients (99.7%). Of the randomized patients, 1438 (98.8%) completed cycle 1 (719 in each treatment group), 1107 (76.1%) completed cycle 4 (548 in the netupitant/palonosetron group and 559 in the palonosetron group), and 388 (26.7%) completed cycle 6 (197 in the netupitant/palonosetron group and 191 in the palonosetron group). The maximum number of cycles was 8 but few patients remained in the study up to cycle 8. Seven patients (5 in FDC and 2 palonosetron) entering cycle 1 or the multiple-cycle extension were excluded for failing to receive study drugs. Safety was assessed at each cycle, and included physical examination, vital signs, 12-lead ECG, safety laboratory tests (hematology, chemistry, urinalysis), and adverse event monitoring.

### **Safety Overall**

In cycle 1 the proportion of patients with at least one TEAE was 76.0% in the study drug and 69.9% in the control. In the extension phase the study drug group had 83.9% TEAEs compared to 81.0% in the control. The most common TEAEs were alopecia (34.9%) and neutropenia (24.5%) in cycle 1. The most frequent TEAE related to study drugs were constipation and headache. The following Table 10 and Table 11 show selected TEAEs in cycle 1 (Table 10) and in the multiple cycle (Table 11). In cycle 1 the number of patients experiencing leukopenia, neutropenia, and alopecia were very similar between the Akynzeo arm and the palonosetron active control arm.

In the multiple cycles leukopenia, neutropenia and alopecia were again very similar between Akynzeo and palonosetron arms. Under the category of infections and infestations there was a slight imbalance between Akynzeo and control. However when the preferred terms are considered there were only 1 to 2 patients in each, not enough to draw any conclusions.

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**Table 10 TEAEs Cycle 1**

System organ class Preferred term	Netu/Palo FDC N=725 n (%) E	Palo alone N=725 n (%) E	Overall N=1450 n (%) E
Number of patients with any TEAE	551 ( 76.0) 1364	507 ( 69.9) 1222	1058 ( 73.0) 2586
Blood and lymphatic system disorders	245 ( 33.8) 351	227 ( 31.3) 337	472 ( 32.6) 688
Agranulocytosis	1 ( 0.1) 1	0 0	1 ( 0.1) 1
Anaemia	26 ( 3.6) 27	24 ( 3.3) 28	50 ( 3.4) 55
Febrile neutropenia	7 ( 1.0) 7	4 ( 0.6) 4	11 ( 0.8) 11
Granulocytopenia	1 ( 0.1) 1	1 ( 0.1) 1	2 ( 0.1) 2
Leukocytosis	5 ( 0.7) 5	2 ( 0.3) 2	7 ( 0.5) 7
<b>Leukopenia</b>	<b>96 ( 13.2) 96</b>	<b>90 ( 12.4) 92</b>	<b>186 ( 12.8) 188</b>
Lymphadenopathy	1 ( 0.1) 1	0 0	1 ( 0.1) 1
Lymphocytosis	0 0	1 ( 0.1) 1	1 ( 0.1) 1
Lymphopenia	21 ( 2.9) 21	14 ( 1.9) 14	35 ( 2.4) 35
Monocytopenia	2 ( 0.3) 2	1 ( 0.1) 1	3 ( 0.2) 3
<b>Neutropenia</b>	<b>173 ( 23.9) 173</b>	<b>182 ( 25.1) 185</b>	<b>355 ( 24.5) 358</b>
Neutrophilia	2 ( 0.3) 2	3 ( 0.4) 3	5 ( 0.3) 5
Pancytopenia	1 ( 0.1) 1	0 0	1 ( 0.1) 1
Thrombocytopenia	8 ( 1.1) 8	2 ( 0.3) 2	10 ( 0.7) 10
Thrombocytosis	5 ( 0.7) 6	4 ( 0.6) 4	9 ( 0.6) 10
System organ class Preferred term	Netu/Palo FDC N=725 n (%) E	Palo alone N=725 n (%) E	Overall N=1450 n (%) E
Skin and subcutaneous tissue disorders	264 ( 36.4) 271	261 ( 36.0) 264	525 ( 36.2) 535
<b>Alopecia</b>	<b>253 ( 34.9) 254</b>	<b>253 ( 34.9) 253</b>	<b>506 ( 34.9) 507</b>
Alopecia totalis	1 ( 0.1) 1	1 ( 0.1) 1	2 ( 0.1) 2
Dermatitis allergic	1 ( 0.1) 1	0 0	1 ( 0.1) 1
Eczema	0 0	1 ( 0.1) 1	1 ( 0.1) 1
Erythema	5 ( 0.7) 6	2 ( 0.3) 2	7 ( 0.5) 8
Hyperhidrosis	2 ( 0.3) 2	0 0	2 ( 0.1) 2
Nail bed disorder	0 0	1 ( 0.1) 1	1 ( 0.1) 1
Pain of skin	1 ( 0.1) 1	2 ( 0.3) 2	3 ( 0.2) 3
Pruritus	1 ( 0.1) 1	0 0	1 ( 0.1) 1
Rash	1 ( 0.1) 1	1 ( 0.1) 1	2 ( 0.1) 2
Rash pruritic	0 0	1 ( 0.1) 1	1 ( 0.1) 1
Red man syndrome	1 ( 0.1) 1	0 0	1 ( 0.1) 1
Scar pain	1 ( 0.1) 1	1 ( 0.1) 1	2 ( 0.1) 2
Skin exfoliation	1 ( 0.1) 1	0 0	1 ( 0.1) 1
Skin fissures	1 ( 0.1) 1	0 0	1 ( 0.1) 1
Urticaria	0 0	1 ( 0.1) 1	1 ( 0.1) 1

Ref: NETU0818CSR, Table 14.3.1.1.2.1, p.968

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**Table 11 TEAE multiple cycles**

System organ class Preferred term	Netu/Palo FDC N=635 n (%) E		Palo alone N=651 n (%) E		Overall N=1286 n (%) E	
Immune system disorders	1 ( 0.2)	1	3 ( 0.5)	3	4 ( 0.3)	4
Hypersensitivity	0	0	1 ( 0.2)	1	1 ( 0.1)	1
Seasonal allergy	1 ( 0.2)	1	2 ( 0.3)	2	3 ( 0.2)	3
<b>Infections and infestations</b>	<b>71 ( 11.2)</b>	<b>85</b>	<b>51 ( 7.8)</b>	<b>65</b>	122 ( 9.5)	150
Appendicitis	1 ( 0.2)	1	0	0	1 ( 0.1)	1
Arthritis infective	0	0	1 ( 0.2)	1	1 ( 0.1)	1
Asymptomatic bacteriuria	0	0	1 ( 0.2)	1	1 ( 0.1)	1
Bacteriuria	10 ( 1.6)	14	5 ( 0.8)	8	15 ( 1.2)	22
Bronchitis	3 ( 0.5)	3	3 ( 0.5)	3	6 ( 0.5)	6
Cystitis	1 ( 0.2)	1	1 ( 0.2)	1	2 ( 0.2)	2
Device related infection	2 ( 0.3)	2	0	0	2 ( 0.2)	2
Diverticulitis	0	0	1 ( 0.2)	1	1 ( 0.1)	1
Enterococcal infection	1 ( 0.2)	1	0	0	1 ( 0.1)	1
Erysipelas	1 ( 0.2)	1	3 ( 0.5)	3	4 ( 0.3)	4
Eye infection	1 ( 0.2)	1	0	0	1 ( 0.1)	1
Fungal oesophagitis	1 ( 0.2)	1	0	0	1 ( 0.1)	1
Fungal skin infection	1 ( 0.2)	1	0	0	1 ( 0.1)	1
Furuncle	0	0	2 ( 0.3)	2	2 ( 0.2)	2
System organ class Preferred term	Netu/Palo FDC N=635 n (%) E		Palo alone N=651 n (%) E		Overall N=1286 n (%) E	
Skin and subcutaneous tissue disorders	175 ( 27.6)	190	176 ( 27.0)	191	351 ( 27.3)	381
<b>Alopecia</b>	<b>152 ( 23.9)</b>	<b>161</b>	<b>151 ( 23.2)</b>	<b>157</b>	<b>303 ( 23.6)</b>	<b>318</b>
Alopecia totalis	0	0	3 ( 0.5)	3	3 ( 0.2)	3
Dermal cyst	0	0	1 ( 0.2)	1	1 ( 0.1)	1
Dermatitis	1 ( 0.2)	1	1 ( 0.2)	1	2 ( 0.2)	2
Dermatitis contact	1 ( 0.2)	1	0	0	1 ( 0.1)	1
Dermatitis exfoliative	1 ( 0.2)	1	0	0	1 ( 0.1)	1
Dry skin	2 ( 0.3)	2	3 ( 0.5)	3	5 ( 0.4)	5
Dyshidrosis	1 ( 0.2)	1	0	0	1 ( 0.1)	1
Erythema	8 ( 1.3)	10	8 ( 1.2)	11	16 ( 1.2)	21
Hyperhidrosis	3 ( 0.5)	3	0	0	3 ( 0.2)	3
Nail discolouration	3 ( 0.5)	3	2 ( 0.3)	2	5 ( 0.4)	5
Nail disorder	0	0	1 ( 0.2)	1	1 ( 0.1)	1
Night sweats	2 ( 0.3)	2	0	0	2 ( 0.2)	2
Onychomadesis	1 ( 0.2)	1	0	0	1 ( 0.1)	1
Pigmentation disorder	0	0	1 ( 0.2)	2	1 ( 0.1)	2
Pruritus	1 ( 0.2)	1	0	0	1 ( 0.1)	1
Rash	1 ( 0.2)	1	4 ( 0.6)	4	5 ( 0.4)	5
System organ class Preferred term	Netu/Palo FDC N=635 n (%) E		Palo alone N=651 n (%) E		Overall N=1286 n (%) E	
Number of patients with any TEAE	533 ( 83.9)	2361	527 ( 81.0)	2183	1060 ( 82.4)	4544
Blood and lymphatic system disorders	291 ( 45.8)	835	294 ( 45.2)	776	585 ( 45.5)	1611
Anaemia	47 ( 7.4)	64	41 ( 6.3)	52	88 ( 6.8)	116
Febrile neutropenia	8 ( 1.3)	8	4 ( 0.6)	4	12 ( 0.9)	12
Granulocytopenia	2 ( 0.3)	2	0	0	2 ( 0.2)	2
Leukocytosis	10 ( 1.6)	14	5 ( 0.8)	6	15 ( 1.2)	20
<b>Leukopenia</b>	<b>138 ( 21.7)</b>	<b>232</b>	<b>141 ( 21.7)</b>	<b>255</b>	<b>279 ( 21.7)</b>	<b>487</b>
Lymph node pain	1 ( 0.2)	1	0	0	1 ( 0.1)	1
Lymphadenopathy	1 ( 0.2)	1	1 ( 0.2)	1	2 ( 0.2)	2
Lymphocytosis	1 ( 0.2)	1	1 ( 0.2)	1	2 ( 0.2)	2
Lymphopenia	25 ( 3.9)	48	26 ( 4.0)	42	51 ( 4.0)	90
Monocytopenia	3 ( 0.5)	3	2 ( 0.3)	2	5 ( 0.4)	5
<b>Neutropenia</b>	<b>226 ( 35.6)</b>	<b>412</b>	<b>238 ( 36.6)</b>	<b>382</b>	<b>464 ( 36.1)</b>	<b>794</b>
Neutrophilia	5 ( 0.8)	9	4 ( 0.6)	5	9 ( 0.7)	14
Pancytopenia	1 ( 0.2)	1	0	0	1 ( 0.1)	1
Thrombocytopenia	21 ( 3.3)	36	15 ( 2.3)	20	36 ( 2.8)	56
Thrombocytosis	3 ( 0.5)	3	4 ( 0.6)	6	7 ( 0.5)	9

Ref: NETU0818CSR, Table 14.3.1.1.2.2 p.990

### **Deaths, Serious TEAEs, Serious TEAEs of special interest**

Two patients died during MEC trial NETU-08-18, both in the palonosetron group. One patient suffered cardiac/respiratory failure in cycle 1. A second patient died of progression of metastatic breast cancer during cycle 3. Twenty-five patients experienced serious TEAEs in cycle 1, with similar proportions between treatment groups: 13 patients in the netupitant/palonosetron and 12 in the palonosetron group. The most frequent serious TEAE was febrile neutropenia. None of the serious TEAEs were assessed as being related to study drugs or to dexamethasone.

### **Discontinuations**

In cycle 1 twelve patients experienced TEAEs leading to discontinuation: 7 in the netupitant/palonosetron group and 5 in the palonosetron group. Two of the TEAEs leading to discontinuation by patients in the palonosetron group were assessed as related to study drug. These were nausea and vomiting, and urticaria. The other TEAEs leading to discontinuation were not assessed as related.

Taking all cycles into account there were 34 TEAEs that lead to discontinuation; 14 in the Netu/Palo arm and 20 in the oral Palo arm. Among the TEAEs leading to discontinuation in the Netu/Palo group were increase in ALT, angina, appendicitis, arthralgia, AST increased, neutropenia, pathological fracture, and increase in troponin. Of the 20 patients in the palonosetron arm that discontinued due to an adverse event, with the exception of urticaria, which occurred in the same patient twice, all TEAEs occurred in only one patient. Among these events were nausea, neutropenia, and increase in troponin, angina, atrial fibrillation and heart failure.

One-hundred sixty (11.0%) patients in cycle 1 experienced severe TEAEs: 94 (13.0%) in the netupitant/palonosetron group and 66 (9.1%) in the palonosetron group. Five patients taking Akynzeo had severe TEAEs assessed as related to study drug; all recovered from the event. Severe TEAEs related to Akynzeo were headache, constipation, abdominal pain, neutropenia, and hypertension (#5606/45). None of the TEAEs were assessed as related to palonosetron.

**Table 12 TEAEs cycle 1 NETU-08-18**

Category, n (%)	Number (%) of Patients Experiencing Event					
	NETU/PALO FDC (N=725)		PALO alone (N=725)		Overall (N=1450)	
Any TEAE	551	(76.0)	507	(69.9)	1058	(73.0)
TEAE related to study drug	59	(8.1)	52	(7.2)	111	(7.7)
TEAE related to dexamethasone	63	(8.7)	57	(7.9)	120	(8.3)
Any related TEAE	98	(13.5)	84	(11.6)	182	(12.6)
TEAE leading to discontinuation of study drug	7	(1.0)	4	(0.6)	11	(0.8)
TEAE related to study drug leading to discontinuation	0		2	(0.3)	2	(0.1)
TEAE related to dexamethasone leading to discontinuation	0		2	(0.3)	2	(0.1)
Any related TEAE leading to discontinuation	0		2	(0.3)	2	(0.1)
TEAE leading to death	0		1	(0.1)	1	(0.1)
Serious TEAE	13	(1.8)	12	(1.7)	25	(1.7)
Serious TEAE related to study drug	0		0		0	
Serious TEAE related to dexamethasone	0		0		0	
Any serious related TEAE	0		0		0	
Severe TEAE	94	(13.0)	66	(9.1)	160	(11.0)
Severe TEAE related to study drug	5	(0.7)	0		5	(0.3)
Severe TEAE related to dexamethasone	2	(0.3)	1	(0.1)	3	(0.2)
Any severe related TEAE	6	(0.8)	1	(0.1)	7	(0.5)

Ref: Netu08-18, Table 32, p.111.

### TEAEs Multiple-Cycle Extension

Of the 1286 patients starting in the multiple-cycle extension 1060 (82.4%) had at least one TEAE. There was little difference between treatment groups; 83.9% TEAEs in the FDC and 81% in the palonosetron group. The proportion of TEAEs assessed as related to Akynzeo or palonosetron were 10.1%, and 7.5% respectively. Other safety findings from the multiple-cycle extension were:

- One patient in the palonosetron group died due to progression of her underlying breast cancer
- There were 23 (3.6%) serious TEAEs in the FDC and 15 (2.3%) in the palonosetron group. A total of 23 (1.8%) patients in total experienced TEAEs leading to discontinuation in the multiple-cycle extension: 8 (1.3%) were in the netupitant/palonosetron group and 15 (2.3%) were in the palonosetron group. Three of these (in palonosetron) were assessed as related to study drug.
- 193 (15.0%) patients experienced severe TEAEs: 98 (15.4%) in the netupitant/palonosetron group and 95 (14.6%) in the palonosetron group. Two patients had a severe TEAE assessed as being related to study drugs (1 patient in each treatment group). Six (0.5%) patients had a severe TEAE assessed as being related to dexamethasone. These results are shown in Table 13.

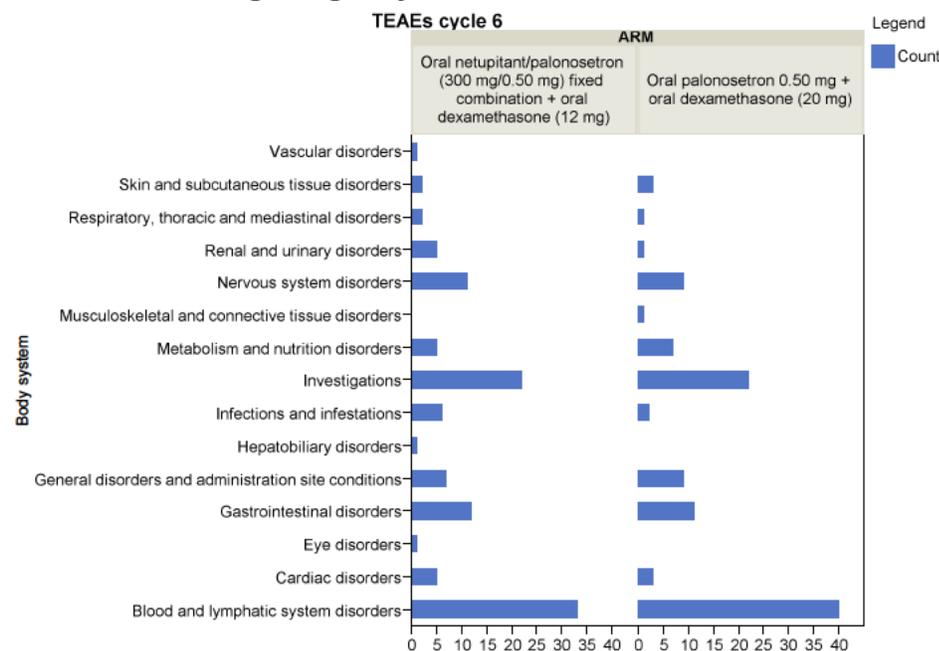
**Table 13 Patients with TEAE multiple-cycle extension**

Category, n (%)	Number (%) of Patients Experiencing Event					
	NETU/PALO FDC (N=635)		PALO alone (N=651)		Overall (N=1286)	
Any TEAE	533	(83.9)	527	(81.0)	1060	(82.4)
TEAE related to study drug	64	(10.1)	49	(7.5)	113	(8.8)
TEAE related to dexamethasone	82	(12.9)	72	(11.1)	154	(12.0)
Any related TEAE	118	(18.6)	102	(15.7)	220	(17.1)
TEAE leading to discontinuation of study drug	8	(1.3)	15	(2.3)	23	(1.8)
TEAE related to study drug leading to discontinuation	0		3	(0.5)	3	(0.2)
TEAE related to dexamethasone leading to discontinuation	0		1	(0.2)	1	(0.1)
Any related TEAE leading to discontinuation	0		3	(0.5)	3	(0.2)
TEAE leading to death	0		1	(0.2)	1	(0.1)
Serious TEAE	23	(3.6)	15	(2.3)	38	(3.0)
Serious TEAE related to study drug	0		0		0	
Serious TEAE related to dexamethasone	3	(0.5)	1	(0.2)	4	(0.3)
Any serious related TEAE	3	(0.5)	1	(0.2)	4	(0.3)
Severe TEAE	98	(15.4)	95	(14.6)	193	(15.0)
Severe TEAE related to study drug	1	(0.2)	1	(0.2)	2	(0.2)
Severe TEAE related to dexamethasone	4	(0.6)	2	(0.3)	6	(0.5)
Any severe related TEAE	5	(0.8)	2	(0.3)	7	(0.5)

Ref: *Netu0818 study report, Table 33, p.113.*

Table 14 shows TEAEs by body system for Netu/Palo FDC versus palonosetron that began at cycle 6.

**Table 14 TEAEs beginning at cycle 6**



Ref: Reviewer's Table

For the most part there did not seem to be a large difference between the two treatment arms at cycle 6, although the number of patients was smaller by this time.

The following Table 15 further breaks down cycle 6 by showing TEAEs in the blood and lymphatic system and cardiac disorders system. Differences in treatment groups are minimal.

**Table 15 TEAEs in Cycle 6**

System organ class Preferred term	Netu/Palo FDC N=197 n (%) E	Palo alone N=191 n (%) E	Overall N=388 n (%) E
Number of patients with any TEAE	61 ( 31.0)	113 59 ( 30.9)	109 120 ( 30.9)
Blood and lymphatic system disorders	23 ( 11.7)	33 29 ( 15.2)	40 52 ( 13.4)
Anaemia	3 ( 1.5)	3 2 ( 1.0)	2 5 ( 1.3)
Leukopenia	11 ( 5.6)	11 17 ( 8.9)	17 28 ( 7.2)
Lymphopenia	1 ( 0.5)	1 0	0 1 ( 0.3)
Neutropenia	15 ( 7.6)	15 18 ( 9.4)	18 33 ( 8.5)
Thrombocytopenia	3 ( 1.5)	3 2 ( 1.0)	3 5 ( 1.3)
Cardiac disorders	5 ( 2.5)	5 3 ( 1.6)	3 8 ( 2.1)
Arrhythmia	1 ( 0.5)	1 0	0 1 ( 0.3)
Atrial fibrillation	0	0 1 ( 0.5)	1 1 ( 0.3)
Cardiac failure	1 ( 0.5)	1 0	0 1 ( 0.3)
Cardiomyopathy	1 ( 0.5)	1 1 ( 0.5)	1 2 ( 0.5)
Cytotoxic cardiomyopathy	1 ( 0.5)	1 0	0 1 ( 0.3)
Metabolic cardiomyopathy	0	0 1 ( 0.5)	1 1 ( 0.3)
Tachycardia	1 ( 0.5)	1 0	0 1 ( 0.3)

Ref: NETU0818, table 14.3.1.1.2.7, p. 1049.

Finally, Table 16 shows treatment emergent adverse events that were related to study drugs that occurred in  $\geq 2\%$  patients. The two events listed, constipation and headache, are known side effects from anti-emetic drugs.

**Table 16 TEAEs related to study drugs in  $\geq 2\%$  patients**

MedDRA SOC PT	NETU/PALO FDC (N=725)		PALO alone (N=725)		Overall (N=1450)	
	n (%)	E	n (%)	E	n (%)	E
Any TEAE related to study drugs	59 (8.1)	84	52 (7.2)	65	111 (7.7)	149
Gastrointestinal disorders	23 (3.2)	23	21 (2.9)	26	44 (3.0)	49
Constipation	15 (2.1)	15	15 (2.1)	16	30 (2.1)	31
Nervous system disorders	27 (3.7)	27	23 (3.2)	23	50 (3.4)	50
Headache	24 (3.3)	24	22 (3.0)	22	46 (3.2)	46

Source: Section 14, Table 14.3.1.1.4.1, Listing 16.2.7.6  
 Patients with multiple events counted only once per line.

### Laboratory

During the trial there were changes from baseline in leukocyte and neutrophil counts, as would be expected in chemotherapy patients. However there appeared to be little difference between the two treatment arms. Similar findings were seen with chemistry parameters.

Increased ALT was the most frequent TEAE in cycle 1 and was reported in 7 (1.0%) patients in the netupitant/palonosetron group and 4 (0.6%) patients in the palonosetron group. None of the events in either treatment group was assessed by the investigator as being related to study drugs or dexamethasone. All but two of the events resolved.

In the multi-cycle extension increase in ALT was the lab abnormality most frequently reported as a TEAE; 23 (3.6%) for Netu/Palo versus 16 (2.5%) for Palonosetron. Increases in AST were seen in 17 (2.7%) patients in Netu/Palo arm versus 11 (1.7%) in Palonosetron arm.

**Table 17 Hematology abnormalities cycle 1**

Parameter	NETU/PALO FDC (N=725)		PALO alone (N=725)		Overall (N=1450)	
	N	(%)	n	(%)	n	(%)
<b>Leukocytes: WBC decreased</b>						
Number of patients with result	725		725		1450	
Any severe grade	80	(11.0)	72	(9.9)	152	(10.5)
Grade 3	65	(9.0)	66	(9.1)	131	(9.0)
Grade 4	15	(2.1)	6	(0.8)	21	(1.4)
<b>Neutrophils: neutrophil count decreased</b>						
Number of patients with result	725		725		1450	
Any severe grade	154	(21.2)	155	(21.4)	309	(21.3)
Grade 3	103	(14.2)	110	(15.2)	213	(14.7)
Grade 4	51	(7.0)	45	(6.2)	96	(6.6)
<b>Hemoglobin: anemia</b>						
Number of patients with result	725		725		1450	
Any severe grade	3	(0.4)	4	(0.6)	7	(0.5)
<b>Platelets: platelet count decreased</b>						
Number of patients with result	724		725		1449	
Any severe grade	3	(0.4)	1	(0.1)	4	(0.3)
Grade 3	3	(0.4)	1	(0.1)	4	(0.3)
Grade 4	0		0		0	

Ref: NETU0818CSR, Table 44, p.147.

**Table 18 Hematology - Grade3 or 4, Extension Study NETU-08-18**

Parameter	NETU/PALO FDC (N=635)		PALO alone (N=651)		Overall (N=1286)	
	n	(%)	n	(%)	n	(%)
<b>Leukocytes: WBC decreased</b>						
Number of patients with result	635		651		1286	
Any severe grade	107	(16.9)	99	(15.2)	206	(16.0)
Grade 3	85	(13.4)	83	(12.7)	168	(13.1)
Grade 4	22	(3.5)	16	(2.5)	38	(3.0)
<b>Neutrophils: neutrophil count decreased</b>						
Number of patients with result	635		651		1286	
Any severe grade	169	(26.6)	154	(23.7)	323	(25.1)
Grade 3	120	(18.9)	111	(17.1)	231	(18.0)
Grade 4	49	(7.7)	43	(6.6)	92	(7.2)
<b>Hemoglobin: anemia</b>						
Number of patients with result	635		651		1286	
Any severe grade	14	(2.2)	8	(1.2)	22	(1.7)
<b>Platelets: platelet count decreased</b>						
Number of patients with result	635		651		1286	
Any severe grade	3	(0.5)	2	(0.3)	5	(0.4)
Grade 3	3	(0.5)	0		3	(0.2)
Grade 4	0		2	(0.3)	2	(0.2)

Source: Section 14, Tables 14.3.4.1.1.3.1.2 to 14.3.4.1.1.3.4.2, Listing 16.2.8.1.1

Percentages are based on the number of patients with any result for the respective time interval and parameter.

**Table 19 Chemistry Abnormalities Cycle 1**

Parameter	NETU/PALO FDC (N=725)		PALO alone (N=725)		Overall (N=1450)	
	n	(%)	n	(%)	n	(%)
<b>ALT increased</b>	725		725		1450	
Number of patients with result						
Any severe grade	2	(0.3)	2	(0.3)	4	(0.3)
Grade 3	2	(0.3)	2	(0.3)	4	(0.3)
Grade 4	0		0		0	
<b>AST increased</b>	723		724		1447	
Number of patients with result						
Any severe grade	1	(0.1)	2	(0.3)	3	(0.2)
Grade 3	1	(0.1)	2	(0.3)	3	(0.2)
Grade 4	0		0		0	
<b>Creatinine increased</b>	725		725		1450	
Number of patients with result						
Any severe grade	0		1	(0.1)	1	(0.1)
Grade 3	0		0		0	
Grade 4	0		1	(0.1)	1	(0.1)
<b>Alkaline phosphatase increased</b>	725		725		1450	
Number of patients with result						
Any severe grade	1	(0.1)	0		1	(0.1)
Grade 3	1	(0.1)	0		1	(0.1)
Grade 4	0		0		0	
<b>Glucose (hyperglycemia)</b>	725		725		1450	
Number of patients with result						
Any severe grade	21	(2.9)	19	(2.6)	40	(2.8)
Grade 3	21	(2.9)	18	(2.5)	39	(2.7)
Grade 4	0		1	(0.1)	1	(0.1)
<b>Potassium (hypokalemia)</b>	725		725		1450	
Number of patients with result						
Any severe grade	3	(0.4)	1	(0.1)	4	(0.3)
Grade 3	3	(0.4)	1	(0.1)	4	(0.3)
<b>Sodium (hyponatremia)</b>	725		725		1450	
Number of patients with result						
Any severe grade	15	(2.1)	10	(1.4)	25	(1.7)
Grade 3	10	(1.4)	6	(0.8)	16	(1.1)
Grade 4	5	(0.7)	4	(0.6)	9	(0.6)

Ref: NETU0818 CSR, Table 45, p.148

**Table 20 Chemistry, Grade 3 or 4, Extension Study NETU-08-18**

Parameter	NETU/PALO FDC (N=635)		PALO alone (N=651)		Overall (N=1286)	
	n	(%)	n	(%)	n	(%)
<b>ALT increased</b>						
Number of patients with result	635		651		1286	
Any severe grade	5	(0.8)	11	(1.7)	16	(1.2)
Grade 3	5	(0.8)	11	(1.7)	16	(1.2)
Grade 4	0		0		0	
<b>AST increased</b>						
Number of patients with result	635		651		1286	
Any severe grade	3	(0.5)	3	(0.5)	6	(0.5)
Grade 3	2	(0.3)	3	(0.5)	5	(0.4)
Grade 4	1	(0.2)	0		1	(0.1)
<b>Total bilirubin increased</b>						
Number of patients with result	635		651		1286	
Any severe grade	0		0		0	
Grade 3	0		0		0	
Grade 4	0		0		0	
<b>Creatinine increased</b>						
Number of patients with result	635		651		1286	
Any severe grade	0		0		0	
Grade 3	0		0		0	
Grade 4	0		0		0	
<b>Alkaline phosphatase increased</b>						
Number of patients with result	635		651		1286	
Any severe grade	1	(0.2)	1	(0.2)	2	(0.2)
Grade 3	1	(0.2)	1	(0.2)	2	(0.2)
Grade 4	0		0		0	
<b>Glucose (hyperglycemia)</b>						
Number of patients with result	635		651		1286	
Any severe grade	54	(8.5)	42	(6.5)	96	(7.5)
Grade 3	49	(7.7)	41	(6.3)	90	(7.0)
Grade 4	5	(0.8)	1	(0.2)	6	(0.5)
<b>Potassium (hypokalemia)</b>						
Number of patients with result	635		651		1286	
Any severe grade	3	(0.5)	5	(0.8)	8	(0.6)
Grade 3	3	(0.5)	5	(0.8)	8	(0.6)
Grade 4	0		0		0	
<b>Sodium (hyponatremia)</b>						
Number of patients with result	635		651		1286	
Any severe grade	25	(3.9)	37	(5.7)	62	(4.8)
Grade 3	24	(3.8)	34	(5.2)	58	(4.5)
Grade 4	1	(0.2)	3	(0.5)	4	(0.3)

Source: Section 14, Table 14.3.4.1.2.3.1.2 to 14.3.4.1.2.3.8.2, Listing 16.2.8.1.1

Percentages are based on the number of patients with any result for the respective time interval and parameter.

## Vital Signs

Systolic blood pressure was measured at baseline and 5 hours post-dose. The mean change in systolic blood pressure from baseline for Netu/Palo was -1.6 and for Palo -0.8. At 24 hours post-dose these values were -3.0 for Netu/Palo, and -2.9 for Palo. The mean change in pulse rate at 5 hours and 24 hours post dose was minimal for all treatment groups.

## ECG monitoring

A 12-lead ECG was recorded for each patient at Visit 1 (screening), Visit 2 (pre-dose and 5 hours after the first study drug administration on Day 1), Visit 3 (24 hours post-dose) and Visit 4 (120 hours post-dose) of each cycle. The ECGs were digitally recorded and transmitted from the site to a central reading facility where they were read by a cardiologist who was blind to study drug.

At baseline mean values for HR and ECG intervals were comparable between treatment groups. Five hours after treatment (approximately T<sub>max</sub> for the netupitant/palonosetron FDC), mean HR had increased from baseline by 2.5 and 4.7 bpm in the netupitant/palonosetron and palonosetron groups, respectively. All mean changes from baseline in HR, PR interval and QRS interval were comparable between treatment groups. At 5 hours after treatment (T<sub>max</sub>), in both treatment groups there was a comparable increase of heart-rate adjusted QTcF interval in the netupitant/palonosetron FDC versus palonosetron alone groups (13.1 and 13.4 ms), with similar results observed at 24 hours (12.2 and 10.5 ms) and a return to baseline values at 120 hours after treatment (QTcF of -2.0 and -0.3 ms). Table 21 shows baseline and 5, 24 and 120 hours QTcF readings for treatment arms. Very little difference is seen between arms, and both Netu/Palo and Palo had a small increase in QT interval at 5-hours that returned to baseline at 120 hours.

Table 21 ECG descriptive summary QTcF cycle 1

Parameter, ms	NETU/PALO FDC (N=725)		PALO alone (N=725)		n	Overall (N=1450)
	n		n			
<b>QTcF</b>						
Baseline	725	412.5 (19.61)	725	412.8 (18.55)	1450	412.6 (19.08)
Day 1, 5 h post-dose		425.7 (21.00)		426.2 (20.40)		425.9 (20.69)
<i>Change from Baseline</i>	719	13.1 (16.92)	721	13.4 (16.91)	1440	13.3 (16.91)
Day 2, 24 h post-dose		424.6 (21.39)		423.3 (21.52)		424.0 (21.46)
<i>Change from Baseline</i>	717	12.2 (18.87)	717	10.5 (18.32)	1434	11.3 (18.61)
Day 6, 120 h post-dose		410.5 (20.06)		412.5 (19.20)		411.5 (19.66)
<i>Change from Baseline</i>	715	-2.0 (16.97)	713	-0.3 (17.29)	1428	-1.1 (17.14)

Source: Section 14, Table 14.3.4.3.1.4.1, Table 14.3.4.3.1.5.1 and Table 14.3.4.3.1.6.1, Listing 16.2.8.3.1

Baseline is defined as the last measurement before the first treatment in cycle 1

Values are mean (SD)

Abbreviations: FDC=Fixed-Dose Combination; h=hour(s); N=number of patients in group; n=number of patients with data; NETU=netupitant; PALO=palonosetron; QTcB=QT interval corrected for heart rate according to Bazett's formula; QTcF=QT interval corrected for heart rate according to Fridericia's formula; SD=standard deviation.

In terms of outliers there was again little difference between treatment groups. In the Netu/Palo arm a total of 5 (0.7%) had an increase in QTcF of >60ms, compared to 8 patients (1.1%) patients in the palonosetron alone group. Finally, in terms of overall ECG abnormalities, Table 22 shows that these were matched between arms.

**Table 22 ECG abnormalities cycle 1**

Grouped Term Abnormality, n (%)	NETU/PALO FDC (N=725)	PALO alone (N=725)	Overall (N=1450)
<b>Rhythm evaluation</b>			
Sinus tachycardia	43 (5.9)	46 (6.3)	89 (6.1)
Sinus bradycardia	0	5 (0.7)	5 (0.3)
Ectopic supraventricular rhythm	1 (0.1)	2 (0.3)	3 (0.2)
Supraventricular tachycardia	1 (0.1)	0	1 (0.1)
<b>Ectopy evaluation</b>			
Premature atrial complexes	20 (2.8)	25 (3.4)	45 (3.1)
Premature ventricular complex	14 (1.9)	11 (1.5)	25 (1.7)
<b>Conduction</b>			
First degree atrioventricular block	24 (3.3)	11 (1.5)	35 (2.4)
QTcB prolongation >500 ms	9 (1.2)	4 (0.6)	13 (0.9)
Nonspecific intraventricular conduction delay	5 (0.7)	5 (0.7)	10 (0.7)
Left anterior fascicular block	1 (0.1)	3 (0.4)	4 (0.3)
QTc prolonged	2 (0.3)	0	2 (0.1)
QTcF prolongation >500 ms	1 (0.1)	1 (0.1)	2 (0.1)
Right bundle branch block	0	1 (0.1)	1 (0.1)
<b>Morphology</b>			
Left atrial enlargement	1 (0.1)	0	1 (0.1)
Left ventricular hypertrophy	1 (0.1)	1 (0.1)	2 (0.1)
Low QRS voltage	0	2 (0.3)	2 (0.1)
<b>ST segment evaluation</b>			
ST depression	47 (6.5)	47 (6.5)	94 (6.5)
<b>T wave evaluation</b>			
Flat T waves	91 (12.6)	88 (12.1)	179 (12.3)
T wave inversion	30 (4.1)	30 (4.1)	60 (4.1)
Biphasic T waves	5 (0.7)	5 (0.7)	10 (0.7)
<b>U wave</b>			
Abnormal	1 (0.1)	0	1 (0.1)

Source: Section 14, Table 14.3.4.3.3.1, Listing 16.2.8.3.2

In cycle 6 an analysis of ECG outliers was not different between treatment groups.

**Table 23 ECG outlier analysis cycle 6**

Parameter Change from same cycle pre-dose, n (%)	NETU/PALO FDC (N=197)	PALO alone (N=191)	Overall (N=388)
<b>QTcF (ms),</b>			
From ≤450 ms to >450 ms	51 (25.9)	52 (27.2)	103 (26.5)
From ≤480 ms to >480 ms	7 (3.6)	8 (4.2)	15 (3.9)
From ≤500 ms to >500 ms	1 (0.5)	2 (1.0)	3 (0.8)
Increase by >30 and ≤60 ms	42 (21.3)	42 (22.0)	84 (21.6)
Increase by >60 ms	3 (1.5)	5 (2.6)	8 (2.1)

Source: Section 14, Table 14.3.4.3.2.2, Listing 16.2.8.3.1

Percentages are calculated based on the number of patients with results, i.e. having the reference value and any post-baseline result of the respective parameter in the respective time interval.

Abbreviations: FDC=Fixed-Dose Combination; ms=milliseconds; N=number of patients in group;; NETU=netupitant; PALO=palonosetron; QTcF=QT interval corrected for heart rate according to Fridericia's formula; SD=standard deviation.

Table 24 may be compared with Table 22. There were greater numbers of abnormalities at later cycles, but these were balanced.

**Table 24 ECG abnormalities multiple-cycle extension**

Grouped Term Abnormality, n (%)	NETU/PALO FDC (N=635)	PALO alone (N=651)	Overall (N=1286)
<b>Rhythm evaluation</b>			
Sinus tachycardia	157 (24.7)	136 (20.9)	293 (22.8)
Ectopic supraventricular rhythm	12 (1.9)	7 (1.1)	19 (1.5)
Sinus bradycardia	8 (1.3)	11 (1.7)	19 (1.5)
Atrial fibrillation	3 (0.5)	1 (0.2)	4 (0.3)
Supraventricular tachycardia	1 (0.2)	1 (0.2)	2 (0.2)
Junction rhythm	0	1 (0.2)	1 (0.1)
<b>Ectopy evaluation</b>			
Premature atrial complexes	79 (12.4)	67 (10.3)	146 (11.4)
Premature ventricular complex	46 (7.2)	47 (7.2)	93 (7.2)
<b>Conduction</b>			
First degree atrioventricular block	47 (7.4)	34 (5.2)	81 (6.3)
QTcB prolongation >500 ms	31 (4.9)	30 (4.6)	61 (4.7)
Nonspecific intraventricular conduction delay	12 (1.9)	16 (2.5)	28 (2.2)
Left anterior fascicular block	5 (0.8)	11 (1.7)	16 (1.2)
QTcF prolongation >500 ms	4 (0.6)	4 (0.6)	8 (0.6)
QTc prolonged	4 (0.6)	3 (0.5)	7 (0.5)
Incomplete right bundle branch block	3 (0.5)	0	3 (0.2)
Right bundle branch block	3 (0.5)	0	3 (0.2)
<b>Morphology</b>			
Left ventricular hypertrophy	3 (0.5)	3 (0.5)	6 (0.5)
Low QRS voltage	3 (0.5)	2 (0.3)	5 (0.4)
Left atrial enlargement	1 (0.2)	0	1 (0.1)
<b>ST segment evaluation</b>			
ST depression	103 (16.2)	104 (16.0)	207 (16.1)
ST elevation	0	1 (0.2)	1 (0.1)
<b>T wave evaluation</b>			
Flat T waves	213 (33.5)	197 (30.3)	410 (31.9)
T wave inversion	84 (13.2)	84 (12.9)	168 (13.1)
Biphasic T waves	14 (2.2)	24 (3.7)	38 (3.0)
<b>U wave</b>			
Abnormal	3 (0.5)	2 (0.3)	5 (0.4)

Source: Section 14, Table 14.3.4.3.3.2, Listing 16.2.8.3.2

**Medical Officer's Comment:**

*Changes in ECG recordings from baseline to post -chemo, and also changes from cycle 1 to cycle 6 are difficult to interpret due to multiple factors, not the least of which are the cumulative effect of chemotherapy and disease progression.*

**Cardiac Monitoring**

Based on concerns of cardiotoxicity seen in another drug of the NK-1 RA class, the sponsor was required to institute increased cardiovascular monitoring. In Phase 3 multicycle studies NETU-08-18 and NETU-10-29 cardiac troponin (cTnI) levels were obtained during screening for cycle 1, and on days 2 (24 hours after study drug administration) and 6 of each subsequent cycle. Patients with cTnI levels  $\geq 0.12$  ng/mL (but  $<0.50$  ng/mL) were required to have cardiovascular follow-up for functional assessment, either within the study or following discontinuation, but could continue in the study at the investigator's discretion. Patients with cTnI values  $\geq 0.50$  ng/mL also had to have cardiovascular follow-up, but were withdrawn from the study. Cardiovascular follow-

up included monitoring of left ventricular ejection fraction (LVEF) by 2D-Echo or MUGA scan, and cardiac assessments, including New York Heart Association (NYHA) classification, vital signs, 12-lead ECG, assessment of cardiotoxic medications, and cardiac-specific concomitant medication.

The following Table 25 shows patients with elevated troponin across all cycles.

**Table 25 Patients with Elevated Troponin - All Cycles**

Troponin	NETU/PALO 300/0.5mg N=1033 n (%)	PALO 0.05mg N=725	Aprepitant+Palo N=104	Total
≥ 0.12 ng/mL and < 0.5 ng/mL	28 (2.7)	17 (2.3)	2 (1.9)	47 (2.5)
≥0.5 ng/mL	5 (0.5)	5 (0.7)	1 (1.0)	11 (0.6)

Ref: Summary Clinical Safety, Table 31, p.129.

Most patients with elevated troponin did not have significant changes in cardiac function (i.e. most had change in ejection fraction from baseline of <10). As Table 26 shows four patients enrolled in NETU-08-18 in the Netupitant/Palo group had significant changes in LVEF ranging from -10 to -39. Two patients in the Palonosetron group had a decline in cardiac function ranging from -14 to -22, and one patient participating in NETU-10-29 and receiving aprepitant + palonosetron had a change in cardiac function of -25.

**Table 26 Patients with Elevated Troponin and Change in LVEF>10**

Study	Arm	Cycle	Measured value (%)	Change from B/L
NETU-08-18	NETU/PALO FDC	6	21	-39
NETU-08-18	NETU/PALO FDC	6	56	-10
NETU-08-18	NETU/PALO FDC	6	50	-20
NETU-08-18	Palo alone	5	47	-22
NETU-08-18	Palo alone	5	54	-14
NETU-08-18	NETU/PALO FDC	Post withdrawal	56	-13
NETU-10-29	Aprepit/Palo	Post withdrawal	30	-25

Ref: Reviewer's table

**Medical Officer's Comment:**

*Most patients with elevated troponin levels were from NETU-08-18, and all patients had elevations during later chemotherapy cycles. Six had notable changes in cardiac function, as determined by echocardiogram. Four received Akynzeo and two received Palonosetron. Patients in NETU-08-18 received the chemotherapy agent anthracycline, which is known to be cardiotoxic. Overall these results do not point to a cardiac safety problem with Akynzeo.*

**Safety Conclusions**

No unexpected findings emerged from this trial. In cycle 1, the proportion of patients with at least one TEAE was 76.0% in the netupitant/palonosetron group and 69.9% in the palonosetron group. In the multiple-cycle extension, the proportion of patients with

TEAEs was similar in both treatment groups (83.9% and 81.0%, respectively). The overall proportion of patients with events related to netupitant/palonosetron or palonosetron alone was relatively low, both in cycle 1 (8.1% and 7.2%, respectively) and in the multiple-cycle extension (10.1% and 7.5%, respectively). The type, frequency and intensity of TEAEs were comparable across treatment groups throughout the study.

The most commonly reported TEAEs were alopecia (34.9%) and neutropenia (24.5%) in cycle 1 and in the multiple-cycle extension (23.6% and 36.1%, respectively). These events are expected and do not raise any particular safety concern. The most frequent TEAEs related to study drugs were constipation (2.1% patients both in cycle 1 and in the multiple-cycle extension), and headache (in 3.2% patients in cycle 1 and in 3.1% patients in the multiple-cycle extension).

### **Summary**

NETU-08-18 was a multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group study in cancer patients receiving moderately emetogenic chemotherapy. The primary aim of the study was to demonstrate the superiority of a single oral dose of the netupitant/palonosetron FDC to a single oral dose of palonosetron. Key secondary objectives compared netupitant/palonosetron FDC to oral palonosetron in terms of CR in the acute and in the overall phases during cycle 1.

The study demonstrated the superiority of the netupitant/palonosetron FDC over palonosetron alone with respect to the primary and key secondary endpoints: CR in the delayed (76.9% vs. 69.5%,  $p=0.001$ ), acute (88.4% vs. 85.0%,  $p=0.047$ ) and overall phases (74.3% vs. 66.6%,  $p=0.001$ ) in cancer patients receiving AC chemotherapy. During clinical development, and as per discussions with the division, the sponsor planned and conducted NETU-8-18 as the pivotal MEC study. Most patients received an AC regimen, which at the time was classified as MEC. In 2011 the American Society of Clinical Oncology (ASCO) changed its classification system and re-classified an AC regimen as HEC. This re-classification was based on a search of the medical literature and analysis of 37 trials meeting prespecified inclusion and exclusion criteria. The conclusion of the review was that an AC regimen causes vomiting in 85% of patients not receiving antiemetic prophylaxis, which was so close to the HEC cutoff of 90% that the society placed AC in the HEC category.

However for purposes of this review, the trials will be discussed as conducted. Primary and key secondary analyses were supported by secondary efficacy endpoints including no emesis, no use of rescue medication, without significant nausea and total protection. The difference in efficacy between treatment groups in favor of the netupitant/palonosetron FDC was maintained across multiple treatment cycles. No significant differences in safety data were observed between the two treatment groups and a similar pattern of results was maintained throughout all treatment cycles. The adverse event profile was as expected from cancer patients in a setting of cytotoxic

chemotherapy. Many patients in both treatment groups experienced decreases in white cell populations and other events generally related to chemotherapy (bone marrow suppression, gastric disorders, and alopecia).

Particular attention was paid to cardiac, CNS and psychiatric adverse events, defined as 'events of special interest'. The very limited number of patients experiencing adverse events of special interest does not raise any safety concern. No medical condition or cluster of events was indicative of any abuse potential of the netupitant/palonosetron FDC. Changes in clinical laboratory tests, vital signs, and 12-lead ECGs, cardiac troponin and measurements of LVEF values did not suggest an increased safety risk with netupitant combined with palonosetron when compared to palonosetron alone. In conclusion, the superiority of the netupitant/palonosetron FDC over palonosetron alone was demonstrated for CR in the delayed, acute and overall phases after MEC. Overall, the netupitant/palonosetron FDC demonstrated better efficacy than palonosetron alone in the prevention of delayed acute and overall nausea and vomiting and maintained a safety profile similar to that of palonosetron alone in patients undergoing initial and repeat cycles of MEC.

**NETU-07-07 (HEC)- A Randomized, Double-Blind, Parallel Group, Dose-Ranging, Multicenter Study Assessing the Effect of Different Doses of Netupitant or Placebo Administered with Palonosetron and Dexamethasone on the Prevention of Highly Emetogenic Chemotherapy-Induced Nausea and Vomiting in Cancer Patients**

This was a Phase 2- study in patients undergoing highly emetogenic cancer chemotherapy (HEC). In addition to being a dose ranging study, it is the pivotal efficacy trial in patients receiving a cisplatin-based ( $\geq 50\text{mg}/\text{m}^2$ ) HEC regimen. In a meeting from 6/18/2010 the division agreed that NETU-07-07 would be acceptable as the lone trial to support the fixed dose combination capsule for the prevention of acute and delayed HEC-CINV, provided review of the data support efficacy and safety.

The main objective of the trial was to compare the efficacy and safety of three single oral doses of netupitant, combined with palonosetron and dexamethasone, to palonosetron and dexamethasone alone in the prevention of highly emetogenic chemotherapy induced nausea and vomiting. An additional arm, aprepitant administered with ondansetron and dexamethasone was included for exploratory purposes.

The patient population consisted of 694 adult patients randomized in equal numbers and stratified by gender into five treatment groups; 670 received study medication. A dynamic adaptive stratification randomization method was employed to balance the five treatment groups. Discussed in further detail in the statistical review, the general strategy of this randomization method was to give additional probability that patients would receive a specific treatment if it was underrepresented in the ongoing

randomization. Patients participated in the trial for one chemotherapy cycle only, up to 25 days, including a screening phase, treatment phase, and follow-up visit or phone call. Table 27 shows the 5 treatment groups.

**Table 27 Treatment arms**

- Group 1 – 0.5 mg oral palonosetron on Day 1 (with dexamethasone standard regimen: 20 mg on Day 1 and 8 mg BID from Day 2 to Day 4)
- Group 2 – 100 mg oral netupitant and 0.5 mg oral palonosetron on Day 1 (with dexamethasone adjusted regimen: 12 mg on Day 1 and 8 mg daily from Day 2 to Day 4)
- Group 3 – 200 mg oral netupitant and 0.5 mg oral palonosetron on Day 1 (with dexamethasone adjusted regimen: 12 mg on Day 1 and 8 mg daily from Day 2 to Day 4)
- Group 4 – 300 mg oral netupitant and 0.5 mg oral palonosetron on Day 1 (with dexamethasone adjusted regimen: 12 mg on Day 1 and 8 mg daily from Day 2 to Day 4)
- Group 5 – 125 mg (on Day 1) and 80 mg daily (for the following two days) oral aprepitant and 32 mg IV ondansetron (with dexamethasone adjusted regimen: 12 mg on Day 1 and 8 mg daily from Day 2 to Day 4)

Ref: NETU0707 study report, p.5.

**Study Sites**

All study sites were in Russia (64%) and Ukraine (36%).

Eligibility criteria are listed below.

**Inclusion criteria**

- Male or female patient  $\geq 18$  years of age
- Naïve to cytotoxic chemotherapy
- Histologically or cytologically confirmed solid tumor malignancy and scheduled to receive the first course of cisplatin-based chemotherapy regimen (dose of cisplatin  $\geq 50$  mg/m<sup>2</sup> to be administered over 1 to 4 hours on day 1 alone or in combination with other chemotherapy agents).
- Karnofsky index  $\geq 70\%$
- Female patients of childbearing potential using reliable contraceptive measures and having negative urine pregnancy test at the pre-treatment (screening) visit (reliable means practicing two forms of contraception, e.g., oral contraception, barrier contraception, spermicide, intrauterine device. Ethinylestradiol and levonorgestrel (CYP3A4 substrates) contraceptive pills were not allowed).
- Able to read, understand, follow the study procedures and complete patient diary
- Written informed consent.

**Exclusion Criteria**

- Current use of illicit drugs or current evidence of alcohol abuse

- Scheduled to receive
  - Moderately or highly-emetogenic chemotherapy (Hesketh Level 3 or above) from Day 2 to Day 5 following cisplatin administration
  - Bone marrow or stem cell transplant
  - Moderately- or highly-emetogenic radiotherapy (MASCC Guidelines) within 1 week prior to Day 1 or scheduled for study Days 2 to 5.
- Any drug with potential antiemetic efficacy taken within 24 hours prior to Day 1, including:
  - 5-HT<sub>3</sub> receptor antagonists (e.g., ondansetron, granisetron, dolasetron or tropisetron)
  - Benzamides (e.g., metoclopramide, alizapride or trimethobenzamide)
  - Phenothiazines (e.g., prochlorperazine, fluphenazine, thiethylperazine, perphenazine or chlorpromazine)
  - Scopolamine, diphenhydramine, chlorpheniramine
  - All benzodiazepines except triazolam or zolpidem which can be used once at night time due to sleep disturbances
- Butyrophenones (e.g., haloperidol or droperidol)
  - Cannabinoids (e.g., tetrahydrocannabinol or nabilone)
  - Domperidone
  - Systemic corticosteroid therapy with dexamethasone, hydrocortisone, methylprednisolone, prednisolone given within 72 hours prior to day 1 (topical or inhaled steroids permitted)
  - NK-1 receptor antagonists or any investigational drugs taken within 4 weeks prior to day 1

### **Duration**

Each patient stayed on the study for a maximum of 22 days, including up to 7 days screening period, 6 days on study (4 days on active treatment), and a follow-up visit or telephone call nine days after treatment completion by the patient.

### **Efficacy Assessment, Primary**

The primary efficacy endpoint defined in the protocol was complete response (no emetic episodes, no use of rescue medication) within 120 hours after the start of the highly emetogenic chemotherapy administration. The analysis population was the full analysis set (MFAS) which included all randomized patients (excluding the aprepitant groups) who received highly emetogenic chemotherapy and at least one study treatment dose. However in order to correspond to other Phase 3 pivotal trials the primary endpoint would be CR in the delayed phase, and the sequential testing procedure would be CR delayed, CR acute and CR overall. The sponsor conducted a post hoc analysis in which CR delayed phase was the primary efficacy variable.

*Medical Officer's Comment:*

*In the other CINV trials conducted to support this NDA the primary endpoint was CR in the delayed phase of 25 to 120 hours. The reason to use CR delayed rather than overall is to better isolate the effect of netupitant, which is expected to exert its effect most in the delayed phase.*

### **Efficacy Assessment, Secondary**

- Complete response for each 24-hour interval, starting from 0-24 hours from the start of Cisplatin administration; cumulative for the 0-96 hours interval; and for the 25-120 hours interval;
- Complete protection (defined as no emesis, no rescue therapy, no significant nausea (nausea <25 mm on VAS)) for each 24-hour interval, starting from 0-24 hours from the start of Cisplatin administration; cumulative, for the 0-120 hours interval, and for the 25-120 hours interval;
- Total control (defined as no emesis, no rescue therapy and no nausea (nausea <5 mm on VAS)) for each 24-hour interval, starting from 0-24 hours from the start of Cisplatin administration; cumulative, for the 0-120 hours interval and for the 25-120 hours interval;
- Time to first emetic episode;
- Time to first rescue medication;
- Time to treatment failure (based on time to the first emetic episode or time to the first rescue medication, whichever occurs first);
- Severity of nausea measured by means of VAS for each 24-hour interval;
- No nausea (VAS <5 mm) for each 24-hour interval, starting from 0-24 hours from the start of Cisplatin administration; cumulative, for the 0-120 hours interval; and for the 25-120 hours interval;
- No significant nausea (VAS <25 mm) for each 24-hour interval, starting from 0-24 hours from the start of Cisplatin administration; cumulative for the 0-120 hours interval; and for the 25-120 hours interval;
- No rescue medication, for each 24-hour interval, starting from 0-24 hours from the start of Cisplatin administration; cumulative for the 0-120 hours interval; and for the 25-120 hours interval;
- No emesis, for each 24-hour interval, starting from 0-24 hours from the start of Cisplatin administration; cumulative for the 0-120 hours interval; and for the 25-120 hours interval;
- Patient global satisfaction with anti-emetic therapy by means of VAS for each 24-hour interval.

### **Safety Assessments**

Physical examination (PE), hematology, blood chemistry, urinalysis, 12-lead electrocardiogram (ECG), vital signs and adverse events (AEs), assessment as outlined in the Schedule of Patient Visits.

### Study Results - Disposition

A total of 694 patients were randomized, and 679 (97.8%) received study medication (safety population). Fifteen patients were randomized but not treated: 5 withdrew consent, 5 were found ineligible for the study, 2 discontinued due to pre-treatment adverse events, 2 were erroneously randomized at screening, and 1 did not have screening results available in time for randomization.

Four patients discontinued after being treated with study medication.

- Patient 128-1404 (netupitant 100 mg) died due to multiple organ failure day 6
- Patient 208-1103 (netupitant 200 mg) discontinued due to an SAE of loss of consciousness approximately one hour after dosing
- Two patients were lost to follow-up (aprepitant) or withdrew consent (palonosetron).

Patient disposition is shown Table 28.

**Table 28 Summary of Patient Disposition - Randomized Patients**

	PALO alone		PALO + 100 NETU		PALO + 200 NETU		PALO + 300 NETU		APREPITANT	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Randomized	136	(100)	135	(100)	142	(100)	143	(100)	138	(100)
Never Treated	0	(0.0)	0	(0.0)	4	(2.8)	7	(4.9)	4	(2.9)
Treated	136	(100)	135	(100)	138	(97.2)	136	(95.1)	134	(97.1)
Completed study	135	(99.3)	134	(99.3)	137	(96.5)	136	(95.1)	133	(96.4)
Discontinued	1	(0.7)	1	(0.7)	5	(3.5)	7	(4.9)	5	(3.6)
<b>Reason for discontinuation</b>										
Adverse event	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)	1	(0.7)
Death	0	(0.0)	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Lost to follow up	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.7)
Other reason	0	(0.0)	0	(0.0)	3	(2.1)	4	(2.8)	1	(0.7)
Withdrew consent	1	(0.7)	0	(0.0)	1	(0.7)	2	(1.4)	2	(1.4)

Ref: NETU0707, Table 8, p.63.

**Medical Officer's Comment:**

*The patient who experienced loss of consciousness is discussed below. The SAE was deemed possibly related to Netu/Palo.*

### Demographics

The safety population was comprised of 387 (57%) males and 292 (43%) females ranging in age from 19 to 82 years. Most patients (678 (99.9%)) were white. Patients were enrolled exclusively at research sites in Russia (64%) and Ukraine (36%).

Alcohol consumption was low, with only 6% of the safety population reporting occasional use and the remainder of the population reporting rare or no consumption. A history of motion sickness was reported for approximately 2% of patients, and 17% of women reported a history of morning sickness during pregnancy. The majority of patients (68%) had a Karnofsky performance status  $\geq$ 90%.

### Cancer History/Chemotherapy:

Cancer diagnoses were similar among groups. The most frequent malignancies were head and neck, lung and respiratory tract, ovarian, urogenital and other. Almost half of patients in the safety population had metastases at entry into the study. The breakdown by cancers is shown in Table 29.

**Table 29 Summary of Cancer History**

Parameter	PALO Alone (N=136)	PALO+ 100 NETU (N=135)	PALO+ 200 NETU (N=138)	PALO +300 NETU (N=136)	Aprepitant (N=134)
<b>Primary cancer diagnosis*</b>					
Lung and Respiratory Tract Cancer	41 (30.1%)	39 (28.9%)	36 (26.1%)	35 (25.7%)	35 (26.1%)
Head and Neck Cancer	24 (17.6%)	27 (20.0%)	31 (22.5%)	3 (24.3%)	26 (19.4%)
Ovarian Cancer	23 (16.9%)	18 (13.3%)	20 (14.5%)	24 (17.6%)	25 (18.7%)
Other Urogenital Cancer	18 (13.2%)	19 (14.1%)	25 (18.1%)	15 (11.0%)	18 (13.4%)
Gastric Cancer	8 (5.9%)	9 (6.7%)	7 (5.1%)	8 (5.9%)	8 (6.0%)
Other Gastro-Intestinal Cancer	10 (7.4%)	4 (3.0%)	7 (5.1%)	6 (4.4%)	10 (7.5%)
Breast Cancer	4 (2.9%)	11 (8.1%)	6 (4.3%)	9 (6.6%)	7 (5.2%)
Other Cancer	5 (3.7%)	4 (3.0%)	4 (2.9%)	3 (2.2%)	2 (1.5%)
Neoplasm Malignant, Site Unspecified	3 (2.2%)	4 (3.0%)	2 (1.4%)	3 (2.2%)	3 (2.2%)
<b>Time since histological diagnosis (days)</b>					
N	135	133	137	136	133
Mean (SD)	79.1 (249)	68.2 (278)	138 (574)	167 (701)	68.8 (203)
Median	16.0	15.0	21.0	16.5	16.0
Min / Max	-7.0 / 1750	-7.0 / 3099	-5.0 / 6187	-4.0 / 6272	-2.0 / 1744
<b>Extent at study entry</b>					
Local Recurrence	3 (2.2%)	2 (1.5%)	6 (4.3%)	4 (2.9%)	4 (3.0%)
Metastatic	67 (49.3%)	70 (51.9%)	58 (42.0%)	61 (44.9%)	67 (50.0%)
Primary	66 (48.5%)	63 (46.7%)	74 (53.6%)	71 (52.2%)	63 (47.0%)
<b>Site of metastasis</b>					
Liver	12 (8.8%)	13 (9.6%)	8 (5.8%)	7 (5.1%)	5 (3.7%)
Lung	11 (8.1%)	15 (11.1%)	10 (7.2%)	8 (5.9%)	9 (6.7%)
Lymph nodes	39 (28.7%)	40 (29.6%)	34 (24.6%)	42 (30.9%)	40 (29.9%)
Bone	4 (2.9%)	6 (4.4%)	10 (7.2%)	3 (2.2%)	4 (3.0%)
Adrenal Gland/Kidney	2 (1.5%)	1 (0.7%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Other	17 (12.5%)	19 (14.1%)	16 (11.6%)	18 (13.2%)	23 (17.2%)

Ref: Netu0707 study report, table 13, p.69.

Chemotherapy administered to the study participants is summarized in Table 30. Approximately 15% of patients were treated with cisplatin alone. In each treatment group about 1/2 of patients received concomitant chemotherapy with an agent of low emetogenic potential (Hesketh level <3) while about 1/3 received concomitant chemotherapy with an agent of higher emetogenic potential (Hesketh level  $\geq$ 3).

**Table 30 Chemotherapy given - safety population**

	PALO alone (N=136)	PALO + 100 NETU (N=135)	PALO + 200 NETU (N=138)	PALO + 300 NETU (N=136)	APREPITANT (N=134)
<b>Type of chemotherapy, n (%)</b>					
Cisplatin alone	21 (15.4)	21 (15.6)	20 (14.5)	19 (14.0)	20 (14.9)
<b>Concomitant</b>					
Hesketh Level <3	72 (52.9)	62 (45.9)	78 (56.5)	65 (47.8)	70 (52.2)
Hesketh Level ≥3	43 (31.6)	52 (38.5)	39 (28.3)	51 (37.5)	44 (32.8)
<b>Chemotherapy post 120 hours, n (%)</b>					
Yes	8 (5.9)	4 (3.0)	10 (7.2)	7 (5.1)	8 (6.0)
<b>Time of concomitant chemotherapy, n (%)</b>					
Day 1 only	73 (53.7)	80 (59.3)	72 (52.2)	75 (55.1)	78 (58.2)
Days 1-5	42 (30.9)	34 (25.2)	45 (32.6)	41 (30.1)	36 (26.9)
<b>Mean cisplatin dose (mg/m<sup>2</sup>)</b>					
n	136	135	137	135	134
Mean (SD)	71.6 (16.5)	71.6 (16.3)	74.1 (15.5)	71.2 (16.2)	73.7 (15.5)
Median	75.0	75.0	75.0	75.0	75.0
Min/Max	50.0 / 100	50.0 / 100	50.0 / 100	50.0 / 100	50.0 / 100

Ref: NETU0707, Table 14, p.70.

Patients received a variety of concomitant chemotherapeutic agents, including cyclophosphamide, fluorouracil, etoposide, and doxorubicin.

**Table 31 Concomitant Chemotherapy**

	PALO Alone (N=136)	PALO+ 100 NETU (N=135)	PALO+ 200 NETU (N=138)	PALO+ 300 NETU (N=136)	Aprepitant (N=134)
	n (%)				
Subjects receiving concomitant chemotherapy	115 (84.6)	114 (84.4)	117 (84.8)	116 (85.3)	114 (85.1)
Cyclophosphamide	40 (29.4)	49 (36.3)	37 (26.8)	46 (33.8)	39 (29.1)
Fluorouracil	31 (22.8)	26 (19.3)	38 (27.5)	32 (23.5)	36 (26.9)
Etoposide	33 (24.3)	26 (19.3)	29 (21.0)	28 (20.6)	25 (18.7)
Doxorubicin	16 (11.8)	28 (20.7)	16 (11.6)	22 (16.2)	16 (11.9)
Paclitaxel	3 (2.2)	5 (3.7)	2 (1.4)	2 (1.5)	3 (2.2)
Gemcitabine	3 (2.2)	1 (0.7)	3 (2.2)	3 (2.2)	4 (3.0)
Bleomycin	2 (1.5)	2 (1.5)	2 (1.4)	3 (2.2)	2 (1.5)
Capecitabine	1 (0.7)	1 (0.7)	2 (1.4)	3 (2.2)	1 (0.7)
Dacarbazine	2 (1.5)	1 (0.7)	2 (1.4)	1 (0.7)	1 (0.7)
Epirubicin	1 (0.7)	1 (0.7)	0	2 (1.5)	3 (2.2)
Vinorelbine	0	2 (1.5)	3 (2.2)	0	1 (0.7)
Methotrexate	0	1 (0.7)	2 (1.4)	1 (0.7)	1 (0.7)
Vincristine	1 (0.7)	2 (1.5)	2 (1.4)	0	0
Vinblastine sulfate	2 (1.5)	0	2 (1.4)	0	0
Cisplatin	1 (0.7)	0	0	1 (0.7)	0
Docetaxel	0	1 (0.7)	0	0	1 (0.7)
Irinotecan	0	0	0	1 (0.7)	1 (0.7)

Ref: NETU0707 study report, Table 15, p.71.

**Primary Efficacy Analysis CR Overall Phase (0-120 hours)**

The primary efficacy endpoint was complete response rate from 0 to 120 hours (overall phase) after administration of highly emetogenic chemotherapy. The primary analysis population was the MFAS. The percent of patients with complete response over 0-120 hours after start of cisplatin administration was 76.5% in the palonosetron alone group and 87.4%, 87.6%, and 89.6% in the netupitant 100 mg, 200 mg, and 300 mg groups, respectively. The differences versus palonosetron for the individual doses of netupitant ranged from 10.9% (netupitant 100 mg) to 13.2% (netupitant 300 mg). Using the protocol specified Holm-Bonferroni procedure; all three doses of netupitant were statistically superior to palonosetron alone.

**Table 32 CR Overall - MFAS Population**

	PALO alone (N=136)	PALO + NETU100 mg (N=135)	PALO + NETU200 mg (N=137)	PALO + NETU 300 mg (N=135)
<b>Overall (0-120 hours)</b>				
Number (%) of Patients	104 (76.5)	118 (87.4)	120 (87.6)	121 (89.6)
Difference from palonosetron alone (%) with 95% CI		10.9 (1.9, 20.0)	11.1 (2.1, 20.1)	13.2 (4.4, 21.9)
p-value <sup>1</sup>		0.018	0.017	0.004

Ref: NETU-07-07 Study Report, Table 16, p.72.

## Secondary efficacy analysis

### Delayed Phase (25-120 hours)

The percent of patients in the modified full analysis set (MFAS) with delayed CR was 80.1% in the palonosetron alone group and 90.4%, 91.2%, and 90.4% in the netupitant 100 mg, 200 mg, and 300 mg plus palonosetron groups, respectively. Differences from palonosetron alone ranged from 10.2% to 11.1%.

### Acute Phase (0-24 hours)

The percent of patients in the MFAS with acute CR was 89.7% in the palonosetron alone group and 93.3%, 92.7%, and 98.5% in the netupitant 100 mg, 200 mg, and 300 mg plus palonosetron groups, respectively. Differences from palonosetron alone ranged from 3.0% to 8.8%. The logistic regression analysis, including gender as covariate, showed that netupitant 300 mg plus palonosetron 0.5 mg was the only dose for which the difference vs. palonosetron alone was statistically significant (p = 0.007).

**Table 33 Complete Response Overall, Acute and Delayed- MFAS**

	Palo alone (N=136)	Palo + Netu 100 mg (N=135)	Palo + Netu 200 mg (N=137)	Palo + Netu 300 mg (N=135)
Overall				
Percent of Patients	76.5	87.4	87.6	89.6
Difference from Palo alone (%)		10.9	11.1	13.2
p-value (*)		0.018	0.017	0.004
Acute				
Percent of Patients	89.7	93.3	92.7	98.5
Difference from Palo alone (%)		3.6	3.0	8.8
p-value (*)		0.278	0.383	0.007
Delayed				
Percent of Patients	80.1	90.4	91.2	90.4
Difference from Palo alone (%)		10.2	11.1	10.2
p-value (*)		0.018	0.010	0.018

(\*) p-value from logistic regression analysis adjusted for gender

NETU-07-07 Study Report p.10.

**Post-Hoc analysis – CR delayed as primary endpoint**

Because of the use of CR overall as the primary efficacy endpoint, the division requested that the sponsor conduct a post-hoc analysis of the following:

- analysis using CR in the delayed phase as the primary efficacy variable (instead of CR in the overall phase)
- analysis using the CMH test stratified for gender (instead of a logistic regression model with gender as covariate)
- hierarchical procedure to control type I error for CR in the delayed, acute and overall phase
- sensitivity analysis on the Intent to Treat (ITT) population defined as all randomized patients

Complete response in the delayed phase was redefined as the primary endpoint using the Cochran-Mantel-Haenszel (CMH) test stratified for gender. Table 34 shows reanalysis with both CMH stratified by gender, and logistic regression with gender as a covariant. The reanalysis confirm the original results and support the original study conclusion.

**Table 34 NETU-07-07 patients with CR (original and post hoc)**

	Palo alone (N=136)	Palo + Netu 100 mg (N=135)	Palo + Netu 200 mg (N=137)	Palo + Netu 300 mg (N=135)
<b>Delayed phase (25-120 hours)</b>				
Number (%) of Patients	109 (80.1)	122 (90.4)	125 (91.2)	122 (90.4)
Difference from palonosetron alone (%) with 95% CI		10.2 (1.9, 18.6)	11.1 (2.9, 19.3)	10.2 (1.9, 18.6)
p-value obtained with logistic regression model*		0.018	0.010	0.018
p-value obtained with CMH analysis*		0.017	0.008	0.016
<b>Acute phase (0-24 hours)</b>				
Number (%) of Patients	122 (89.7)	126 (93.3)	127 (92.7)	133 (98.5)
Difference from palonosetron alone (%) with 95% CI		3.6 (-3.0, 10.2)	3.0 (-3.7, 9.7)	8.8 (3.3, 14.3)
p-value obtained with logistic regression model*		0.278	0.383	0.007
p-value obtained with CMH analysis*		0.278	0.383	0.002
<b>Overall phase (0-120 hours)</b>				
Number (%) of Patients	104 (76.5)	118 (87.4)	120 (87.6)	121 (89.6)
Difference from palonosetron alone (%) with 95% CI		10.9 (1.9, 20.0)	11.1 (2.1, 20.1)	13.2 (4.4, 21.9)
p-value obtained with logistic regression model*		0.018	0.017	0.004
p-value obtained with CMH analysis*		0.018	0.016	0.003

\*including gender as covariate

Source: Study report NETU-07-07 (1) Section 14, Table 12.1, Table 13.1

Source: Addendum to clinical study report Appendix A Table 1, Table 2, Table 3

Ref: NETU0707 study report, p.633.

Based on these results the sponsor chose the 300mg dose of netupitant to be used in combination with the 0.50mg dose of oral palonosetron in the fixed dose combination. Although all netupitant doses were superior to palonosetron alone for CR overall, the 300mg dose of netupitant in combination with palonosetron performed better in the delayed and acute phase post chemotherapy.

**Medical Officer's Comments:**

*The reanalysis supports the original analysis. More detailed analysis can be found in the FDA statistical reviewer's NDA review.*

**Site 120 Re-Analysis**

As previously noted, when NETU-07-07 was selected as a pivotal HEC study the sponsor conducted an in-depth quality assurance audit of 55% of records of all patients enrolled in the study. One site in Russia (site No. 120) presented multiple major audit findings. To further investigate the protocol violations the division asked the sponsor to perform the following sensitivity analyses for the complete response (CR) in all three phase (i.e., the delayed, acute and overall):

- a. Excluding the patients with major protocol violations (including taking disallowed concomitant medications) in Site 120
- b. Excluding the patients with any protocol violations in Site 120

- c. Including all patients in Site 120 but treating the patients with major protocol violations including taking disallowed concomitant medications) as “treatment failures”
- d. Including all patients in Site 120 but treating the patients with any protocol violations as “treatment failures”
- e. Per-protocol analyses for the CR-delayed phase and -acute phase (including and excluding Site 120)

*The statistical reviewer confirmed the sponsor’s sensitivity analysis and concluded that based on the sensitivity analyses results, the impact of Site #120 on the efficacy of PALO+NETU in the three doses do not seem to be markedly severe and should not be a concern although not all the efficacy results shown for the PALO+NETU 300 mg are statistically significant.*

Table 35 shows that CR by country was consistently high for both Russia and Ukraine, and higher than seen in other trials.

**Table 35 Complete Response by Country (NETU-07-07)**

Overall Response (0-120 hours)	PALO alone	PALO + NETU 100 mg	PALO + NETU 200 mg	PALO + NETU 300 mg
<b>Russia (N)</b>	86	86	88	87
<b>Complete Response</b>				
Number (%) of Patients	65 (75.6)	77 (89.5)	77 (87.5)	79 (90.8)
Difference from palonosetron alone (%) with 95% CI		14.0 (2.8, 25.1)	11.9 (0.5, 23.3)	15.2 (4.3, 26.1)
p-value <sup>1</sup>		0.022	0.043	0.008
<b>Ukraine (N)</b>	50	49	49	48
<b>Complete Response</b>				
Number (%) of Patients	39 (78.0)	41 (83.7)	43 (87.8)	42 (87.5)
Difference from palonosetron alone (%) with 95% CI		5.7 (-9.8, 21.1)	9.8 (-4.9, 24.5)	9.5 (-5.3, 24.3)
p-value <sup>1</sup>		0.348	0.203	0.213

**Medical Reviewer’s Comment:**

*The proportion of patients with CR in the overall phase was consistently high in Russian and Ukrainian study sites, and somewhat higher than the CR rate seen in other geographic locations in other trials. This same pattern has been observed with other antiemetic products. Although vomiting is directly observable, the use of rescue medication, and a patient’s ability to tolerate nausea are more subjective, and may be rooted in cultural differences, or other factors less evident.*

**Safety Evaluations**

A total of 333 (49%) of the 679 subjects enrolled in this study experienced at least one TEAE. TEAEs ranged from 40.7% in the netupitant 100 mg group to 53.0% in the aprepitant group. Adverse events reported by ≥5.0% of patients in any treatment group

were leukocytosis, neutrophilia, dyspepsia, asthenia, alanine aminotransferase (ALT) increased, increased blood urea, anorexia, headache, and hiccups.

### Deaths

One patient (#128-1404) in the Netu/Palo 200mg arm with a diagnosis of non-small cell lung cancer died on day 6 of the study. He had medical history of myocardial fibrosis and ischemia, loss of consciousness and dyspnea. He received both cisplatin (150mg/m<sup>2</sup>) and paclitaxel (300 mg/m<sup>2</sup>) and developed multiorgan failure on day 4. Cause of death was not attributed to study drug.

### Severe and Serious TEAE

Thirty-three (4.9%) patients experienced severe TEAEs, 9 (1.3%) of which were considered related to study drugs.

Three **serious** TEAEs occurred in patients in the palonosetron group and two occurred in patients treated with netupitant, one in the 100 mg group and one in the 200 mg group. The patients in the palonosetron group had SAEs of pneumonia, hydrocephalus, and atrial fibrillation. In addition to the patient death in the 100mg netu/palo group another patient in the 200 mg Netu/Palo had loss of consciousness that may have been related to study medication. This last patient was withdrawn from the study before receiving chemotherapy. Table 36 provides a summary of the proportion of patients with TEAEs, severe TEAEs, deaths, and serious TEAEs.

**Table 36 Proportion of Patients with TEAEs NETU-07-07**

MedDRA SOC Preferred Term	Palo Alone (N=136) n (%)	PALO+ 100 NETU (N=135) n (%)	PALO+ 200 NETU (N=138) n (%)	PALO + 300 NETU (N=136) n (%)	Aprepitant (N=134) n (%)
Any TEAE	68 (50.0%)	55 (40.7%)	71 (51.4%)	68 (50.0%)	71 (53.0%)
TEAE related to study drugs	17 (12.5%)	18 (13.3%)	24 (17.4%)	21 (15.4%)	26 (19.4%)
TEAE related to dexamethasone	15 (11.0%)	23 (17.0%)	21 (15.2%)	17 (12.5%)	24 (17.9%)
Any related TEAE	27 (19.9%)	31 (23.0%)	38 (27.5%)	34 (25.0%)	39 (29.1%)
Severe TEAE	7 ( 5.1%)	4 ( 3.0%)	8 ( 5.8%)	8 ( 5.9%)	6 (4.5%)
Severe TEAE related to study drugs	2 ( 1.5%)	0 ( 0.0%)	3 ( 2.2%)	0 ( 0.0%)	4 ( 3.0%)
Severe TEAE related to dexamethasone	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)
Any related severe TEAE	2 ( 1.5%)	0 ( 0.0%)	3 ( 2.2%)	0 ( 0.0%)	4 ( 3.0%)
Serious TEAE	3 ( 2.2%)	1 ( 0.7%)	1 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)
Serious TEAE related to study drugs	0 ( 0.0%)	0 ( 0.0%)	1 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)
Serious TEAE related to dexamethasone	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)
Any serious related TEAE	0 ( 0.0%)	0 ( 0.0%)	1 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)
Deaths	0 ( 0.0%)	1 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)
TEAE leading to study discontinuation	0 ( 0.0%)	1 ( 0.7%)	1 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)
TEAE related to study drugs leading to study discontinuation	0 ( 0.0%)	0 ( 0.0%)	1 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)
TEAE related to dexamethasone leading to study discontinuation	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)
Any related TEAE leading to study discontinuation	0 ( 0.0%)	0 ( 0.0%)	1 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)

Ref: NETU0707 study report, Table 29, p.94.

Table 37 shows the system organ classes (SOC) in which there were 5% or more patients with TEAEs. Gastrointestinal disorders (dyspepsia), general disorders and administration (asthenia), and investigations (ALT increased) had the most TEAEs.

**Table 37 TEAE ≥ 5% Patients any treatment group**

MedDRA SOC Preferred Term	Palo Alone (N=136)	PALO+ 100 NETU (N=135)	PALO+ 200 NETU (N=138)	PALO + 300 NETU (N=136)	Aprepitant (N=134)
Number of Patients with TEAE	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders	12 ( 8.8%)	14 (10.4%)	10 ( 7.2%)	9 ( 6.6%)	13 ( 9.7%)
Leukocytosis	10 ( 7.4%)	10 ( 7.4%)	7 ( 5.1%)	5 ( 3.7%)	6 ( 4.5%)
Neutrophilia	4 ( 2.9%)	5 ( 3.7%)	4 ( 2.9%)	5 ( 3.7%)	7 ( 5.2%)
Gastrointestinal disorders	18 (13.2%)	16 (11.9%)	22 (15.9%)	20 (14.7%)	26 (19.4%)
Dyspepsia	2 ( 1.5%)	3 ( 2.2%)	9 ( 6.5%)	6 ( 4.4%)	5 ( 3.7%)
General disorders and administration	20 (14.7%)	12 (8.9%)	17 (12.3%)	20 (14.7%)	19 (14.2%)
Asthenia	13 (9.6%)	4 (3.0%)	12 (8.7%)	12 (8.8%)	13 (9.7%)
Investigations	21 (15.4%)	12 ( 8.9%)	24 (17.4%)	19 (14.0%)	17 (12.7%)
Alanine aminotransferase increased	9 ( 6.6%)	6 ( 4.4%)	7 ( 5.1%)	9 ( 6.6%)	6 ( 4.5%)
Blood urea increased	9 ( 6.6%)	2 ( 1.5%)	5 ( 3.6%)	3 ( 2.2%)	3 ( 2.2%)
Neutrophil count increased	3 ( 2.2%)	4 ( 3.0%)	10 ( 7.2%)	2 ( 1.5%)	5 ( 3.7%)
Metabolism and nutrition disorders	14 (10.3%)	10 ( 7.4%)	10 ( 7.2%)	9 ( 6.6%)	13 ( 9.7%)
Anorexia	11 ( 8.1%)	4 ( 3.0%)	5 ( 3.6%)	5 ( 3.7%)	9 ( 6.7%)
Nervous system disorders	13 ( 9.6%)	10 ( 7.4%)	15 (10.9%)	7 ( 5.1%)	16 (11.9%)
Headache	10 ( 7.4%)	5 ( 3.7%)	11 ( 8.0%)	5 ( 3.7%)	12 ( 9.0%)
Respiratory, thoracic and mediastinal disorders	10 ( 7.4%)	8 ( 5.9%)	6 ( 4.3%)	8 ( 5.9%)	2 ( 1.5%)
Hiccups	7 ( 5.1%)	6 ( 4.4%)	6 ( 4.3%)	7 ( 5.1%)	0 ( 0.0%)

Ref: NETU0707 study report, Table 30, p.95.

The following Table 38 shows TEAEs by preferred term for all doses of Netu/Palo combined compared to Palo alone. No major differences were seen between the Netupitant arms and the Palonosetron arm.

**Table 38 TEAE by treatment NETU0707**

<b>Comparison TEAEs Netu/Palo vs. Palo by preferred term NETU07-07</b>						
<i>PT</i>	<i>All NETU+PALO (N=420)</i>			<i>PALONOSETRON 0.50 mg (N = 136)</i>		
	<i>Events</i>	<i>#subjects</i>	<i>(%)</i>	<i>Events</i>	<i>#subjects</i>	<i>(%)</i>
Asthenia	32	28	6.85	13	13	9.56
Hiccups	27	19	4.65	7	7	5.15
Leukocytosis	26	24	5.87	12	12	8.82
Dyspepsia	24	18	4.4	2	2	1.47
Headache	23	22	5.38	10	10	7.35
Neutrophil increased	22	20	4.89	4	4	2.94
ALT inc.	22	22	5.38	10	9	6.62
Fatigue	17	16	3.91	3	3	2.21
AST inc.	17	16	3.91	5	5	3.68
Neutrophilia	14	14	3.42	4	4	2.94
Constipation	12	12	2.93	1	1	0.74
Hyperglycemia	12	12	2.93	2	2	1.47
Blood urea increased	10	10	2.44	9	9	6.62

Ref: Reviewer's Table

Table 39 compares only the 300mg Netu/Palo (to-be-marketed) dose to Palo alone. In both tables all TEAEs are listed, not just those deemed related.

**Table 39 TEAEs Netu 300/Palo vs. Palo**

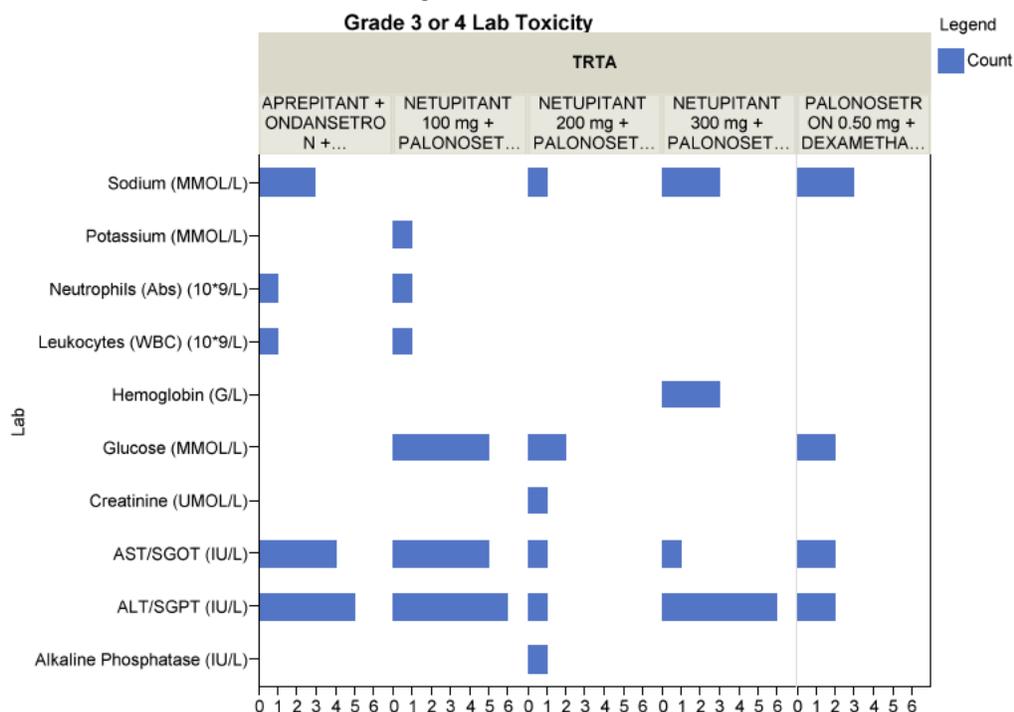
<b>Comparison TEAEs Netu/Palo vs. Palo by preferred term</b>						
<i>PT</i>	<i>Netupitant 300mg + Palonosetron 0.50mg</i>			<i>Palonosetron 0.50mg</i>		
	<i>Events</i>	<i># subjects</i>	<i>(%)</i>	<i>Events</i>	<i># subjects</i>	<i>(%)</i>
Asthenia	14	12	8.82	13	13	9.56
ALT	9	9	6.62	10	9	6.62
Hiccups	9	7	5.15	7	7	5.15
Leukocytosis	6	5	3.68	12	12	8.82
Dyspepsia	6	6	4.41	2	2	1.47
Headache	6	5	3.68	10	10	7.35
Fatigue	6	6	4.41	3	3	2.21
AST	6	6	4.41	5	5	3.68
Neutrophilia	5	5	3.68	4	4	2.94
Constipation	4	4	2.94	1	1	0.74
Lymphocytosis	4	3	2.21	1	1	0.74
Erythema	4	4	2.94	2	2	1.47

Ref: Reviewer's table

### Laboratory values

Most changes in laboratory values from baseline were minimal. However some patients experienced clinically significant abnormalities which were reported as TEAEs. Table 40 shows a comparison between treatment arms for those laboratory values graded as 3 or 4 toxicities. For the most part these changes were distributed among the treatment arms, so that no one group stands out.

**Table 40 Grade 3 or 4 Lab Toxicity**



Ref: Reviewer's Table.

### Electrocardiograms

The treatment groups were comparable at baseline, and the mean changes from baseline were small and similar across treatment groups at each study timepoint. A QTcF prolongation of >500 msec was observed in one patient in the netupitant 300 mg combination group and a QTcB prolongation >500 msec occurred in one patient in the aprepitant regimen group.

The percent of patients with a treatment emergent abnormality for rhythm, conduction, morphology, ST segment, T wave, and ectopy was comparable across treatment groups; the percentages were 33.1%, 36.3%, 47.1%, 31.6%, and 40.3% in the palonosetron alone, netupitant 100 mg, 200 mg, and 300 mg doses, and aprepitant groups, respectively. Some chemotherapeutic agents administered with cisplatin

(doxorubicin, 5-FU, cyclophosphamide) are known to cause ECG abnormalities, e.g. nonspecific ST segment changes, sinus tachycardia, premature ventricular and atrial complexes and T-wave abnormalities.

### **Conclusions**

The type, frequency, and intensity of TEAEs were comparable across treatment groups suggesting that netupitant at doses of 100 mg, 200 mg, and 300 mg can be administered safely in combination with palonosetron 0.5 mg for preventing nausea and vomiting following highly emetogenic chemotherapy. The sponsor chose the 300mg dose of netupitant to be used in combination with the 0.50mg dose of oral palonosetron in the fixed dose combination based on primary and secondary endpoint analysis, and favorable safety assessment. Although all netupitant doses were superior to palonosetron alone for CR overall, the 300mg dose of netupitant in combination with palonosetron performed better in the delayed and acute phase.

***PALO-10-01 (HEC)- Single-dose, multicenter, randomized, double-blind, double-dummy, parallel group study to assess the efficacy and safety of oral palonosetron 0.50 mg compared to I.V. palonosetron 0.25 mg administered with dexamethasone for the prevention of chemotherapy-induced nausea and vomiting in cancer patients receiving highly emetogenic cisplatin-based chemotherapy.***

This study was a Phase 3 study to assess the non-inferiority, safety, and tolerability of a single oral dose of palonosetron 0.50 mg versus a single I.V. dose of palonosetron 0.25 mg (each given with oral dexamethasone) prior to HEC. Randomization was on a 1:1 basis. Duration of the study was for a single cycle only.

The purpose of the trial was to show the efficacy of oral palonosetron 0.50 mg for the prevention of highly emetogenic CINV in order to confirm its suitability as an active comparator in other CINV clinical studies conducted with the fixed dose combination.

The 0.50-mg palonosetron oral capsule was approved in the US in 2008 for prevention of acute CINV-MEC. It is not approved for the prevention of nausea and vomiting induced by HEC. Only the I.V. formulation is approved for HEC. Therefore in order to use oral palonosetron 0.50mg as part of the fixed-dose combination for HEC it was necessary to demonstrate its efficacy and safety in prevention of CINV-HEC. The sponsor sought to do this by showing that 0.50mg oral palonosetron was not inferior to 0.25mg I.V. palonosetron.

### **Treatment groups**

Patients were randomized to one of the 2 treatments groups:

- Group 1 – oral palonosetron 0.50 mg and oral dexamethasone 20 mg both given on Day 1, then dexamethasone 8 mg twice daily (bid) from Days 2 to 4.

- Group 2 – I.V. palonosetron 0.25 mg and oral dexamethasone 20 mg both given on Day 1, then dexamethasone 8 mg bid from Days 2 to 4.

### **Number of Patients**

The number of patients planned to be randomized was estimated to be 740, or 370 patients per group.

### **Study Population**

Eligible patients must be treatment naïve, and diagnosed with a malignant solid tumor and scheduled to receive their first course of highly emetogenic cisplatin-based chemotherapy.

### **Duration**

Each patient was to stay on the study for a maximum of 37 days, including up to 14 days screening period, 6+2 days on study of which 4 days are on active treatment, and a follow-up visit or a telephone call 21±2 days after day 1. Total number of visits per patient will be 5 visits, or 4 visits plus phone call.

### **Study Sites**

A total of 80 study sites were activated in 12 countries. These are seen in Table 20.

**Table 41 Study Sites Palo10-01**

Region Country	Activated Sites	Sites Enrolling Patients	Patients Randomized
<b>Asia</b>			
India	6	5	96
<b>Commonwealth of Independent States</b>			
Russian Federation	11	9	133
Ukraine	8	6	87
<b>Europe</b>			
Bulgaria	6	6	21
Croatia	5	4	10
Germany	4	3	34
Hungary	6	5	117
Italy	4	4	46
Poland	6	6	128
Romania	8	6	55
<b>Latin America</b>			
Argentina	7	4	12
United States	9	2	4
<b>Total</b>	<b>80</b>	<b>60</b>	<b>743</b>

Ref: Palo10-01 Study Report, Table 1, p.21.

The greatest proportion of patients was randomized from Europe, followed by the Commonwealth of Independent States, former Soviet Republics.

### Eligibility Criteria

#### Inclusion Criteria (selected criteria)

- Male or female ≥18 years of age
- naïve to cytotoxic chemotherapy
- diagnosed with malignant solid tumor and schedule to receive cisplatin as a single I.V. dose of ≥70mg/m<sup>2</sup> over 1-4 hours on day 1, either alone or in combination with other chemotherapy agents

#### Exclusion Criteria

- scheduled to receive MEC or HEC from Day 2 to Day 5 following cisplatin
- received or scheduled to receive radiation therapy to abdomen or pelvis within 1 week prior to Day 1 or between Days 1 to 5
- active peptic ulcer disease, GI obstruction, increased intracranial pressure, hypercalcemia, active infection, any uncontrolled medical condition that may confound results

## **Efficacy Assessments**

### **Primary efficacy endpoint**

The primary efficacy endpoint is the proportion of patients with Complete Response (CR) (defined as no emesis, no rescue medication) within 24 hours after the start of the HEC administration on Day 1. Oral palonosetron 0.50 mg will be declared non-inferior to I.V. palonosetron 0.25 mg if the lower limit of the two-sided 99% CI for the difference between oral and I.V. palonosetron in terms of percentage of patients with CR in the acute phase is greater (i.e. closer to zero) than the pre-specified non-inferiority margin set at -15%. Calculations for the primary analysis will be based on the Cochran-Mantel-Haenszel (CMH) for the risk difference, 99% CI for the risk difference will be calculated. The model will include gender and region as strata. Odds Ratio (OR) from CMH test, 99% CI for OR and p-value will be displayed as well.

**Secondary efficacy endpoints** are defined as follows:

- the proportion of patients with complete response during the delayed and overall phase
- the proportion of patients with no emesis during the acute, delayed and overall phase
- the proportion of patients with no rescue medication during the acute, delayed and overall phase
- the proportion of patients with no significant nausea (maximum Visual Analogue Scale, VAS <25 mm) during the acute, delayed and overall phase
- the proportion of patients with no nausea (maximum VAS <5 mm) during the acute, delayed and overall phase
- the proportion of patients with complete protection (no emetic episode, no rescue medication and no significant nausea) during the acute, delayed and overall phase
- the proportion of patients with total control (no emetic episode, no rescue medication and no nausea) during the acute, delayed and overall phase;
- severity of nausea, defined as the maximum nausea on the VAS in the acute, delayed and overall phase
- time to first emetic episode, time to first rescue medication intake, time to treatment failure (based on time to the first emetic episode or time to the first rescue medication intake, whichever occurs first)

Numbers and percentages of patients with no emesis, no rescue, no nausea and no significant nausea, complete protection and total control in the acute phase will be descriptively summarized. Comparison between treatments on these endpoints will be performed using the same CMH test above described without testing for non-inferiority. OR, two-sided 95% CI and p-values will be presented.

Medical Officer's Comment:

The non-inferiority margin of -15% Was agreed upon prior to the trial initiation. This margin was derived from available historical information and has been used in other pivotal CINV studies for 5-HT3 antagonists, including Aloxi and Sancuso.

### Safety Assessments

Physical examination (PE), vital signs, 12-lead electrocardiogram (ECG), laboratory test (hematology, blood chemistry, urinalysis), and adverse events (AEs) assessment.

### Chemotherapy

All patients except one in the oral palonosetron group received treatment with cisplatin. Patients could also receive concomitant chemotherapeutic agents, and 85.4% of patients receiving oral Palonosetron did so, compared to 87.3% of patients receiving I.V. Palonosetron. Cancer types were evenly distributed in the population (Table 42).

**Table 42 Cancer History**

Parameter	Oral PALO (N=370)		I.V. PALO (N=369)		Overall (N=739)	
<b>Primary cancer diagnosis, n (%)</b>						
Gastric	25	(6.8)	24	(6.5)	49	(6.6)
Head and neck	62	(16.8)	71	(19.2)	133	(18.0)
Lung and respiratory tract	174	(47.0)	170	(46.1)	344	(46.5)
Ovarian	15	(4.1)	18	(4.9)	33	(4.5)
Bladder	8	(2.2)	3	(0.8)	11	(1.5)
Other	86	(23.2)	83	(22.5)	169	(22.9)
<b>Time since histological diagnosis (days)</b>						
n	370		368		738	
Mean (SD)	92.7 (265.54)		66.8 (179.00)		79.8 (226.78)	
Median	23.0		23.0		23.0	
Min, max	-1, 2533		0, 1875		-1, 2533	
<b>Extent at study entry, n (%)</b>						
Primary	184	(49.7)	193	(52.3)	377	(51.0)
Metastatic	176	(47.6)	161	(43.6)	337	(45.6)
Local recurrence	10	(2.7)	15	(4.1)	25	(3.4)
<b>Site of metastasis<sup>†</sup>, n (%)</b>						
Liver	22	(5.9)	32	(8.7)	54	(7.3)
Lung	59	(15.9)	34	(9.2)	93	(12.6)
Lymph nodes	112	(30.3)	110	(29.8)	222	(30.0)
Bone	25	(6.8)	24	(6.5)	49	(6.6)
Brain	7	(1.9)	7	(1.9)	14	(1.9)
Other	53	(14.3)	42	(11.4)	95	(12.9)

Ref: Palo10-01 study report, Table 10, p.65.

**Table 43 Chemotherapy - Safety Population**

Parameter	Oral PALO (N=370)	I.V. PALO (N=369)	Overall (N=739)
Cisplatin, n (%)	369 (99.7)	369 (100.0)	738 (99.9)
Cisplatin: total dose (mg)			
n	369	369	738
Mean (SD)	135.93 (24.912)	136.92 (25.802)	136.43 (25.349)
Median	133.70	135.00	135.00
Min, max	90.0, 329.8	84.0, 312.8	84.0, 329.8

Ref: Palo10-01, Table 11, P.67.

### Patient disposition

A total of 743 patients were randomized. Four patients did not receive treatment, so 739 (99.5%) received study medications and comprised the safety population. A total of 710 (95.6%) patients completed the study. Thirty-three (4.4%) prematurely discontinued the study after randomization. As Table 44 shows, the main reason for discontinuation was patient deaths (1.6% oral palonosetron, 3.0% I.V. palonosetron). Other reasons include lost to follow-up and withdrawal of consent. See the safety section below for further discussion of adverse events.

**Table 44 Summary of Patient Disposition - ITT (PALO-10-01)**

	Oral PALO		I.V. PALO		Overall	
	n	(%)	n	(%)	n	(%)
Randomized	371	(100.0)	372	(100.0)	743	(100.0)
Treated	370	(99.7)	369	(99.2)	739	(99.5)
Discontinued after randomization	12	(3.2)	21	(5.6)	33	(4.4)
Completed study	359	(96.8)	351	(94.4)	710	(95.6)
Reason for discontinuation						
Adverse event	1	(0.3)	1	(0.3)	2	(0.3)
Death	6	(1.6)	11	(3.0)	17	(2.3)
Protocol violation	0		3	(0.8)	3	(0.4)
Lost to follow-up	1	(0.3)	3	(0.8)	4	(0.5)
Withdrawal of consent	2	(0.5)	3	(0.8)	5	(0.7)
Lack of efficacy	0		0		0	
Sponsor's decision	1	(0.3)	0		1	(0.1)
Other	1	(0.3)	0		1	(0.1)

Source: Section 14, Table 14.1.1.1.

Abbreviations: I.V. = Intravenous; n = number of patients in category; PALO = Palonosetron.

### Safety

Seven (1.9%) patients in the oral palonosetron group and 12 (3.3%) in the I.V palonosetron group had a TEAE leading to death. Two patients (one in each treatment group) died after the study ended. Causes of the seven patient deaths in the oral palonosetron arm were: tumor lysis syndrome (2), cerebrovascular accident (2),

metastasis to CNS (1), multi-organ failure (1), and pneumonia and hemoptysis (1). In the I.V. palonosetron arm four patients died of unknown causes, and the others died of heart failure (2), lung cancer, multi-organ failure, pneumonia, intestinal obstruction, renal failure, and cardio-pulmonary failure. None of the deaths were considered related to study drugs or dexamethasone but rather due to underlying malignancy, chemotherapy, or progression of disease.

*Medical Officer's Comment:*

*The sponsor's assessment that none of the deaths were caused by palonosetron (I.V or oral) or dexamethasone seems correct. Patients enrolled in the study had progressive malignancies that were difficult to treat and required cytotoxic chemotherapy. Deaths in this patient population would not be unexpected.*

The number of serious TEAEs was balanced between the two drug groups. Two serious TEAEs that occurred in patients taking oral palonosetron were considered related to study drug: diarrhea and constipation. Constipation is a known potential side effect of the medication, and the other patient developed diarrhea 5 days after administration of study drug.

**Table 45 Summary of TEAEs**

Category	Number (%) of Patients Experiencing Event					
	Oral PALO (N=370)		I.V. PALO (N=369)		Overall (N=739)	
Any TEAE	180	(48.6)	191	(51.8)	371	(50.2)
TEAE related to study drug	12	(3.2)	24	(6.5)	36	(4.9)
TEAE related to dexamethasone	21	(5.7)	20	(5.4)	41	(5.5)
Any related TEAE	27	(7.3)	37	(10.0)	64	(8.7)
TEAE leading to discontinuation of study drug	1	(0.3)	1	(0.3)	2	(0.3)
TEAE related to study drugs leading to discontinuation	0		0		0	
TEAE related to dexamethasone leading to discontinuation	0		1	(0.3)	1	(0.1)
Any related TEAE leading to discontinuation	0		1	(0.3)	1	(0.1)
TEAE leading to death	7	(1.9)	12	(3.3)	19	(2.6)
Serious TEAE	36	(9.7)	36	(9.8)	72	(9.7)
Serious TEAE related to study drug	2	(0.5)	0		2	(0.3)
Serious TEAE related to dexamethasone	4	(1.1)	4	(1.1)	8	(1.1)
Any serious related TEAE	5	(1.4)	4	(1.1)	9	(1.2)
Severe TEAE	38	(10.3)	38	(10.3)	76	(10.3)
Severe TEAE related to study drug	2	(0.5)	0		2	(0.3)
Severe TEAE related to dexamethasone	4	(1.1)	4	(1.1)	8	(1.1)
Any severe related TEAE	5	(1.4)	4	(1.1)	9	(1.2)

Ref: Palo10-01, Study Report, Table 25, p.95.

**Table 46 TEAEs reported by >=5% patients either treatment**

MedDRA SOC PT	Oral PALO (N=370)		I.V. PALO (N=369)		Overall (N=739)	
	n (%)	E	n (%)	E	n (%)	E
Any TEAE	180 (48.6)	465	191 (51.8)	497	371 (50.2)	962
Blood and lymphatic system disorders	45 (12.2)	72	46 (12.5)	75	91 (12.3)	147
Neutropenia	21 (5.7)	21	28 (7.6)	29	49 (6.6)	50
Gastrointestinal disorders	57 (15.4)	83	67 (18.2)	92	124 (16.8)	175
Constipation	23 (6.2)	23	20 (5.4)	20	43 (5.8)	43
General disorders and administration site conditions	46 (12.4)	54	64 (17.3)	72	110 (14.9)	126
Asthenia	31 (8.4)	31	28 (7.6)	28	59 (8.0)	59
Investigations	41 (11.1)	74	45 (12.2)	79	86 (11.6)	153
Metabolism and nutrition disorders	39 (10.5)	50	30 (8.1)	36	69 (9.3)	86
Decreased appetite	21 (5.7)	21	11 (3.0)	11	32 (4.3)	32
Nervous system disorders	18 (4.9)	22	28 (7.6)	30	46 (6.2)	52
Headache	9 (2.4)	9	21 (5.7)	22	30 (4.1)	31
Respiratory, thoracic and mediastinal disorders	22 (5.9)	24	18 (4.9)	22	40 (5.4)	46

Ref: Palo10-01 study report, Table 26, p.98.

Table 46 shows TEAEs in 5% or more of patients in either group. These are generally balanced between the two groups and expected in patients receiving cytotoxic cancer chemotherapy. Constipation and headache are known side effects of anti-emetic drugs.

### Efficacy

The primary efficacy objective of PALO-10-01 was to demonstrate the non-inferiority of a single dose of oral palonosetron 0.50mg compared to a single dose of I.V. palonosetron 0.25mg as assessed by proportion of patients with complete response during the acute phase of 0-24 hours post chemotherapy. These results are shown in Table 47.

**Table 47 Non-inferiority based on complete response acute phase**

	Oral PALO (N=369)	I.V. PALO (N=369)
Acute phase (0-24 hours)		
Responder, n (%)	330 (89.4)	318 (86.2)
95% CI <sup>a</sup>	[85.9; 92.2]	[82.3; 89.3]
Risk difference, % (99% CI) <sup>b</sup>	3.21 (-2.74; 9.17)	

Ref: Palo-10-01 Study Report, Table 13, p.70.

Secondary efficacy analysis was to assess CR rate during the delayed and overall phases. These results supported the conclusion of non-inferiority of oral palonosetron to I.V. palonosetron.

**Table 48 CR delayed and overall phases**

	Oral PALO (N=369)	I.V. PALO (N=369)
<b>Delayed phase (25-120 hours)</b>		
Responder, n (%)	281 (76.2)	276 (74.8)
95% CI <sup>a</sup>	71.5, 80.2	70.1, 79.0
Difference from I.V. palonosetron, % (95% CI <sup>b</sup> )		1.4 (-4.8, 7.5)
Odds ratio (95% CI) <sup>c</sup>		1.09 (0.77, 1.52)
p-value <sup>d</sup>		0.637
<b>Overall phase (0-120 hours)</b>		
Responder, n (%)	272 (73.7)	259 (70.2)
95% CI <sup>a</sup>	69.0, 77.9	65.3, 74.6
Difference from I.V. palonosetron, % (95% CI <sup>b</sup> )		3.5 (-3.0, 10.0)
Odds ratio (95% CI) <sup>c</sup>		1.20 (0.87, 1.67)
p-value <sup>d</sup>		0.269

Ref: Palo10-01 study report, Table 15, p.71.

### Conclusion:

Clinical trial PALO-10-01 was conducted so that the oral dosage form of palonosetron could be used in the combination product for the treatment of CINV-HEC. This trial showed that oral palonosetron works as well as I.V. palonosetron for the prevention of CINV-HEC.

### **NETU-10-29 (MEC and HEC) - A phase III, multicenter, randomized, double-blind, unbalanced (3:1) active control study to assess the safety and describe the efficacy of netupitant and palonosetron for the prevention of chemotherapy-induced nausea and vomiting in repeated chemotherapy cycles.**

The primary objective of HEC and MEC trial NETU-10-29 was to assess the safety and tolerability of a single oral dose of the FDC in initial and repeated cycles of cancer chemotherapy. The secondary objective was to describe the efficacy during the acute, delayed and overall phases of initial and repeated cycles of cancer chemotherapy.

### Treatment Groups

Group 1 – oral netupitant/palonosetron (300 mg/0.50 mg) fixed combination on Day 1 (with oral dexamethasone)

Group 2 – oral aprepitant 125 mg (on Day 1) + 80 mg daily (for the following two days) and oral palonosetron 0.50 mg (on Day 1) (with oral dexamethasone).

Oral dexamethasone administration was to be open-label and identical in both treatment groups. Based on the emetogenicity of the chemotherapeutic regimen, the dose schedule of dexamethasone was one of the following:

- HEC: 12 mg on Day 1, then 8 mg daily on Days 2 through 4
- MEC: 12 mg on Day 1

### Inclusion Criteria

- Signed written informed consent.
- Male or female patient  $\geq 18$  years of age.
- Naïve to cytotoxic chemotherapy. Previous biological or hormonal therapy is permitted.
- Diagnosed with a malignant tumor.
- A single dose of one or more of the following agents administered on Day 1 is allowed:
  - HEC: any I.V. dose of cisplatin, mechlorethamine, streptozocin, cyclophosphamide  $\geq 1500$  mg/m<sup>2</sup>, carmustine, dacarbazine
  - MEC: any I.V. dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin, cyclophosphamide I.V. ( $< 1500$  mg/m<sup>2</sup>), cytarabine I.V. ( $> 1$  g/m<sup>2</sup>), azacitidine, alemtuzumab, bendamustine, or clofarabine.
- If scheduled to receive combination regimens, the most emetogenic agent is to be given first on Day 1 and the infusion must be completed within 6 hours.
- If scheduled to receive chemotherapy agents of minimal to low emetogenic potential, they are to be given on Day 1 following the most emetogenic agent, or on a subsequent study day.
- ECOG Performance Status of 0, 1, or 2.
- Female patients of either:
  - **non-childbearing potential** (i.e., physiologically incapable of becoming pregnant, including any female who is postmenopausal. For purposes of this study, postmenopausal is defined as 12 consecutive months of amenorrhea)
  - **child-bearing potential** with a negative urine dipstick pregnancy test within 24 hours prior to the first dose of investigational product on Day 1 of each cycle and use of one of the following contraceptive methods throughout the clinical trial:
    - whose male partner is sterile prior to the female patient's entry into the study and is the sole sexual partner using double-barrier method of contraception consisting of spermicide with either condom or diaphragm, also if taking any oral contraceptive, for a period after the trial to account for a potential drug interaction (minimum four weeks)
    - with intrauterine device (IUD)
    - with complete abstinence from intercourse for two weeks before exposure to the investigational product and throughout the clinical trial.
- Hematologic and metabolic status adequate:
  - a) Total Neutrophils  $\geq 1500$ /mm<sup>3</sup>
  - b) Platelets  $\geq 100,000$ /mm<sup>3</sup>
  - c) Bilirubin  $\leq 1.5$  x Upper Limit of Normal (ULN)
  - d) Liver enzymes:

- Without known liver metastases, AST and/or ALT  $\leq 2.5 \times$  ULN
- With known liver metastases, AST and/or ALT  $\leq 5.0 \times$  ULN
- Serum Creatinine  $\leq 1.5$  mg/dL or Creatinine Clearance  $\geq 60$  mL/min.
- Able to read, understand, follow the study procedure and complete patient diary.

#### Exclusion Criteria (selected criteria only)

- lactating or pregnant female
- current illicit drugs or alcohol abuse
- Scheduled to receive either:
  - cyclophosphamide I.V. (500 to 1500 mg/m<sup>2</sup>) and I.V. doxorubicin ( $\geq 40$  mg/m<sup>2</sup>)
  - cyclophosphamide I.V. (500 to 1500 mg/m<sup>2</sup>) and I.V. epirubicin ( $\geq 60$  mg/m<sup>2</sup>).
- HEC or MEC on day 2 to 5 following day 1
- active infection or uncontrolled disease
- hypersensitivity or contraindication to 5-HT<sub>3</sub> RA or dexamethasone
- prior receipt of NK1 RA
- history of risk factors for Torsade de Pointe
- Severe cardiovascular diseases within 3 months prior to Day 1

#### Safety Assessments

Safety was assessed by TEAEs and physical examination (PE), vital signs, 12-lead electrocardiogram (ECG), Left Ventricular Ejection Fraction (LVEF), cardiac troponin levels (cTnI), laboratory test (hematology, blood chemistry, and urinalysis). LVEF was assessed at screening cycle 1 and at the end of study, while all the other safety assessments were obtained in each cycle. During the conduct of the trial, a Data Safety Monitoring Board (DSMB) will periodically review safety data.

#### Efficacy Assessment

Efficacy evaluations were based on documentation of emetic episodes (episodes of retching or vomiting) and nausea assessed by Visual Analogue Scale (VAS) and intake of rescue medication. To collect these data, patients were given a diary covering Days 1 to 5 of each cycle. Efficacy parameters were evaluated in the delayed phase (25 to 120 hours after the start of chemotherapy), acute phase (0 to 24 hours after the start of chemotherapy) and overall phase (0 to 120 hours after the start of chemotherapy). An emetic episode was defined as one or more continuous vomits (expulsion of stomach contents through the mouth) or retches (an attempt to vomit that is not productive of stomach contents). Emetic episodes were considered distinct if separated by absence of vomiting and retching for at least 1 minute.

#### Study Results - Disposition

Of the 413 patients randomized, approximately 25% of patients received HEC, and 75% MEC. More than 75% of patients continued on to cycle 4, and more than 40% of patients reached cycle 6. A total of twenty-three (5.6%) patients prematurely discontinued the study after randomization and 154 (37.3%) patients completed a cycle but did not continue into further cycles.

**Table 49 Patient Disposition**

	NETU/PALO FDC		Aprepitant+ PALO		Overall	
	n	(%)	n	(%)	n	(%)
Randomized	309	(100.0)	104	(100.0)	413	(100.0)
Treated	309	(100.0)	103	(99.0)	412	(99.8)
Completed planned/unplanned chemotherapy cycles	181	(58.6)	55	(52.9)	236	(57.1)
Completed planned chemotherapy cycles but discontinued during additional unplanned cycle	0		0		0	
Completed a cycle but not continuing in the next planned cycle	111	(35.9)	43	(41.3)	154	(37.3)
Discontinued after randomization and during any planned chemotherapy cycle	17	(5.5)	6	(5.8)	23	(5.6)
Reason for not continuing or for discontinuation						
Adverse event	19	(6.1)	12	(11.5)	31	(7.5)
Death	12	(3.9)	0		12	(2.9)
Protocol violation	4	(1.3)	1	(1.0)	5	(1.2)
Lost to follow-up	5	(1.6)	1	(1.0)	6	(1.5)
Withdrawal of consent	17	(5.5)	7	(6.7)	24	(5.8)
Lack of efficacy	0		0		0	
Sponsor's decision	1	(0.3)	0		1	(0.2)
Other	70	(22.7)	28	(26.9)	98	(23.7)
Entered a within-study cardiovascular follow-up*	6	(1.9)	2	(1.9)	8	(1.9)
Entered a post-withdrawal cardiovascular follow-up*	1	(0.3)	1	(1.0)	2	(0.5)

Ref: Netu1029, Table 4, p.59

**Medical Officer's Comment:**

*This trial assessed safety over a period of expected use of the drug, determined to be 6 chemotherapy cycles. Treatment of 100 patients for at least six cycles is consistent with ICH guidelines and addressed the need for safety data beyond cycle 1.*

**Demographics**

The gender of patients was almost evenly divided between treatment arms. Over 80% of patients in each treatment arm were white, and approximately 16% Asian. Enrollment of patients of other races was negligible. Other baseline characteristics such as tobacco use, alcohol, and ECOG performance status were also evenly distributed.

Cancer history was also an important demographic. As Table 50 shows lung and respiratory, other, ovarian, colon and head/neck cancers were the most represented. Although generally balanced, there were more lung and respiratory cancers in the Akynzeo arm, and more ovarian cancers in the Aprepitant+Palo arm.

**Table 50 Cancer Histories - Safety Population**

Parameter	NETU/PALO FDC (N=308)		Aprepitant+ PALO (N=104)		Overall (N=412)	
<b>Primary cancer diagnosis, n (%)</b>						
Colorectal	17	(5.5)	5	(4.8)	22	(5.3)
Colon	24	(7.8)	13	(12.5)	37	(9.0)
Rectal	9	(2.9)	5	(4.8)	14	(3.4)
Gastric cancer	7	(2.3)	1	(1.0)	8	(1.9)
Head and neck cancer	20	(6.5)	11	(10.6)	31	(7.5)
Lung and respiratory tract cancer	122	(39.6)	32	(30.8)	154	(37.4)
Ovarian cancer	33	(10.7)	18	(17.3)	51	(12.4)
Bladder cancer	4	(1.3)	3	(2.9)	7	(1.7)
Other	72	(23.4)	16	(15.4)	88	(21.4)

Ref: NETU1029 Study Report, Table 10, p.68.

### Study Sites

Patients were enrolled from 59 study sites in 10 countries. Countries enrolling patients are listed below.

**Table 51 Study Sites NETU-10-29**

Region Country	Sites Activated for Recruitment	Sites Enrolling Patients	Patients Randomized
<b>Asia</b>			
India	8	7	62
<b>Commonwealth of Independent States</b>			
Russian Federation	10	8	30
Ukraine	8	8	96
<b>Europe</b>			
Bulgaria	5	4	31
Czech Republic	5	5	32
Germany	11	8	36
Hungary	5	4	18
Poland	7	6	62
Serbia	3	3	29
<b>United States</b>	10	6	17
<b>Total</b>	<b>72</b>	<b>59</b>	<b>413</b>

Ref: Table 1, Study Report, p.22.

*Medical Officer's Comment:*

*The majority of patients are from the Ukraine and India. Although the US had a comparable number of sites as other countries in which sites were activated, the number of patients enrolled from the US is small.*

### Efficacy

The efficacy analyses uses delayed phase, acute phase, and overall phase to measure CINV in the intervals from 25-120 hours (i.e. >24 hours to ≤120 hours), 0-24 hours and 0-120 hours, respectively, after beginning MEC or HEC administration. The number of patients who continued in the study after cycle 6 (33 and 13 patients in the netupitant/palonosetron FDC and aprepitant+palonosetron groups, respectively) was too low to permit efficacy evaluation.

**Table 52 Number and % patients with CR cycle 1**

	NETU/PALO FDC (N=309)	Aprepitant+PALO (N=103)
<b>Cycle 1 delayed phase (25-120 hours)</b>		
Patients with complete response, n (%)	257 (83.2)	80 (77.7)
95% CI <sup>a</sup>	(78.6;86.9)	(68.7;84.6)
Difference in response rate <sup>b</sup> , % (95% CI <sup>b</sup> )	5.5 (-2.8;15.2)	
<b>Cycle 1 acute phase (0-24 hours)</b>		
Patients with complete response, n (%)	287 (92.9)	97 (94.2)
95% CI <sup>a</sup>	(89.5;95.3)	(87.9;97.3)
Difference in response rate <sup>b</sup> , % (95% CI <sup>b</sup> )	-1.3 (-5.9;5.4)	
<b>Cycle 1 overall phase (0-120 hours)</b>		
Patients with complete response, n (%)	249 (80.6)	78 (75.7)
95% CI <sup>a</sup>	(75.8;84.6)	(66.6;83.0)
Difference in response rate <sup>b</sup> , % (95% CI <sup>b</sup> )	4.9 (-3.8;14.8)	

Ref: Netu1029, Study Report, Table 11, p.72.

*Medical Officer's Comment:  
 Efficacy results are descriptive only.*

### Safety

A total of 412 patients were included in the safety population; 308 were exposed to the netupitant/palonosetron and 104 to aprepitant+palonosetron during cycle 1. A total of 167 patients were treated up to cycle 6 (124 in the netupitant/palonosetron arm and 43 in the aprepitant+palonosetron arm). Adverse events were collected during all cycles.

### Deaths

Twelve (3.9%) patients in the NETU/PALO FDC discontinued due to death. No patients died in the Aprepitant+PALO group. There were 5 other patients who discontinued due to a TEAE that resulted in death. Four were in the FDC and one was in the active control. In total there were 16 deaths in the netupitant/palo arm and one in active control. Among the causes of death were disease progression (5 patients), lung/pulmonary embolism (2 patients), and hemoptysis and dyspnea due to disease complication, lower respiratory tract infection and pancytopenia, cancer intoxication, pulmonary heart insufficiency, ischemic stroke, pneumothorax, weakness, circulatory

and respiratory failure and pneumonia (one patient each). Seven deaths occurred in cycle 1, one death in cycle 2, 3 deaths in cycle 3, and 2 deaths in cycle 4, 5, and 6, each.

#### NETU-10-29

- 3106/04 (PALO+NETU) 69yo male with primary lung and respiratory tract cancer. His chemotherapeutic agents were **gemcitabine and carboplatin**. He was hospitalized 24 days after the first dose of study drug due to neutropenia and frequent stools. Prior to hospitalization his white blood cell count was  $1.2 \times 10^9/L$ , with a neutrophil count of  $0.3 \times 10^9/L$  (normal  $1.6-7.4 \times 10^9$ ). Three days into hospitalization he developed hemoptysis and dyspnea and died on the same day. The event of neutropenia was assessed as related to chemotherapy, and hemoptysis and dyspnea due to disease progression.
- 3107/08, (PALO+NETU) 72-year-old male with metastatic lung and respiratory tract cancer for which he was treated with **carboplatin and etoposide**. Seven days after study drug during cycle 3 he developed severe respiratory tract infection and pancytopenia and was diagnosed with sepsis. While hospitalized he had mild respiratory distress, atrial fibrillation and metabolic acidosis. He was discharged with a feeding tube and died at home. Cause of death was attributed to cytotoxic chemotherapy, cancer, and comorbidities.
- 3107/09, (PALO+NETU) 35-year-old male with primary esophageal carcinoma treated with **carboplatin and paclitaxel**. During his third cycle of chemotherapy he had several episodes of hemoptysis and collapsed. During CPR he had copious amount of bleeding from the mouth.
- 4205/01, (PALO+NETU) 63-year-old female with lung and respiratory tract cancer receiving **etoposide, epirubicin, and cyclophosphamide**. The patient had undergone 4 courses of chemotherapy with carboplatin and a fifth with cisplatin. The sixth cycle was postponed because of increased fatigue, dyspnea and decreased blood pressure. The patient died during her sleep (28 days after the last administration of study drugs). Cause of death attributed to multi-organ failure due to cancer intoxication.
- 4205/08 (PALO+NETU) 69-year-old male patient with lung and respiratory tract cancer given **doxorubicin and cyclophosphamide**. Fifteen days after administration of study drugs the patient had worsening dyspnea and chest pain. No corrective treatment was administered and the patient died on the same day. Cause of death attributed to cancer intoxication.
- 4205/36, (PALO+NETU) a 56-year-old female patient with primary lung and respiratory tract cancer treated with **carboplatin and etoposide**. Five days after administration of the first dose of study drugs the patient had weakness of the right hand and a speech disorder, diagnosed by CT as cerebrovascular accident. During hospitalization she had increased dyspnea, tachypnea and tachycardia. Despite treatment the patient died of cardio-pulmonary failure. Cause of death attributed to concomitant disease and lung cancer.

- 5102/03, (PALO+NETU) 62-year-old male patient with primary carcinoma of the tonsil treated with **cisplatin and 5-fluorouracil**. Had worsening of disease during cycle 4, and fifteen days after the administration of study drugs the patient died suddenly. Cause of death disease progression.
- 5105/05, (PALO+NETU) 50-year-old male patient with metastatic lung cancer treated with **carboplatin and gemcitabine** hydrochloride. The patient had worsening back pain which was found to be a progression of bone metastases. At day after the first administration of study drugs the patient lost ability to speak and experienced right hemiparesis. CT scan showed ischemic stroke and the patient was discontinued from the study due to ischemic stroke. No explanation for stroke was given.
- 5303/04, (PALO+NETU) 57-year-old female patient with metastatic lung cancer treated with **cisplatin and etoposide**. Diagnosed with long QT syndrome caused by hypocalcemia ( $\text{Ca}^+$  1.54mmol/l). Recovered from this event. Several weeks later had worsening general pain. Progression of cancer was diagnosed and the patient died shortly thereafter.
- 5309/07, (PALO+NETU) 74-year-old male patient with metastatic lung and respiratory tract cancer treated with **carboplatin, bevacizumab and docetaxel**. Had pneumothorax in cycle 1, 20 days after the last administration of study drugs. The patient had extensive skin and mediastinal emphysema associated with fistulous tumor in the chest wall. A decision against surgical treatment was made.
- 5603/13, (PALO+NETU) 74-year-old female patient with metastatic ovarian cancer treated with **carboplatin and vinorelbine**. Hospitalized for weakness and electrolyte imbalance. During hospitalization had cardiac arrest from which, despite corrective treatment, resuscitation and mechanical ventilation, she died. Cause of death connected to chemotherapy and electrolyte imbalance.
- 5607/31, (PALO+NETU) 55-year-old female patient with primary lung and respiratory tract cancer treated with **vinorelbine and carboplatin**. Twenty days after the last administration of study drugs the patient was hospitalized to start the next cycle of chemotherapy. She experienced malaise, weakness, dyspnea at rest, and circulatory and respiratory failure. Chest X-ray revealed progression of lung cancer and acidosis. Despite treatment patient died on the same day, cause of death lung and respiratory tract carcinoma.
- 6001/03, (PALO+NETU) 66-year-old male with primary lung and respiratory tract cancer treated with **cisplatin and vinorelbine**. The patient developed pneumonia in cycle 2 (1 day after last administration of study drugs). Despite attempts at corrective treatment the patient died.
- 6001/04, (PALO+NETU) 55-year-old female patient with metastatic lung and respiratory tract cancer treated with **vinorelbine and cisplatin**. Six days after the last administration of study drugs computed tomography (CT) scan showed regression of lung carcinoma but the patient died suddenly at home. Cause of death was cited as probable pulmonary embolism in cycle 6 due to lung cancer.

- 6006/07, (PALO+NETU) 61-year-old male patient with metastatic lung and respiratory tract cancer given **gemcitabine and carboplatin**. Two days after the last administration of study drugs (cycle 3) the patient experienced a sudden onset of dyspnea and was hospitalized. An autopsy confirmed pulmonary embolism as the cause of the death.
- 6006/10, (PALO+NETU) 56-year-old female patient with metastatic endometrial cancer treated with **carboplatin and gemcitabine**. The patient completed the chemotherapy course but worsening of her health did not allow further chemotherapy administration and patient was discontinued from the study. On day 21 after the last administration of study drugs the patient was hospitalized due to anemia, hypokalemia and hypocalcaemia, and a diagnosis of endometrial cancer progression was made. The reason for discontinuation was adverse event which led to death.
- 5303/02 (aprepitant+palo) 64-year-old male with metastatic adenocarcinoma of lung and respiratory tract treated with **vinorelbine and cisplatin**. Patient developed renal insufficiency 3 days after the last administration of study drugs in cycle 6. Also had brain metastases and developed severe convulsions. Renal dysfunction was attributed to cisplatin exposure and neurological manifestations due to brain metastases.

Of the 16 patients in the NETU+PALO arm who died, 4 (0.2%) received cyclophosphamide, 8 (2.6%) received etoposide and 5 (4.7%) received docetaxel.

*Medical Officer's Comment:*

*At baseline patients were suffering from life-threatening conditions, and received cytotoxic chemotherapy. Because the randomization was 3:1, more SAEs would be expected in the Akynzeo arm than the Aprepitant+Palo arm. In addition, there was a greater proportion of lung and respiratory cancer in the Akynzeo arm, and more metastatic disease.*

**TEAEs**

During the overall study the percentage of patients with at least one TEAE related to study drugs was 10.1% in the netupitant/palonosetron group and 5.8% in the aprepitant+palonosetron group. Overall, 69 (16.7%) patients experienced serious TEAEs: 16.2% in the netupitant/palonosetron FDC and 18.3% aprepitant+palonosetron groups. A total of 41 (10.0%) patients experienced TEAEs leading to discontinuation of the study: 28 (9.1%) in the netupitant/palonosetron FDC group and 13 (12.5%) in the aprepitant+palonosetron group. These results are shown in Table 53.

**Table 53 TEAE in whole study period - safety population**

Category, n (%)	Number (%) of Patients Experiencing Event		
	NETU/PALO FDC (N=308)	Aprepitant+ PALO (N=104)	Overall (N=412)
Any TEAE	265 (86.0)	95 (91.3)	360 (87.4)
TEAE related to study drug	31 (10.1)	6 (5.8)	37 (9.0)
TEAE related to dexamethasone	36 (11.7)	15 (14.4)	51 (12.4)
Any related TEAE	52 (16.9)	19 (18.3)	71 (17.2)
TEAE leading to discontinuation of study drug	28 (9.1)	13 (12.5)	41 (10.0)
TEAE related to study drug leading to discontinuation	1 (0.3)	0	1 (0.2)
TEAE related to dexamethasone leading to discontinuation	2 (0.6)	0	2 (0.5)
Any related TEAE leading to discontinuation	2 (0.6)	0	2 (0.5)
TEAE leading to death	16 (5.2)	1 (1.0)	17 (4.1)
Serious TEAE	50 (16.2)	19 (18.3)	69 (16.7)
Serious TEAE related to study drug	2 (0.6)	0	2 (0.5)
Serious TEAE related to dexamethasone	3 (1.0)	0	3 (0.7)
Any serious related TEAE	4 (1.3)	0	4 (1.0)
Severe TEAE	77 (25.0)	34 (32.7)	111 (26.9)
Severe TEAE related to study drug	1 (0.3)	0	1 (0.2)
Severe TEAE related to dexamethasone	4 (1.3)	3 (2.9)	7 (1.7)
Any severe related TEAE	4 (1.3)	3 (2.9)	7 (1.7)

Ref: Netu10-29, Table 13, p.84.

A further breakdown of TEAE by MEC or HEC shows a balance between the two in terms of experience of adverse events: MEC 88% and HEC 86%. Comparing the percentage of patients with TEAE by chemotherapy and treatment shows that 86% of patients treated with Akynzeo for MEC and 85% of patients treated with Akynzeo for HEC had TEAEs. This contrasts with 92% patients receiving Aprepitant+Palonosetron for MEC and 88% patients receiving Aprepitant+Palonosetron for HEC. The only TEAE judged related to the study drugs reported by  $\geq 2\%$  of patients in any treatment group was constipation (7 [3.0%] patients in the netupitant/palonosetron FDC group and none in the aprepitant+palonosetron groups, respectively).

The following Table 54 shows TEAEs in  $\geq 5\%$  patients in either treatment group for the entire study period. This table shows that Netu/Palo performed well against Aprepitant+Palo in terms of more common TEAEs. Neutropenia and alopecia are highlighted as examples.

Table 54 TEAE's in >=5% patients in either TX arm

MedDRA SOC PT	NETU/PALO FDC (N=308)		Aprepitant+PALO (N=104)		Overall (N=412)	
	n (%)	E	n (%)	E	n (%)	E
<b>General disorders and administration site conditions</b>	<b>85 (27.6)</b>	<b>148</b>	<b>35 (33.7)</b>	<b>72</b>	<b>120 (29.1)</b>	<b>220</b>
Asthenia	30 (9.7)	34	12 (11.5)	18	42 (10.2)	52
Fatigue	29 (9.4)	38	15 (14.4)	25	44 (10.7)	63
Pyrexia	19 (6.2)	25	10 (9.6)	11	29 (7.0)	36
<b>Investigations</b>	<b>66 (21.4)</b>	<b>208</b>	<b>25 (24.0)</b>	<b>80</b>	<b>91 (22.1)</b>	<b>288</b>
Blood creatinine increased	6 (1.9)	6	6 (5.8)	7	12 (2.9)	13
Neutrophil count decreased	17 (5.5)	39	4 (3.8)	11	21 (5.1)	50
<b>Metabolism and nutrition disorders</b>	<b>59 (19.2)</b>	<b>103</b>	<b>19 (18.3)</b>	<b>29</b>	<b>78 (18.9)</b>	<b>132</b>
Decreased appetite	20 (6.5)	22	7 (6.7)	8	27 (6.6)	30
Hypokalaemia	16 (5.2)	22	4 (3.8)	5	20 (4.9)	27
<b>Nervous system disorders</b>	<b>49 (15.9)</b>	<b>77</b>	<b>24 (23.1)</b>	<b>44</b>	<b>73 (17.7)</b>	<b>121</b>
Headache	15 (4.9)	20	7 (6.7)	9	22 (5.3)	29
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>50 (16.2)</b>	<b>69</b>	<b>19 (18.3)</b>	<b>38</b>	<b>69 (16.7)</b>	<b>107</b>
Cough	14 (4.5)	16	8 (7.7)	11	22 (5.3)	27
<b>Skin and subcutaneous tissue disorders</b>	<b>90 (29.2)</b>	<b>106</b>	<b>37 (35.6)</b>	<b>41</b>	<b>127 (30.8)</b>	<b>147</b>
<b>Alopecia</b>	<b>77 (25.0)</b>	<b>77</b>	<b>32 (30.8)</b>	<b>32</b>	<b>109 (26.5)</b>	<b>109</b>

MedDRA SOC PT	NETU/PALO FDC (N=308)		Aprepitant+PALO (N=104)		Overall (N=412)	
	n (%)	E	n (%)	E	n (%)	E
<b>Any TEAE</b>	<b>265 (86.0)</b>	<b>1761</b>	<b>95 (91.3)</b>	<b>720</b>	<b>360 (87.4)</b>	<b>2481</b>
<b>Blood and lymphatic system disorders</b>	<b>139 (45.1)</b>	<b>502</b>	<b>48 (46.2)</b>	<b>186</b>	<b>187 (45.4)</b>	<b>688</b>
Anaemia	58 (18.8)	88	26 (25.0)	44	84 (20.4)	132
Leukopenia	55 (17.9)	122	18 (17.3)	50	73 (17.7)	172
<b>Neutropenia</b>	<b>95 (30.8)</b>	<b>194</b>	<b>29 (27.9)</b>	<b>54</b>	<b>124 (30.1)</b>	<b>248</b>
Thrombocytopenia	38 (12.3)	59	16 (15.4)	24	54 (13.1)	83
<b>Gastrointestinal disorders</b>	<b>100 (32.5)</b>	<b>246</b>	<b>38 (36.5)</b>	<b>109</b>	<b>138 (33.5)</b>	<b>355</b>
Constipation	26 (8.4)	34	9 (8.7)	9	35 (8.5)	43
Diarrhoea	32 (10.4)	47	19 (18.3)	27	51 (12.4)	74
Dyspepsia	16 (5.2)	29	3 (2.9)	4	19 (4.6)	33
Nausea	18 (5.8)	29	11 (10.6)	20	29 (7.0)	49
Stomatitis	9 (2.9)	10	6 (5.8)	7	15 (3.6)	17

Reviewer's Table.

**TEAEs by chemotherapy cycle**

As noted, TEAEs were collected during each chemotherapy cycle. In cycle one 65% of patients had at least one TEAE, whereas by cycle 6 the number had fallen to 35%. The following tables show TEAEs in cycle 1, cycle 6, and overall.

**Table 55 TEAEs cycle 1**

Treatment-Emergent Adverse Events Cycle 1 Number (%) patients experiencing event		
	NETU/PALO (n=309)	Aprepitant+Palo (n=104)
Any TEAE	199 (64.6)	64 (61.5)
Serious TEAE	18 (5.6)	4 (3.0)
Serious TEAE related	1 (0.3)	0
Deaths	7 (2.3)	0

Ref: Reviewer's Table

**Table 56 TEAEs cycle 6**

Treatment-Emergent Adverse Events Cycle 6 Number (%) patients experiencing event		
	NETU/PALO (n=124)	Aprepitant/Palo (n=43)
Any TEAE	43 (34.7)	14 (32.6)
Serious TEAE	3 (2.4)	2 (4.7)
Serious TEAE related	1 (0.8)	0
Deaths	1 (0.8)	1 (2.3)

Ref: Reviewer's Table

**Table 57 TEAEs overall (all cycles combined)**

Treatment-Emergent Adverse Events Overall Number (%) patients experiencing event		
	NETU/PALO (n=308)	Aprepitant/Palo (n=104)
Any TEAE	265 (86)	95 (91.2)
Serious TEAE	50 (16.2)	19 (18.3)
Serious TEAE related	2 (0.6)	0
Deaths	16 (5.2)	1 (1.0)

Ref: Reviewer's Table

### Summary

Clinical study NETU10-29 was conducted in approximately 1/3 HEC patients and 2/3 MEC patients. It was designed to explore safety with repeat cycles of chemotherapy, and the sponsor enrolled patients through cycle 14. The number of patients continuing beyond cycle 6 was small, and reflects real world conditions in which chemotherapy beyond cycle 6 is less common.

### Conclusion

Although the study was not designed to formally assess efficacy, it supports other HEC and MEC studies of the fixed-dose combination of netupitant and palonosetron. Safety

is difficult to assess in this critically ill population, but overall TEAEs are balanced between the two arms, with the exception of deaths. Discussed above, and in the overall safety section of the NDA review, the imbalance in deaths was explored, and does not raise concerns about the safety of the drug.

## 6 Review of Efficacy

### 6.1 Indication

The target indications for this application are:

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (CINV-HEC)
- prevention of acute and delayed nausea and vomiting associated with initial repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC)

*Medical Officer's Comment:*

*The labeled indication will be “prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.” This indication fairly reflects the data obtained from the clinical trials, and will allow for the use of Akynzeo for both HEC and MEC.*

#### 6.1.1 Methods

Based on an agreement between the company and the FDA, there is no formal integration of efficacy data based on the fact that patient populations and type of chemotherapy administered were different for each study. Four pivotal studies provided vital information to support the combination of netupitant+palonosetron for acute and delayed CINV associated with HEC and MEC for single and repeat chemotherapy courses. While each component of the clinical development of Akynzeo adds to the whole, there are no confirmatory studies. The following four trials were reviewed:

- NETU-07-07: Superiority HEC; single cycle
- PALO-10-01: Non-Inferiority: HEC; single cycle
- NETU-08-18: Superiority MEC; single and multiple cycles
- NETU-10-29: Safety; MEC and HEC; multiple cycles

*Medical Officer's Comment:*

*The FDA statistical team leader stated in her review that with the collective evidence from these three efficacy studies, the netupitant 300mg and palonosetron 0.5mg FDC*

*shows benefit in the prevention of both acute and delayed CINV as assessed by the efficacy endpoint of CR.*

### 6.1.2 Demographics

The differences in patient demographics between studies of Akynzeo were due to the different types of cancers being treated, and chemotherapies used. NETU-08-18 studied females with breast cancer (>98%), whereas NETU-07-07 and NETU-10-29 were more diverse in terms of cancer diagnosis. Racial diversity was affected in where the trial was conducted as seen, for example, in NETU-07-07 where 99.9% of patients were white due to the trial being conducted exclusively in Russia and the Ukraine. Most patients had a good performance status as per the ECOG or Karnofsky rating system. Table 58 shows basic demographic data for patients in the three phase 3 trials.

**Table 58 Patient Demographics Cycle 1 - All Netu/Palo (Safety Pop)**

	NETU-07-07 (N=679) HEC	NETU-08-18 (N=1450) MEC	NETU-10-29 (N=412) HEC/MEC
<b>Gender , n (%)</b>			
Male	387 (57)	28 (1.9)	206 (50)
Female	292 (43)	1422 (98.1)	206 (50)
<b>Age (years)</b>			
Mean (SD)	54.4 (9.79)	53.9 (10.65)	56.6 (10.76)
Median	55	54	58
Range	19-82	22-79	21-80
<b>Race , n (%)</b>			
White	678 (99.9)	1153 (79.5)	345 (83.7)
Black	-	4 (0.3)	3 (0.7)
Asian	1 (0.1)	204 (14.1)	64 (15.5)
Hispanic	-	82 (5.7%)	-
Other	-	7 (0.5)	-
<b>ECOG performance status , n (%)</b>			
Grade 0	-	1006 (69.4)	196 (47.6)
Grade 1	-	437 (30.1)	209 (50.7)
Grade 2	-	7 (0.5)	7 (1.7)
<b>Karnofsky performance status , n (%)</b>			
70%	17 (2.5)	-	-
80%	197 (29.0)	-	-
90%	397 (58.5)	-	-
100%	68 (10.0)	-	-

Ref: Clinical Overview, Table 3, p.35.

### Cancer History

In NETU-07-07 and NETU-10-29 the most frequent cancer diagnoses were lung and respiratory tract whereas NETU-08-18 was almost entirely comprised of breast cancer patients. HEC trial PALO-10-01 was not conducted using the FDC. In PALO-10-01 most

patients received a cisplatin-based chemotherapy. Almost half of patients in NETU-07-07 and NETU-10-29 had metastatic disease at the time of entry into the study (47.6% and 49.8%) while over 80% of patients in NETU-08-18 had primary disease.

### **6.1.3 Subject Disposition**

Over 77% of cancer patients in the Phase 2/3 trials for this NDA completed their chemotherapy cycles. About 20% of patients completed a cycle but did not continue into the next planned cycle. The main reason for not continuing into a subsequent cycle was closing of the trial, which occurred when the protocol stipulated that the study would close when the last enrolled patients had completed their final chemotherapy cycle. For these patients the reason for discontinuation was given as “other”.

Table 59 shows discontinuations after randomization and during any cycle, and patients completing one cycle but not continuing into the next. Main reasons for discontinuation were multicycle screen failure, other, withdrawal by subject, and adverse events.

**Table 59 Disposition Subjects Phase 2/3 Cancer Patients (Safety Pop)**

	Netupitant-Palonosetron (mg)				Palonosetron Alone (mg)			Comparators			All Patients
	100/0.50 (N=135) n (%)	200/0.50 (N=138) n (%)	300/0.50 (N=1169) n (%)	Total (N=1442) n (%)	IV 0.25 (N=369) n (%)	Oral 0.50 (N=1231) n (%)	Total (N=1600) n (%)	Aprepitant plus:		Total (N=238) n (%)	
								PALO (N=104) n (%)	OND (N=134) n (%)		
Completed planned/unplanned chemotherapy cycles	134 (99.3)	137 (99.3)	770 (65.9)	1041 (72.2)	351 (95.1)	957 (77.7)	1308 (81.8)	55 (52.9)	133 (99.3)	188 (79.0)	2537 (77.3)
Completed planned/unplanned chemotherapy cycles but discontinued during additional unplanned cycle	-	-	2 (0.2)	2 (0.1)	-	-	-	-	-	-	2 (0.1)
Other	-	-	1 (0.1)	1 (0.1)	-	-	-	-	-	-	1 (0.0)
Completed a cycle but not continuing in the next planned cycle	-	-	365 (31.2)	365 (25.3)	-	244 (19.8)	244 (15.3)	43 (41.3)	-	43 (18.1)	652 (19.9)
Adverse event	-	-	27 (2.3)	27 (1.9)	-	15 (1.2)	15 (0.9)	8 (7.7)	-	8 (3.4)	50 (1.5)
Death	-	-	4 (0.3)	4 (0.3)	-	1 (0.1)	1 (0.1)	-	-	-	5 (0.2)
Protocol violation	-	-	7 (0.6)	7 (0.5)	-	-	-	1 (1.0)	-	1 (0.4)	8 (0.2)
Lost to follow-up	-	-	5 (0.4)	5 (0.3)	-	2 (0.2)	2 (0.1)	1 (1.0)	-	1 (0.4)	8 (0.2)
Withdrawal by subject	-	-	69 (5.9)	69 (4.8)	-	36 (2.9)	36 (2.3)	6 (5.8)	-	6 (2.5)	111 (3.4)
Lack of efficacy	-	-	1 (0.1)	1 (0.1)	-	3 (0.2)	3 (0.2)	-	-	-	4 (0.1)
Sponsor decision	-	-	1 (0.1)	1 (0.1)	-	-	-	-	-	-	1 (0.0)
Other	-	-	198 (16.9)	198 (13.7)	-	122 (9.9)	122 (7.6)	27 (26.0)	-	27 (11.3)	347 (10.6)
Multicycle screen failure	-	-	53 (4.5)	53 (3.7)	-	65 (5.3)	65 (4.1)	-	-	-	118 (3.6)

	Netupitant-Palonosetron (mg)				Palonosetron Alone (mg)			Comparators			All Patients
	100/0.50 (N=135) n (%)	200/0.50 (N=138) n (%)	300/0.50 (N=1169) n (%)	Total (N=1442) n (%)	IV 0.25 (N=369) n (%)	Oral 0.50 (N=1231) n (%)	Total (N=1600) n (%)	Aprepitant plus:		Total (N=238) n (%)	
								PALO (N=104) n (%)	OND (N=134) n (%)		
Discontinued after randomization and during any planned chemotherapy cycle	1 (0.7)	1 (0.7)	32 (2.7)	34 (2.4)	18 (4.9)	30 (2.4)	48 (3.0)	6 (5.8)	1 (0.7)	7 (2.9)	89 (2.7)
Adverse event	-	1 (0.7)	3 (0.3)	4 (0.3)	1 (0.3)	4 (0.3)	5 (0.3)	4 (3.8)	-	4 (1.7)	13 (0.4)
Death	1 (0.7)	-	8 (0.7)	9 (0.6)	11 (3.0)	7 (0.6)	18 (1.1)	-	-	-	27 (0.8)
Protocol violation	-	-	1 (0.1)	1 (0.1)	1 (0.3)	3 (0.2)	4 (0.3)	-	-	-	5 (0.2)
Lost to follow-up	-	-	-	-	3 (0.8)	4 (0.3)	7 (0.4)	-	1 (0.7)	1 (0.4)	8 (0.2)
Withdrawal by subject	-	-	11 (0.9)	11 (0.8)	2 (0.5)	9 (0.7)	11 (0.7)	2 (1.9)	-	2 (0.8)	24 (0.7)
Sponsor decision	-	-	-	-	-	1 (0.1)	1 (0.1)	-	-	-	1 (0.0)
Other	-	-	7 (0.6)	7 (0.5)	-	1 (0.1)	1 (0.1)	-	-	-	8 (0.2)
Multicycle screen failure	-	-	2 (0.2)	2 (0.1)	-	1 (0.1)	1 (0.1)	-	-	-	3 (0.1)

Summary Clinical Safety, Table 7. p.43.

### 6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for Phase 2/3 trials was complete response (CR), defined as no emetic episodes and no use of rescue medication. The endpoint of CR has been used for other anti-emetic drug approvals. An emetic episode is defined as one or more continuous vomits (expulsion of stomach contents through the mouth) or retches (an attempt to vomit that is not productive of stomach contents). Emetic episodes are considered distinct if separated by the absence of vomiting and retching for at least 1 minute. Rescue medication is defined as any medication taken to alleviate nausea or vomiting, and was permitted on an as-needed basis. The patient recorded the drug name, the dosage and the time of intake for each medication taken for the treatment of nausea and vomiting for the 0-120 hour interval (Day 1 to Day 5) at each cycle in the patient diary.

### **Primary Endpoint by Trial**

The primary endpoint for PALO-10-01 was the proportion of patients with complete response (CR) in the acute, 0-24 hour period post highly emetogenic cancer chemotherapy administration on day 1. The division agreed to this endpoint in a SPA letter dated 11/03/2010. The trial met the pre-specified non-inferiority margin of -15, thus making it possible to use the oral dosage form of palonosetron in the FDC for HEC as well as MEC. The lower bound of the 99% confidence interval was -2.74, well within the non-inferiority margin of -15.

Pivotal HEC study NETU-07-07 was originally conducted as a phase 2 trial in which CR overall (0-120 hours post chemo) was the primary endpoint. The design of the trial was found acceptable by the agency after consultation with the FDA Office of Medical Policy. In addition to being the pivotal HEC study, NETU-07-07 compared three doses of netupitant for use in the combination product. The statistical reviewer notes in her review that in order for NETU-07-07 to provide confirmatory evidence, efficacy should be based on CR in the delayed phase instead of CR in the overall phase, even though the analysis can only be post hoc.

Phase 3 MEC trial NETU-08-18 used the primary endpoint of CR in the delayed (25-120 hours) phase. The trial was designed to show the superiority of oral netupitant/palonosetron FDC to oral palonosetron in terms of the proportion of patients reporting CR in the time interval 25-120 hours from the start of MEC at cycle 1, and to reject the null hypothesis that there was no difference between treatment. The primary analysis was performed on the full analysis set (FAS) using a 2-sided stratum-adjusted CMH test including treatment, age class and region as strata. All missing data were imputed as treatment failures. Superiority of the FDC versus oral palonosetron alone was demonstrated if the 2-sided p-value from the CMH test was less than or equal to 0.050 and in the right direction i.e., the Odds Ratio (OR) was in favor of the fixed combination.

Table 60 shows results of the protocol specified primary and secondary endpoints for the three Phase 3 studies conducted in support of the Akynzeo application. NETU-10-29 was not designed for efficacy; it was set to explore safety during repeat chemotherapy cycles, and collected efficacy data as a secondary endpoint.

**Table 60 Primary and Secondary Endpoints**

Trial Number	Primary Endpoint	Main Secondary Endpoint (s)
NETU-07-07*	Complete Response: overall phase	Complete response: acute phase Complete response: delayed phase
NETU-08-18	Complete Response: delayed phase Cycle 1	Complete response: acute phase at Cycle 1** Complete response: overall phase at Cycle 1**
NETU-10-29	Safety	Complete response: acute, delayed and overall phases

\*Post-hoc analysis of CR in acute and delayed at FDA request

\*\*Key secondary endpoint

Ref: Summary clinical efficacy, table 3, p27

Table 61 presents primary and secondary endpoint results for the 3 trials in which Akynzeo was tested against active control. These results show that Akynzeo (+dexamethasone) provided better protection against chemotherapy induced nausea and vomiting than palonosetron (+ dexamethasone) alone.

**Table 61 Patients with CR cycle 1 all NETU/PALO trials**

	NETU-07-07 HEC				NETU-08-18 MEC		NETU-10-29 HEC/MEC	
	Palo alone (N=136)	Palo + Netu 100 mg (N=135)	Palo + Netu 200 mg (N=137)	Palo + Netu 300 mg (N=135)	Netu/Palo FDC (N=724)	Palo alone (N=725)	Netu/Palo FDC (N=309)	Aprep + Palo (N=103)
<b>Delayed phase (25-120 hours)</b>								
Number (%) of patients	109 (80.1)	122 (90.4)	125 (91.2)	122 (90.4)	557 (76.9)	504 (69.5)	257 (83.2)	80 (77.7)
Difference between groups (%), [95% CI]	-	10.2[1.9, 18.6]	11.1[2.9, 19.3]	10.2[1.9, 18.6]	7.4 [2.9, 11.9]		5.5 [-2.8; 15.2]	
CMH Odds ratio (95% CI)					1.48 (1.16, 1.87)		-	
p-value, logistic reg*	-	0.018	0.010	0.018	-		-	
p-value, CMH test**	-	0.017	0.008	0.016	0.001		-	
<b>Acute phase (0-24 hours)</b>								
Number (%) of patients	122 (89.7)	126 (93.3)	127 (92.7)	133 (98.5)	640 (88.4)	616 (85.0)	287 (92.9)	97 (94.2)
Difference between groups (%), [95% CI]	-	3.6 [-3.0, 10.2]	3.0 [-3.7, 9.7]	8.8 [3.3, 14.3]	3.4 [-0.1, 6.9]		-1.3 [-5.9; 5.4]	
CMH Odds ratio (95% CI)					1.37 (1.00, 1.87)		-	
p-value, logistic reg*	-	0.278	0.383	0.007			-	
p-value, CMH test**	-	0.278	0.383	0.002	0.047		-	
<b>Overall phase (0-120 hours)</b>								
Number (%) of patients	104 (76.5)	118 (87.4)	120 (87.6)	121 (89.6)	538 (74.3)	483 (66.6)	249 (80.6)	78 (75.7)
Difference between groups (%), [95% CI]	-	10.9 [1.9,20.0]	11.1[2.1,20.1]	13.2[4.4,21.9]	7.7[3.0,12.3]		4.9 [-3.8; 14.8]	
CMH Odds ratio (95% CI)					1.47 (1.17,1.85)		-	
p-value, logistic reg*	-	0.018	0.017	0.004			-	
p-value, CMH test**	-	0.018	0.016	0.003	0.001		-	

Ref: Summary Clinical Efficacy, Table 38, p.108.

### 6.1.5 Analysis of Secondary Endpoints(s)

NETU-08-18 had 2 key secondary endpoints, CR in the acute phase cycle 1, and CR in the overall phase cycle 1. In a SPA agreement letter to the sponsor dated 4-May-2010 the agency stated that non key secondary endpoints are supportive only, (b) (4)

**Table 62 Complete Response Acute Phase Cycle 1 NETU-08-18**

	NETU/PALO N=724	PALO N=725
Cycle 1 Acute Phase		
Responder (95% CI)	640 (88.4) [85.9;90.5]	616 (85.0) [82.2; 87.4]
Difference in response rate [95% CI]	3.4 [-0.1; 6.9]	

Ref: Table 14.2.2.1.1.1

**Table 63 Complete Response Overall Phase Cycle 1 NETU-08-18**

	NETU/PALO N=724	PALO N=725
Cycle 1 Overall		
Responder (95% CI)	538 (74.3) [71.0;77.4]	483 (66.6) [63.1; 70.0]
Difference in response rate [95% CI]	7.7 [3.0; 12.3]	

Ref: table 14.2.2.1.2.1

For NETU-07-07 protocol defined secondary endpoints were not designated as key secondary endpoints. The following were the protocol designed secondary endpoints assessed in the trial:

- Complete response for the 0-24 hours interval from the start of cisplatin administration (acute phase); and for the 25-120 hours interval (delayed phase)
- Complete protection (no emesis, no rescue therapy, no significant nausea (nausea <25 mm on VAS)); Total control (no emesis, no rescue therapy and no nausea (nausea <5 mm on VAS)); No nausea (VAS <5 mm); No significant nausea (VAS <25 mm); No rescue medication; No emesis. These endpoints were evaluated for the 0-120 hours interval (overall), the first 0-24 hours (acute phase) and 25-120 hours (delayed phase). In addition they were evaluated for each 24 hours interval and cumulative for the 0-120 hour intervals.
- Time to first emetic episode, time to first rescue medication, time to treatment failure (based on time to first emetic episode or time to first rescue medication, whichever is first)
- Severity of nausea measured by VAS for each 24-hour interval
- Patient global satisfaction with anti-emetic therapy by means of VAS for each 24-hour interval

**Table 64 Secondary Efficacy Results MFAS NETU-07-07**

	Palo alone (N=136)	Palo + Netu 100 mg (N=135)	Palo + Netu 200 mg (N=137)	Palo + Netu 300 mg (N=135)
<b>No Emesis</b>				
Overall	76.5	87.4*	87.6*	91.1*
Acute	89.7	93.3	92.7	98.5*
Delayed	80.1	90.4*	91.2*	91.9*
<b>No Rescue</b>				
Overall	95.6	97.8	100	98.5
Acute	97.8	99.3	100	100
Delayed	97.1	97.8	100	98.5
<b>No Nausea</b>				
Overall	50.7	54.8	62.0	61.5
Acute	75.0	72.6	77.4	80.0
Delayed	53.7	59.3	65.0	68.1*
<b>No Significant Nausea</b>				
Overall	79.4	80.0	86.1	89.6*
Acute	93.4	94.1	94.2	98.5*
Delayed	80.9	81.5	89.8*	90.4*
<b>Total Control</b>				
Overall	50.0	54.8	61.3	59.9
Acute	71.3	71.9	76.6	80.0
Delayed	52.2	59.3	65.0*	65.9*
<b>Complete Protection</b>				
Overall	69.9	76.3	80.3*	83.0*
Acute	87.5	89.6	88.3	97.0*
Delayed	73.5	80.0	87.6*	84.4*

\*p-value ≤0.05 compared with palo alone  
 Ref: Netu-07-07 CSR, Table 3, p.12

Palo+Netu 300 mg was superior to palonosetron alone for no emesis overall, acute and delayed, no significant nausea (maximum VAS <25mm) overall, acute and delayed, and complete protection overall, acute and delayed. For no nausea (VAS<5mm) and total control (no emesis, no rescue, and no nausea) only in the delayed phase was Palo+Netu 300 mg superior to palonosetron alone. As noted, there was no SPA submitted for NETU-07-07 since it was a Phase 2 trial, not planned initially as a pivotal efficacy trial.

*Medical Officer's Comments:*

*The endpoints of no nausea, no significant nausea, total control, and complete protection do not correspond with secondary endpoints used in more recent CINV trials*

(b) (4)

**6.1.6 Other Endpoints**

Not applicable.

**6.1.7 Subpopulations**

More details of subpopulation analyses are contained in the statistical review. All subgroup analyses were exploratory. Each trial had subgroup analyses based on stratification factor. NETU-07-07 also had subgroup analysis based on region/country.

*NETU-07-07 (HEC)*

Subgroups were analyzed for the primary efficacy analysis (CR 0-120 hrs) by gender, and region (Ukraine, Russia). Secondary analyses were repeated by gender for CR 0-24 hrs, CR 25-120 hrs. Among secondary efficacy endpoints, only CR 0-24 hrs and CR 25-120 hrs were analyzed by gender.

*NETU-08-18 (MEC)*

The primary (CR 25-120 hrs) and key secondary efficacy analyses (CR 0-24, CR 0-120 hrs) were repeated based on the stratification factors used in the trial i.e. age class (<55 years, ≥55 years) and region (US, Latin America including Mexico, Europe, Commonwealth of Independent States [i.e., former Soviet Republics] and Asia). The other efficacy analyses were repeated for the delayed, acute and overall phases by age class only.

*NETU-10-29 (MEC and HEC)*

Efficacy data were presented based on the stratification factors used in the trial, i.e. emetogenicity at randomization (MEC, HEC) and gender (female, male) for the complete response and no significant nausea endpoints. These were descriptive analyses performed for exploratory purposes only.

**6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations**

See review of NETU-07-07.

**6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects**

Efficacy was only measured only for cycle 1 of NETU-08-18, and NETU-10-29. However efficacy was explored for repeat cycles, and the results seen in cycle 1 were maintained for the duration of the extension phase of the trials. The adverse event profile did not change notably with increased exposure over multiple cycles.

**6.1.10 Additional Efficacy Issues/Analyses**

Efficacy issues discussed elsewhere in review.

## 7 Review of Safety

### **Safety Summary**

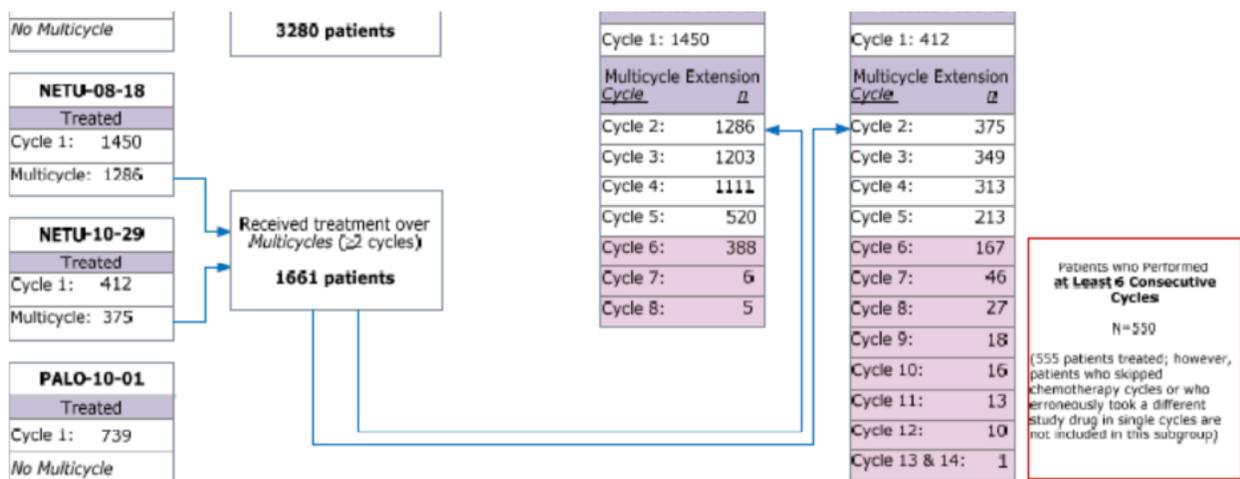
#### 7.1 Methods

##### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation focuses mainly on Phase 2/3 studies in cancer patients during their first cycle of cytotoxic chemotherapy. Two phase 3 studies provide additional data on the safety of Akynzeo over multiple cycles. Below is a display of the major trials, and the number of cycles for each. For each of the multicycle studies the number of patients falls considerably after cycle 6.

**Figure 2 Diagrams of Analyses and Populations Presented in Pooled Database**

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Ref: Summary clinical safety, Figure 2, p.23.

Table 65 lists the four primary studies from which safety data are obtained.

**Table 65 Studies in Akynzeo Pooled Safety Analysis**

Study (n <sup>a</sup> )	Population	Design/Blinding	Treatments and Doses	Control
NETU-07-07 (n = 679)	Patients with solid tumors, receiving single-cycle HEC	Phase 2, randomized, double-blind, parallel-group, active-controlled; dose-finding study	Netupitant (single doses of 100, 200, and 300 mg) + single dose of palonosetron 0.50 mg	Oral palonosetron 0.50 mg and Oral aprepitant (125 mg day 1; 80 mg days 2 and 3) + intravenous (IV) ondansetron (32 mg)
NETU-08-18 (n = 1450)	Patients with solid tumors, receiving single and multicycle MEC	Phase 3, randomized, double-blind, parallel-group active-controlled; Efficacy study (superiority) Single cycle and multicycle extension	Netupitant/Palonosetron FDC (300 mg/0.50 mg)	Oral palonosetron 0.50 mg
NETU-10-29 (n = 412)	Patients with tumors, receiving single and multicycle MEC and HEC	Phase 3, randomized, double-blind, parallel-group, unbalanced (3:1), active-controlled; Safety study Multiple cycles of chemotherapy	Netupitant/Palonosetron FDC (300 mg/0.50 mg)	Oral aprepitant (125 mg day 1; 80 mg days 2 and 3) + oral palonosetron (0.50 mg)
PALO-10-01 (n = 739)	Patients with solid tumors, receiving single-cycle HEC	Phase 3, randomized, double-blind, parallel-group, active-controlled; Efficacy noninferiority study	Single dose oral palonosetron (0.50 mg)	Single dose IV palonosetron (0.25 mg)

Ref: Summary of Clinical Safety, Table 1, p.14.

**Medical Officer's Comment:**

*Because PALO-10-01 did not use the combination of netupitant and palonosetron, it is not the primary focus of the safety assessment of Akynzeo. Ample postmarketing data are available for palonosetron since both the I.V. and oral formulation are approved for CINV.*

**7.1.2 Categorization of Adverse Events**

Adverse events were coded using the MedDRA central coding dictionary, version 14.0. The coding in each Phase 3 study matches the codes used in the Summary of Clinical Safety (SCS) and Integrated Summary of Safety (ISS). One study, NETU-07-07 was originally coded with MedDRA version 11.0, and re-coded with version 14.0.

**7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence**

For the integrated safety data (Phase 2/3 studies in cancer patients and Phase 3 multicycle studies) summary tables of TEAEs are presented for Phase 2/3 studies in patients with cancer, and Phase 3 multicycle studies. Because patients differed in terms of chemotherapy received and types of malignancy, and the same comparators were not used in all trials, pooling of data across studies was difficult.

**7.2 Adequacy of Safety Assessments**

**7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**

### Exposure

There were 28 studies conducted during the overall clinical development of Akynzeo. Twenty were conducted in healthy volunteers, 4 in cancer patients, and 4 in special populations. A total of 1939 subjects received any dose of netupitant in combination with palonosetron (i.e. as FDC or extemporaneous formulation), including 1442 patients in Phase 2/3 studies, 393 in healthy volunteers, and 104 subjects in special populations. A total of 1538 subjects/patients were exposed to the netupitant-palonosetron combination (300/0.50 mg) during the clinical program; of these, 1169 patients with cancer received at least one dose in one of the key Phase 2/3 trials; the remaining subjects were exposed to the proposed market combination dose during Phase 1 studies in healthy volunteers (N = 265) and studies in special populations (N = 104). Data on exposure are presented in Table 66.

Table 66 Subjects Exposed to Netupitant-Palonosetron

	Netupitant / Palonosetron Combination (mg) <sup>a</sup>				TOTAL (N=1939) n (%)
	100/0.50 (N=135) n (%)	> 100 - < 300 (N=199) n (%)	300/0.50 (N=1538) n (%)	> 300 (N=67) n (%)	
	Healthy Volunteer Studies		61 (30.7)	265 (17.2)	
Phase 2/3 Cancer Patients	135 (100.0)	138 (69.3)	1169 (76.0)		1442 (74.4)
Phase 3 Multicycle			1033 (67.2)		1033 (53.3)
Special Populations					
NETU-08-03					
NETU-09-11			28 (1.8)		28 (1.4)
NETU-10-09			40 (2.6)		40 (2.1)
NETU-10-10			36 (2.3)		36 (1.9)

Ref: Summary of Clinical Safety, Table 5, p.37.

Table 67 provides an overview of patients exposed to Palonosetron alone.

Table 67 Patients exposed to Palonosetron

	Palonosetron (mg)			TOTAL (N=1679)
	IV	Oral		
	0.25 (N=369)	0.50 (N=1271)	0.75 (N=29)	
	n (%)	n (%)	n (%)	n (%)
Healthy volunteer studies			29 (100.0)	29 (1.8)
Phase 2/3 Cancer Patients	369 (100.0)	1231 (96.9)		1600 (95.9)
Phase 3 Multicycle		725 (57.0)		725 (43.4)
Special populations				
NETU-08-03				
NETU-09-11				
NETU-10-09		40 (3.1)		40 (2.4)
NETU-10-10				

Ref: Summary Clinical Safety, Table 5, p.38.

In multicycle studies NETU-08-18 and NETU-10-29 a total of 1868 patients were randomized and 1862 were part of the safety population; 1033 in the FDC group, 725 in the palonosetron group, and 104 in the aprepitant+palonosetron group. Overall 62% of patients completed their chemotherapy cycles while 35% of patients completed their current cycle but did not continue into the next planned cycle. The numbers of patients were similar in the FDC and palonosetron groups with slightly fewer patients completing the chemotherapy cycle in the aprepitant+palonosetron groups (53%).

More patients received a MEC regimen than a HEC regimen based on initial classification of AC as MEC. However, as discussed earlier, the patients in NETU-08-18 who received a MEC AC regimen are now considered to have received a HEC regimen based on a 2011 ASCO reclassification.

Table 68 Patients Exposed to Study Treatment by Emetogenicity

Dose (mg)	Palonosetron		Netupitant / Palonosetron Combination			Comparators		TOTAL (N = 3280)
	IV N=369	Oral N=1231	100/0.50 N=135	200/0.50 N=138	300/0.50 N=1169	Aprepitant in combination with: Palonosetron N=104    Ondansetron N=134		
Phase 2/3 – cancer patients <sup>1</sup>								n (%)
HEC	369	506	135	138	211	25	134	1518 (46.3)
MEC	-	725	-	-	958	79	-	1762 (53.7)
Phase 3 multicycle <sup>2</sup>								
HEC	-	-	-	-	75	25	-	100 (5.4)
MEC	-	725	-	-	958	79	-	1762 (94.6)
< 6 consecutive cycles	-	534	-	-	716	62	-	1312 (70.5)
≥ 6 consecutive cycles	-	191	-	-	317	42	-	550 (29.5)

HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy

1 From Studies NETU-07-07, NETU-08-18, NETU-10-29, and PALO-10-01,

2 From Studies NETU-08-18 and NETU-10-29

Ref: SCS, Table 6, p.40.

**Medical Officer's Comment:**

*Exposure was more than adequate for a drug intended for short term use only. The safety population includes more than 300 patients receiving the FDC for cycle 6 and beyond.*

**Demographics**

Most of patients were female, white, and <65 years of age. This is partly due to the fact that NETU-08-18 was a study of breast cancer patients receiving AC chemotherapy. Table 69 provides demographic and baseline characteristics for the study drugs and control arms for phase 3 trials.

Table 69 Demographics Phase 3 Multicycle Studies (Safety pop)

	Netupitant- Palonosetron 300/0.50 mg (N=1033)	Palonosetron 0.50 mg (N=725)	Aprepitant plus Palonosetron (N=104)	TOTAL (N=1862)
<b>Age (years)</b>				
Mean (SD)	54.6 (10.668)	54.1 (10.646)	56.9 (11.704)	54.5 (10.731)
Median	55.0	54.0	58.5	55.0
Minimum, maximum	22.0, 79.0	28.0, 78.0	21.0, 80.0	21.0, 80.0
<b>Age stratification – n (%)</b>				
< 65 Years	839 (81.2)	602 (83.0)	78 (75.0)	1519 (81.6)
≥ 65 Years	194 (18.8)	123 (17.0)	26 (25.0)	343 (18.4)
< 75 Years	1014 (98.2)	708 (97.7)	99 (95.2)	1821 (97.8)
≥ 75 Years	19 (1.8)	17 (2.3)	5 (4.8)	41 (2.2)
<b>Gender – n (%)</b>				
Male	167 (16.2)	14 (1.9)	53 (51.0)	234 (12.6)
Female	866 (83.8)	711 (98.1)	51 (49.0)	1628 (87.4)
<b>Race – n (%)</b>				
White	832 (80.5)	579 (79.9)	87 (83.7)	1498 (80.5)
Black	4 (0.4)	3 (0.4)	–	7 (0.4)
Hispanic or Latino	47 (4.5)	37 (5.1)	–	84 (4.5)
Asian	148 (14.3)	103 (14.2)	17 (16.3)	268 (14.4)
Am. Indian / AK Nat	1 (0.1)	–	–	1 (0.1)
Nat HI / Pac Isl	–	1 (0.1)	–	1 (0.1)
Other	1 (0.1)	2 (0.3)	–	3 (0.2)
<b>Weight (kg)</b>				
Mean (SD)	71.0 (16.369)	71.8 (15.881)	67.5 (14.317)	71.1 (16.093)
Median	70.0	70.0	65.5	70.0
Minimum, maximum	34.0, 136.0	30.2, 169.0	40.0, 106.0	30.2, 169.0
<b>Height (cm)</b>				
Mean (SD)	162.3 (8.799)	160.7 (7.186)	165.6 (9.029)	161.9 (8.302)
Median	162.0	161.0	165.0	162.0
Minimum, maximum	120.7, 192.0	139.0, 186.0	148.0, 193.0	120.7, 193.0
<b>BMI (calculated as kg/m<sup>2</sup>)</b>				
Mean (SD)	26.9 (5.827)	27.8 (5.693)	24.6 (4.675)	27.1 (5.762)
Median	26.4	27.3	23.9	26.5
Minimum, maximum	14.1, 54.7	12.6, 57.5	15.4, 35.6	12.6, 57.5

Ref: Summary Clinical Safety, Table 10, p.49

## 7.2.2 Explorations for Dose Response

Of the key studies reviewed for the clinical safety and efficacy review only one, NETU-07-07, examined three doses of netupitant, in combination with palonosetron, as candidates for the to-be-marketed fixed dose combination. The primary objective of NETU-07-07 was to determine if any of the three proposed doses of netupitant combined with palonosetron was more effective than palonosetron given alone (all treatment arms received dexamethasone). Assessment was based on complete response rates from 0 to 120 hours. As with other antiemetics, the dose-response of Akynzeo is not closely linked to plasma concentrations. In the acute phase the 300mg Netu+Palo performed better than the lower doses of Netu+Palo in preventing vomiting and use of rescue medication, compared to palonosetron alone. In the other time frames analyzed (delayed and overall) all three netupitant + palonosetron doses performed better than palonosetron alone. NETU-07-07 did not compare different doses of netupitant with each other.

### 7.2.3 Special Animal and/or In Vitro Testing

Details of animal and/or In Vitro Testing can be found in the Pharmacology/Toxicology review of Dr. Ke Zhang.

### 7.2.4 Routine Clinical Testing

The variables measured for the four main studies in the safety database are shown in Table 70.

**Table 70 Overview of Safety Variables Measure**

Variable	NETU-07-07	NETU-08-18	NETU-10-29	PALO-10-01
Adverse events (TEAE)	X	X	X	X
Clinical laboratory values				
Hematology	X	X	X	X
Blood chemistry	X	X	X	X
Urinalysis	X	X	X	X
Cardiac troponin (cTnI)		X	X	
Physical exam	X	X	X	X
Vital signs	X	X	X	X
Left ventricular ejection fraction		X	X	
12-lead ECG	X	X	X	X

TEAE = Treatment emergent adverse events; cTnI = cardiac troponin; ECG = electrocardiogram  
 Ref: Summary of Clinical Safety, Table 2, p.16

*Medical Officer's Comment:*

*The measures of adverse events, laboratory parameters, vital signs, ECGs, and left ventricular ejection fraction are adequate to assess safety.*

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Netupitant is excreted primarily in the liver. Renal clearance is less than 5%. Four metabolites have been detected in human plasma at netupitant doses of 30 mg and higher (M1, M2, M3 and M4). M1, M2 and M3 are considered major metabolites. In a human ADME study, mean C<sub>max</sub> was approximately 11%, 47% and 16% of the parent for M1, M2 and M3, respectively. Extent of exposure (AUC) indicates that M2 has the lowest exposure relative to the parent (14%) whereas M1 and M3 are approximately 29% and 33% of the parent. M4 was a minor metabolite based on C<sub>max</sub> (< 7%), and AUC (3%) of the parent.

Netupitant is a CYP3A4 substrate and inhibitor. When a CYP3A4 inhibitor (ketoconazole) was administered with netupitant, an approximately 2-fold increase in netupitant exposure

was observed. Co-administration of a CYP3A4 inducer (rifampicin) resulted in a 5- to 6-fold reduction in netupitant exposure. An interaction study with netupitant and dexamethasone showed that at the 300 mg dose level, exposure of netupitant was increased 1.7- to 2.4-fold from Days 1 to 4. Therefore, when co-administered with netupitant and palonosetron in the clinical study, the dose of dexamethasone was reduced. Mean netupitant PK parameters obtained in each of the 3 chemotherapy groups (administered with docetaxel, etoposide or cyclophosphamide) after netupitant/palonosetron FDC co-administration were similar. The PK of palonosetron was not strongly affected by administration of CYP3A4 inducers, inhibitors or other substrates. Full details of metabolism, clearance, and drug interactions can be found in the Clinical Pharmacology review.

*Medical Officer's Comment:*

*The label will contain information on inhibition and induction of CYP3A4 by netupitant.*

### **7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class**

As noted previously, of the NK1 receptor antagonist class, there is only one approved drug, Emend®. In the 5-HT3 receptor antagonist class, in addition to palonosetron, there are granisetron, dolasetron and ondansetron.

The Emend label lists two contraindications:

- Hypersensitivity to any component of this medication
- EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride, since inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.

The Warning and Precautions for Emend state:

- Co-administration of aprepitant with warfarin (a CYP2C9 substrate) may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time.
- The efficacy of hormonal contraceptives during and for 28 days following the last dose of EMEND may be reduced. Alternative or back-up methods of contraception should be used
- EMEND is a dose-dependent inhibitor of CYP3A4, and should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4
- Caution should be exercised when administered in patients with severe hepatic impairment

As noted, Netupitant is also an inhibitor of CYP3A4 and the labeling will apprise prescribers of the potential of the drug to increase plasma concentrations of concomitantly administered oral medications metabolized by CYP3A4.

Most drugs of the 5-HT<sub>3</sub> RA class have the potential to affect the heart rate, PR interval, QRS interval duration and cardiac morphology. A thorough QT study (NETU-07-20) of Akynzeo did not demonstrate clinically important effects on these parameters. A prior tQT study of palonosetron (PALO-03-11) also did not demonstrate QT prolongation with palonosetron, even at supratherapeutic doses.

### 7.3 Major Safety Results

#### 7.3.1 Deaths

Out of a total of 3280 patients in Phase 2/3 studies in cancer patients, 39 patients (1.2%) died. Five deaths occurred post-study. Most deaths occurred during the first cycle of chemotherapy, and the proportion of deaths did not increase with increased number of chemotherapy cycles. For example in cycle 1 there were 7 (0.7%) deaths in the Netu/Palo FDC arm, compared to 3 (0.4%) in cycle 3. Two of the deaths that occurred in later cycles were in NETU-08-18, and the remaining deaths were from NETU-10-29.

**Table 71 Deaths in Multiple Cycle Safety Extension Trials by cycle**

NETU-08-18, NETU-10-29				
Cycle	Netu/Palo FDC N=1033	Palo N=720	Aprepitant/Palo N=104 (%)	Total
1	7 (0.7)	1 (0.1)		8 (0.4)
2	1 (0.1)			1 (0.1)
3	3 (0.4)	1 (0.2)		4 (0.3)
4	2 (0.3)			2 (0.1)
5	2 (0.5)			2 (0.3)
6	2 (0.3)		1 (2.3)	3 (0.4)

Ref: Reviewer's table.

Table 72 provides an overview of the TEAEs that lead to death. No particular organ system stands out, and when safety data from all Phase 2/3 trials are combined the number of deaths in the palonosetron/netupitant FDC and palonosetron alone are similar. There are fewer deaths in patients receiving aprepitant, but the numbers of patients in this group overall is lower than the other two.

**Table 72 TEAEs leading to death – Phase 2/3 cancer patients (all cycles)**

Preferred Term	Netupitant–Palonosetron (mg)				Palonosetron Alone (mg)			Comparators			All Patients (N=3280)
	100/0.50 (N=135)	200/0.50 (N=138)	300/0.50 (N=1169)	Total (N=1442)	IV 0.25 (N=369)	Oral 0.50 (N=1231)	Total (N=1600)	Aprepitant plus: PALO OND (N=104) (N=134)		Total (N=238)	
Patients with fatal TEAE –n (%)	1 (0.7)	-	16 (1.4)	17 (1.2)	12 (3.3)	9 (0.7)	21 (1.3)	1 (1.0)	-	1 (0.4)	39 (1.2)
Multi-organ failure	1 (0.7)	-	2 (0.2)	3 (0.2)	1 (0.3)	1 (0.1)	2 (0.1)	-	-	-	5 (0.2)
Death	-	-	-	-	4 (1.1)	-	4 (0.3)	-	-	-	4 (0.1)
Cardiac failure acute	-	-	-	-	2 (0.5)	1 (0.1)	3 (0.2)	-	-	-	3 (0.1)
Cardiopulmonary failure	-	-	2 (0.2)	2 (0.1)	1 (0.3)	-	1 (0.1)	-	-	-	3 (0.1)
Pneumonia	-	-	1 (0.1)	1 (0.1)	1 (0.3)	1 (0.1)	2 (0.1)	-	-	-	3 (0.1)
Renal failure	-	-	-	-	2 (0.5)	-	2 (0.1)	1 (1.0)	-	1 (0.4)	3 (0.1)
Tumor lysis syndrome	-	-	-	-	-	2 (0.2)	2 (0.1)	-	-	-	2 (0.1)
Neoplasm progression	-	-	2 (0.2)	2 (0.1)	-	-	-	-	-	-	2 (0.1)
Ischaemic stroke	-	-	1 (0.1)	1 (0.1)	-	1 (0.1)	1 (0.1)	-	-	-	2 (0.1)
Haemoptysis	-	-	1 (0.1)	1 (0.1)	-	1 (0.1)	1 (0.1)	-	-	-	2 (0.1)
Pulmonary embolism	-	-	2 (0.2)	2 (0.1)	-	-	-	-	-	-	2 (0.1)
Neutropenia	-	-	-	-	1 (0.3)	-	1 (0.1)	-	-	-	1 (0.0)
Pancytopenia	-	-	1 (0.1)	1 (0.1)	-	-	-	-	-	-	1 (0.0)
Thrombocytopenia	-	-	-	-	1 (0.3)	-	1 (0.1)	-	-	-	1 (0.0)
Cardiac arrest	-	-	1 (0.1)	1 (0.1)	-	-	-	-	-	-	1 (0.0)
Intestinal obstruction	-	-	-	-	1 (0.3)	-	1 (0.1)	-	-	-	1 (0.0)
Upper gastrointestinal haemorrhage	-	-	1 (0.1)	1 (0.1)	-	-	-	-	-	-	1 (0.0)
Asthenia	-	-	1 (0.1)	1 (0.1)	-	-	-	-	-	-	1 (0.0)
Lower respiratory tract infection	-	-	1 (0.1)	1 (0.1)	-	-	-	-	-	-	1 (0.0)

Preferred Term	Netupitant–Palonosetron (mg)				Palonosetron Alone (mg)			Comparators			All Patients (N=3280)
	100/0.50 (N=135)	200/0.50 (N=138)	300/0.50 (N=1169)	Total (N=1442)	IV 0.25 (N=369)	Oral 0.50 (N=1231)	Total (N=1600)	Aprepitant plus: PALO OND (N=104) (N=134)		Total (N=238)	
Acidosis	-	-	1 (0.1)	1 (0.1)	-	-	-	-	-	-	1 (0.0)
Electrolyte imbalance	-	-	1 (0.1)	1 (0.1)	-	-	-	-	-	-	1 (0.0)
Malnutrition	-	-	-	-	1 (0.3)	-	1 (0.1)	-	-	-	1 (0.0)
Breast cancer metastatic	-	-	-	-	-	1 (0.1)	1 (0.1)	-	-	-	1 (0.0)
Metastases to CNS	-	-	-	-	-	1 (0.1)	1 (0.1)	-	-	-	1 (0.0)
Neoplasm malignant	-	-	1 (0.1)	1 (0.1)	-	-	-	-	-	-	1 (0.0)
Cerebral infarction	-	-	-	-	1 (0.3)	-	1 (0.1)	-	-	-	1 (0.0)
Cerebrovascular accident	-	-	-	-	-	1 (0.1)	1 (0.1)	-	-	-	1 (0.0)
Convulsion	-	-	-	-	-	-	-	1 (1.0)	-	1 (0.4)	1 (0.0)
Acute respiratory failure	-	-	-	-	-	1 (0.1)	1 (0.1)	-	-	-	1 (0.0)
Dyspnoea	-	-	1 (0.1)	1 (0.1)	-	-	-	-	-	-	1 (0.0)
Pneumothorax	-	-	1 (0.1)	1 (0.1)	-	-	-	-	-	-	1 (0.0)
Shock hemorrhagic	-	-	-	-	-	1 (0.1)	1 (0.1)	-	-	-	1 (0.0)

Ref: Summary clinical safety, table 20, p.84.

Below are narratives for patients who died in the four major studies/trials that comprise this NDA.

**NETU-07-07**

- 128-1404 (PALO+100NETU) 55yo white male patient with a history of metastatic non-small cell lung cancer, treated with **cisplatin and paclitaxel**. Cause of death was multi-organ failure.

**NETU-08-18**

- 84106/01 (PALO 0.5mg) 49yo female with diagnosis of infiltrating lobular breast cancer. Experienced continuous vomiting a few hours after study drug and chemotherapy (**anthracycline/cytoxan**) administration. On the

following day had tachycardia, nausea and chest pain. ECG showed posterior and inferior wall ischemia and ST depression. Patient died of cardiac and respiratory failure in cycle 1.

- 83116/07 (PALO) 33 yo died in cycle 3 due to progression of breast cancer and lesions to bone and liver. Last dose of study drug was 2 April, and date of death (b) (6)

*Medical Officer's Comment:*

*Patient 84106/01 received only one dose of Palonosetron. The patient received anthracycline/cytosine chemotherapy. The cause of death may have been ischemia due to decreased perfusion (volume depletion due to vomiting), cardiotoxic chemotherapy, and severe stress leading to catecholamine surge and ischemia.*

**NETU-10-29**

- 3106/04 (PALO+NETU) 69yo male with primary lung and respiratory tract cancer. His chemotherapeutic agents were **gemcitabine and carboplatin**. He was hospitalized 24 days after the first dose of study drug due to neutropenia and frequent stools. Prior to hospitalization his white blood cell count was  $1.2 \times 10^9/L$ , with a neutrophil count of  $0.3 \times 10^9/L$  (normal  $1.6-7.4 \times 10^9$ ). Three days into hospitalization he developed hemoptysis and dyspnea and died on the same day. The event of neutropenia was assessed as related to chemotherapy, and hemoptysis and dyspnea due to disease progression.
- 3107/08, (PALO+NETU) 72-year-old male with metastatic lung and respiratory tract cancer for which he was treated with **carboplatin and etoposide**. Seven days after study drug during cycle 3 he developed severe respiratory tract infection and pancytopenia and was diagnosed with sepsis. While hospitalized he had mild respiratory distress, atrial fibrillation and metabolic acidosis. He was discharged with a feeding tube and died at home. Cause of death was attributed to cytotoxic chemotherapy, cancer, and comorbidities.
- 3107/09, (PALO+NETU) 35-year-old male with primary esophageal carcinoma treated with **carboplatin and paclitaxel**. During his third cycle of chemotherapy he had several episodes of hemoptysis and collapsed. During CPR he had copious amount of bleeding from the mouth.
- 4205/01, (PALO+NETU) 63-year-old female with lung and respiratory tract cancer receiving **etoposide, epirubicin, and cyclophosphamide**. The patient had undergone 4 courses of chemotherapy with carboplatin and a fifth with cisplatin. The sixth cycle was postponed because of increased fatigue, dyspnea and decreased blood pressure. The patient died during her sleep (28 days after the last administration of study drugs). Cause of death attributed to multi-organ failure due to cancer intoxication.
- 4205/08 (PALO+NETU) 69-year-old male patient with lung and respiratory tract cancer given **doxorubicin and cyclophosphamide**. Fifteen days after administration of study drugs the patient had worsening dyspnea and chest pain. No

corrective treatment was administered and the patient died on the same day. Cause of death attributed to cancer intoxication.

- 4205/36, (PALO+NETU) a 56-year-old female patient with primary lung and respiratory tract cancer treated with **carboplatin and etoposide**. Five days after administration of the first dose of study drugs the patient had weakness of the right hand and a speech disorder, diagnosed by CT as cerebrovascular accident. During hospitalization she had increased dyspnea, tachypnea and tachycardia. Despite treatment the patient died of cardio-pulmonary failure. Cause of death attributed to concomitant disease and lung cancer.
- 5102/03, (PALO+NETU) 62-year-old male patient with primary carcinoma of the tonsil treated with **cisplatin and 5-fluorouracil**. Had worsening of disease during cycle 4, and fifteen days after the administration of study drugs the patient died suddenly. Cause of death disease progression.
- 5105/05, (PALO+NETU) 50-year-old male patient with metastatic lung cancer treated with **carboplatin and gemcitabine** hydrochloride found to have progression of bone metastases. At 18 days after the first administration of study drugs the patient lost ability to speak and experienced right hemiparesis. CT scan showed ischemic stroke and the patient was discontinued from the study due to ischemic stroke. No explanation for stroke was given.
- 5303/04, (PALO+NETU) 57-year-old female patient with metastatic lung cancer treated with **cisplatin and etoposide**. Diagnosed with long QT syndrome caused by hypocalcemia ( $\text{Ca}^+$  1.54mmol/l). Recovered from this event. Several weeks later had worsening general pain. Progression of cancer was diagnosed and the patient died shortly thereafter.
- 5309/07, (PALO+NETU) 74-year-old male patient with metastatic lung and respiratory tract cancer treated with **carboplatin, bevacizumab and docetaxel**. Had pneumothorax in cycle 1, 20 days after the last administration of study drugs. The patient had extensive skin and mediastinal emphysema associated with fistulous tumor in the chest wall. A decision against surgical treatment was made.
- 5603/13, (PALO+NETU) 74-year-old female patient with metastatic ovarian cancer treated with **carboplatin and vinorelbine**. Hospitalized for weakness and electrolyte imbalance. During hospitalization had cardiac arrest from which, despite corrective treatment, resuscitation and mechanical ventilation, she died. Cause of death connected to chemotherapy and electrolyte imbalance.
- 5607/31, (PALO+NETU) 55-year-old female patient with primary lung and respiratory tract cancer treated with **vinorelbine and carboplatin**. Twenty days after the last administration of study drugs the patient was hospitalized to start the next cycle of chemotherapy. She experienced malaise, weakness, dyspnea at rest, and circulatory and respiratory failure. Chest X-ray revealed progression of lung cancer and acidosis. Despite treatment patient died on the same day, cause of death lung and respiratory tract carcinoma.

- 6001/03, (PALO+NETU) 66-year-old male with primary lung and respiratory tract cancer treated with **cisplatin and vinorelbine**. The patient developed pneumonia in cycle 2 (1 day after last administration of study drugs). Despite attempts at corrective treatment the patient died.
- 6001/04, (PALO+NETU) 55-year-old female patient with metastatic lung and respiratory tract cancer treated with **vinorelbine and cisplatin**. Six days after the last administration of study drugs computed tomography (CT) scan showed regression of lung carcinoma but the patient died suddenly at home. Cause of death was cited as probable pulmonary embolism in cycle 6 due to lung cancer.
- 6006/07, (PALO+NETU) 61-year-old male patient with metastatic lung and respiratory tract cancer given **gemcitabine and carboplatin**. Two days after the last administration of study drugs (cycle 3) the patient experienced a sudden onset of dyspnea and was hospitalized. An autopsy confirmed pulmonary embolism as the cause of the death.
- 6006/10, (PALO+NETU) 56-year-old female patient with metastatic endometrial cancer treated with **carboplatin and gemcitabine**. The patient completed the chemotherapy course but worsening of her health did not allow further chemotherapy administration and patient was discontinued from the study. On day 21 after the last administration of study drugs the patient was hospitalized due to anemia, hypokalemia and hypocalcaemia, and a diagnosis of endometrial cancer progression was made. The reason for discontinuation was adverse event which led to death.
- 5303/02 (aprepitant+palo) 64-year-old male with metastatic adenocarcinoma of lung and respiratory tract treated with **vinorelbine and cisplatin**. Patient developed renal insufficiency 3 days after the last administration of study drugs in cycle 6. Also had brain metastases and developed severe convulsions. Renal dysfunction was attributed to cisplatin exposure and neurological manifestations due to brain metastases.

#### **PALO-10-01**

There were 7 deaths in patients receiving oral palonosetron and 12 in patients receiving IV palonosetron.

- 2104/02 (Palo IV) 65 yr. old male with lung cancer. Two days after study drug and chemotherapy he developed vomiting, inability to drink liquids, and progressive renal and hepatic function. The patient continued to deteriorate and died of multi-organ failure and sepsis.
- 4101/26 (Palo IV) 59yo male with lung cancer with metastases to skin and soft tissue. Twenty days after study drug the patient developed acute heart failure and death.
- 4101/27 (Palo IV) 59yo male with lung cancer died 7 days after administration of study drug and cisplatin and etoposide, due to acute heart failure. Assessed as related to chemotherapy agents.

- 5302/24 (Palo IV) 53 yo male with metastatic small cell lung cancer. One day after study drug and chemotherapy with **cisplatin and etoposide** the patient had acute renal failure and died a few days later from multiple organ failure.
- 5403/05 (IV Palo) 73yo with metastatic carcinoma of the head and neck. Chemotherapeutic agents were **cisplatin, docetaxel and 5-fluorouracil**. Twelve days later the patient died in another hospital. No information on cause of death was available and it was attributed to underlying malignancy.
- 5403/06 (PALO IV) 50 yo male with metastatic carcinoma of head and neck. Seven days after study drug administration the patient died at home. Cause of death was attributed to underlying malignancy.
- 5406/18 (Palo IV) 56 yo male with head and neck cancer. Patient was unable to eat and drink due to pain with swallowing. This lead to weight loss, weakness and cachexia. Sixteen days after study drug the patient developed pneumonia from which he did not recover.
- 5502/02 (Palo IV) 68 yo male with lung cancer. Patient had a stroke 4 days after administration of cisplatin and study drug. Patient died at home a few days later.
- 5602/21 (Palo IV) 61 yo female with metastatic lung cancer. Patient had pericardial fluid and tumor mass involving the left ventricle. Twelve days after administration of study drug she had loss of consciousness and died suddenly.
- 5602/31 (Palo IV) 61 yo male with metastatic non-small cell lung cancer. Developed bowel obstruction and renal insufficiency.
- 5605/09 (Palo IV) 60yo male with non-small cell lung cancer. Developed hemoptysis but was stabilized to be discharged to home. Died at home 8 days after discharge.
- 5607/11 (Palo IV) 57 yo male with lung cancer. Developed neutropenia and thrombocytopenia, hypotension and weakness. Cause of death attributed to above.
- 4101/35 (oral Palo) 65yo male with small cell lung cancer, treated with cisplatin and etoposide. Four days after study drug administration had an ischemic stroke. Sent home for palliative care.
- 4105/04 (oral Palo) 65yo with head and neck cancer, treated with **cisplatin and 5-FU**. Post-chemotherapy the patient experienced multiple problems, including renal failure and electrolyte abnormalities, and oral bleeding. The patient declined further medical care and died at home.
- 4104/07 (oral Palo) 60yo male with squamous cell cancer of head and neck, treated with **cisplatin and 5-FU**. Post-chemotherapy patient had multi-organ failure and electrolyte abnormalities. Cause of death given as tumor lysis syndrome.
- 5106/03 (oral Palo) 50 yo with squamous cell cancer of lung and respiratory tract. Patient experienced hemoptysis, pneumonia, and died of hemorrhagic shock.
- 5406/14 (oral Palo) 65yo with head and neck cancer. Patient died of cerebrovascular accident.

- 5602/04 (oral Palo) 52yo with non-small cell lung cancer in mediastinum. Eleven days after study drug the patient was hospitalized for reduced level of consciousness and overall deterioration. Brain metastases were thought to be cause of death.
- 5608/16 (oral Palo) 64yo with metastatic lung cancer. On study day 1 the patient had loss of consciousness and multi-organ failure.

Most deaths occurred in PALO-10-01 and NETU-10-29. In PALO-10-01 deaths were fairly well balanced between the oral and I.V. forms of palonosetron. These deaths are not unexpected in a severely ill group of cancer patients receiving cancer chemotherapy of a highly emetogenic potential.

In NETU-10-29 there were 16 deaths in the Akynzeo arm compared to 1 death in the aprepitant/palonosetron arm. None of the deaths appear to be drug related, as evidenced from the patient narratives. The sponsor posits several factors to explain the difference between the two treatment arms. Randomization was 3:1, so that 2/3 of all patients received the FDC, compared to 1/3 who received aprepitant/palonosetron. A comparison of demographic characteristics for gender and age did not reveal significant differences. However, there was a small difference in cancer diagnoses. There were a greater number of lung and respiratory tract cancers in the FDC (39.6%) compared to Aprepitant+Palo (30.8). Conversely there were more ovarian and colon cancers seen with Aprepitant+Palo than NETU/PALO. There were also more primary and less metastatic cancers in the Aprepitant+Palo group than in the NETU/PALO group. Most deaths occurred in early cycles of chemotherapy usually many days after administration of study drug, suggesting there was no cumulative risk from Akynzeo. Seven of the deaths occurred in cycle 1, one in cycle 2, 3 in cycle 3, and 2 in cycles 4, 5, and 6 each.

At FDA request the sponsor provided additional analysis of SAEs and TEAEs of interest in patients receiving docetaxel, etoposide, cyclophosphamide and ifosfamide. As noted earlier in this review netupitant is a mild inhibitor of CYP3A4, and increased systemic exposure was seen when netupitant was given to patients also receiving CYP3A4 substrates docetaxel, etoposide and cyclophosphamide. Of the 2129 patients who received docetaxel, etoposide, cyclophosphamide and ifosfamide 104 (4.9%) experienced at least one SAE (including death).

The percentage of patients experiencing at least one SAE was 3.8% (67/1765) in the subpopulation of patients administered cyclophosphamide, 8.0% (25/311) in the subpopulation of patients administered etoposide and 18.9% (20/106) in the subpopulation of patients administered docetaxel. No SAE occurred in the very small subpopulation of patients administered with ifosfamide. Overall 16 patients (0.8%) died: 4 (0.2%) patients received cyclophosphamide, 8 (2.6%) patients received etoposide, and 5 (4.7%) patients received docetaxel. No death occurred in the ifosfamide

subpopulation. One patient in the FDC group received both cyclophosphamide and etoposide and is counted in both subpopulations.

The following three sponsor-provided tables offer details on SAEs and TEAEs by chemotherapy agent of interest.

**Table 73 SAEs and TEAEs Cyclophosphamide subpopulation**

	Palo IV 0.25 mg N=30 C=30	Palo OS 0.50 mg N=790 C=3051	FDC N=806 C=3178	Apre plus Palo N=14 C=75
Number (%) of pts with at least one SAE	1 (3.3)	26 (3.3)	39 (4.8)	1 (7.1)
Number (%) of pts with any TEAE of interest	-	16 (2.0)	32 (4.0)	1 (7.1)
Anaemia	-	3 (0.4)	12 (1.5)	1 (7.1)
Leukopenia	-	7 (0.9)	17 (2.1)	1 (7.1)
Neutropenia	-	9 (1.1)	19 (2.4)	1 (7.1)
Thrombocytopenia	-	1 (0.1)	8 (1.0)	-
Serious Diarrhoea	-	-	-	-
Infections	-	11 (1.4)	24 (3.0)	-

N = number of patients

C=number of cycles

The percentage is calculated based on N

**Table 74 SAEs and TEAEs Etoposide subpopulation**

	Palo IV 0.25 N=45 C=45	Palo OS 0.50 N=85 C=88	FDC N=89 C=300	Apre plus Palo N=12 C=53
Number (%) of pts with at least one SAE	6 (13.3)	8 (9.4)	8 (9.0)	3 (25.0)
Number (%) of pts with any TEAE of interest	6 (13.3)	4 (4.7)	7 (7.9)	2 (16.7)
Anaemia	2 (4.4)	1 (1.2)	5 (5.6)	2 (16.7)
Leukopenia	2 (4.4)	1 (1.2)	4 (4.5)	2 (16.7)
Neutropenia	4 (8.9)	1 (1.2)	3 (3.4)	2 (16.7)
Thrombocytopenia	1 (2.2)	-	-	-
Serious Diarrhoea	-	-	-	-
Infections	-	3 (3.5)	2 (2.2)	-

N = number of patients

C=number of cycles

The percentage is calculated based on N

**Table 75 SAEs and TEAEs Docetaxel subpopulation**

	Palo IV 0.25 N=13 C=13	Palo OS 0.50 N=37 C=77	FDC N=49 C=196	Apre plus Palo N=5 C=21
Number (%) of pts with at least one SAE	4 (30.8)	5 (13.5)	10 (20.4)	1 (20.0)
Number (%) of pts with any TEAE of interest	2 (15.4)	3 (8.1)	10 (20.4)	-
Anaemia	-	-	5 (10.2)	-
Leukopenia	-	1 (2.7)	7 (14.3)	-
Neutropenia	1 (7.7)	2 (5.4)	6 (12.2)	-
Thrombocytopenia	1 (7.7)	1 (2.7)	4 (8.2)	-
Serious Diarrhoea	-	-	1 (2.0)	-
Infections	1 (7.7)	1 (2.7)	9 (18.4)	-

N = number of patients

C=number of cycles

The percentage is calculated based on N

The sponsor points that that “the frequency of patients with at least one SAE and of patients with any TEAE of interest in the docetaxel subpopulation across treatment groups is higher compared to the subpopulation of patients who received other chemotherapeutic agents. The sponsor concludes that this is probably related to docetaxel specific toxicity (myelosuppression) and patients’ demographics, cancer diagnosis and stage and concomitant chemotherapeutic agents. The toxicity of this agent should be taken into consideration when evaluating the safety of patients exposed to repeat cycles. Therefore, the higher frequency of TEAEs of interest observed in the FDC group might be explained by the higher number of cycles.” The sponsor’s overall conclusion is that there is no evidence of an increased frequency in SAEs (including death) and TEAEs of interest in the FDC group compared to other treatment groups.

*Medical Officer’s Comment:*

*The medical reviewer agrees with the sponsor’s conclusions. The additional information concerning chemotherapeutic agent does not change the overall safety profile of the drug.*

**7.3.2 Nonfatal Serious Adverse Events**

The most common nonfatal serious adverse events were neutropenia, febrile neutropenia and leukopenia. The next most common SAEs were in the gastrointestinal category, and these included nausea, vomiting, diarrhea, constipation, and abdominal pain. An assessment of SAEs related to the cardiovascular system shows one case of cardiomyopathy, one case of heart failure in the netupitant/palonosetron arm, and one case of myocardial ischemia in the aprepitant arm.

The following Table 76 shows serious TEAEs during cycle 1 occurring in more than one patient.

Table 76 Serious TEAE occurring >1 patient cycle 1

Preferred Term	Netupitant-Palonosetron (mg)				Palonosetron Alone (mg)			Comparators			All Patients (N=3280) n (%)
	100/0.50 (N=135) n (%)	200/0.50 (N=138) n (%)	300/0.50 (N=1169) n (%)	Total (N=1442) n (%)	IV 0.25 (N=369) n (%)	Oral 0.50 (N=1231) n (%)	Total (N=1600) n (%)	Aprepitant plus:		Total (N=238) n (%)	
								PALO (N=104) n (%)	OND (N=134) n (%)		
Patients with any serious TEAE	1 (0.7)	1 (0.7)	31 (2.7)	33 (2.3)	36 (9.8)	51 (4.1)	87 (5.4)	4 (3.8)	-	4 (1.7)	124 (3.8)
Neutropenia	-	-	3 (0.3)	3 (0.2)	9 (2.4)	6 (0.5)	15 (0.9)	-	-	-	18 (0.5)
Febrile neutropenia	-	-	5 (0.4)	5 (0.3)	4 (1.1)	6 (0.5)	10 (0.6)	-	-	-	15 (0.5)
Anaemia	-	-	1 (0.1)	1 (0.1)	6 (1.6)	1 (0.1)	7 (0.4)	-	-	-	8 (0.2)
Thrombocytopenia	-	-	-	-	5 (1.4)	2 (0.2)	7 (0.4)	-	-	-	7 (0.2)
Vomiting	-	-	2 (0.2)	2 (0.1)	2 (0.5)	3 (0.2)	5 (0.3)	-	-	-	7 (0.2)
Nausea	-	-	1 (0.1)	1 (0.1)	1 (0.3)	4 (0.3)	5 (0.3)	-	-	-	6 (0.2)
Pneumonia	-	-	1 (0.1)	1 (0.1)	1 (0.3)	4 (0.3)	5 (0.3)	-	-	-	6 (0.2)
Haemoptysis	-	-	2 (0.2)	2 (0.1)	2 (0.5)	2 (0.2)	4 (0.3)	-	-	-	6 (0.2)
Asthenia	-	-	1 (0.1)	1 (0.1)	1 (0.3)	3 (0.2)	4 (0.3)	-	-	-	5 (0.2)
Leukopenia	-	-	2 (0.2)	2 (0.1)	1 (0.3)	1 (0.1)	2 (0.1)	-	-	-	4 (0.1)
Diarrhoea	-	-	1 (0.1)	1 (0.1)	-	3 (0.2)	3 (0.2)	-	-	-	4 (0.1)
Death	-	-	-	-	4 (1.1)	-	4 (0.3)	-	-	-	4 (0.1)
Multi-organ failure	1 (0.7)	-	1 (0.1)	2 (0.1)	1 (0.3)	1 (0.1)	2 (0.1)	-	-	-	4 (0.1)
Cardiac failure acute	-	-	-	-	2 (0.5)	1 (0.1)	3 (0.2)	-	-	-	3 (0.1)
Cardiopulmonary failure	-	-	2 (0.2)	2 (0.1)	1 (0.3)	-	1 (0.1)	-	-	-	3 (0.1)
Stomatitis	-	-	2 (0.2)	2 (0.1)	1 (0.3)	-	1 (0.1)	-	-	-	3 (0.1)
Urinary tract infection	-	-	3 (0.3)	3 (0.2)	-	-	-	-	-	-	3 (0.1)
Ischaemic stroke	-	-	1 (0.1)	1 (0.1)	-	2 (0.2)	2 (0.1)	-	-	-	3 (0.1)

Preferred Term	Netupitant-Palonosetron (mg)				Palonosetron Alone (mg)			Comparators			All Patients (N=3280) n (%)
	100/0.50 (N=135) n (%)	200/0.50 (N=138) n (%)	300/0.50 (N=1169) n (%)	Total (N=1442) n (%)	IV 0.25 (N=369) n (%)	Oral 0.50 (N=1231) n (%)	Total (N=1600) n (%)	Aprepitant plus:		Total (N=238) n (%)	
								PALO (N=104) n (%)	OND (N=134) n (%)		
Loss of consciousness	-	1 (0.7)	-	1 (0.1)	-	2 (0.2)	2 (0.1)	-	-	-	3 (0.1)
Renal failure	-	-	-	-	2 (0.5)	-	2 (0.1)	1 (1.0)	-	1 (0.4)	3 (0.1)
Dyspnoea	-	-	1 (0.1)	1 (0.1)	1 (0.3)	1 (0.1)	2 (0.1)	-	-	-	3 (0.1)
Deep vein thrombosis	-	-	1 (0.1)	1 (0.1)	-	1 (0.1)	1 (0.1)	1 (1.0)	-	1 (0.4)	3 (0.1)
Atrial fibrillation	-	-	-	-	-	2 (0.2)	2 (0.1)	-	-	-	2 (0.1)
Femur fracture	-	-	2 (0.2)	2 (0.1)	-	-	-	-	-	-	2 (0.1)
Hypokalemia	-	-	1 (0.1)	1 (0.1)	-	1 (0.1)	1 (0.1)	-	-	-	2 (0.1)
Tumor lysis syndrome	-	-	-	-	-	2 (0.2)	2 (0.1)	-	-	-	2 (0.1)
Cancer pain	-	-	-	-	1 (0.3)	1 (0.1)	2 (0.1)	-	-	-	2 (0.1)
Neoplasm malignant	-	-	1 (0.1)	1 (0.1)	-	-	-	1 (1.0)	-	1 (0.4)	2 (0.1)
Renal impairment	-	-	-	-	2 (0.5)	-	2 (0.1)	-	-	-	2 (0.1)
Pulmonary embolism	-	-	-	-	-	1 (0.1)	1 (0.1)	1 (1.0)	-	1 (0.4)	2 (0.1)
Thrombosis	-	-	-	-	-	2 (0.2)	2 (0.1)	-	-	-	2 (0.1)

Ref: Summary Clinical Safety, Table 21, p.86.

Four patients (cycle 1) had serious TEAEs related to investigational product: 2 patients in the netupitant-palonosetron groups (*loss of consciousness* and *acute psychosis*) and 2 in the oral palonosetron group (*abdominal pain* and *constipation* in 1 patient, and *diarrhea* and *asthenia* in 1 patient). These patients are described below.

**Patient NETU-10-29/5307/07 (netupitant/palonosetron FDC): *acute psychosis***; 42-year-old female with primary ovarian adenocarcinoma. Scheduled chemotherapy course (cycle 1) with **carboplatin and paclitaxel**. Approximately 4 days after her initial dose of

the investigational product, the patient developed acute and severe psychosis requiring hospitalization. She was treated with haloperidol and olanzapine. The patient's mental condition worsened and she was discontinued from the study. The serious TEAE of acute psychosis was assessed as possibly related to the study drug, and probably related to dexamethasone.

**Patient NETU-07-07/208-1103 (netupitant 200 mg plus palonosetron 0.50 mg): *loss of consciousness*** 63-year-old male with squamous cell carcinoma of lung diagnosed 14 days prior to enrollment. Medical history of myocardial fibrosis, myocardial ischemia, and gastric ulcer. Approximately 1 hour after dosing with netupitant 200 mg (cycle 1), the patient lost consciousness, recovering approximately 30 minutes later. The investigator described this serious TEAE as being of moderate intensity, possibly related to netupitant, and not related to dexamethasone. The patient was withdrawn from the study before receiving chemotherapy

**Patient PALO-10-01/3104/08 (Palonosetron 0.50 mg PO): *[1] diarrhea and [2] asthenia***; 54-year-old male with lung and respiratory tract carcinoma with brain metastases. Scheduled chemotherapy course (cycle 1) with cisplatin and paclitaxel. Five days after administration of the investigational product, the patient experienced diarrhea and generalized weakness resulting in hospitalization. Treatment included metronidazole, IV fluids, loperamide, and levofloxacin. These serious TEAEs, both of which resolved 3 days after onset, did not require interruption of the investigational product or withdrawal from the study. In the opinion of the investigator, the serious TEAEs of diarrhea and asthenia were related to the investigational product and to dexamethasone.

**Patient PALO-10-01/5304/05 (Palonosetron 0.50 mg PO): *[1] abdominal pain and [2] constipation***; 63-year-old male with metastatic lung carcinoma. Scheduled chemotherapy course (cycle 1) with cisplatin and etoposide. On the day after administration of the investigational product, the patient developed constipation; 2 days later, he experienced severe abdominal pain and was hospitalized. The serious TEAEs of abdominal pain and constipation resolved 1 and 3 days after onset. The investigator described both serious TEAEs as being of severe intensity, probably related to investigational product, and not related to dexamethasone.

In addition to the 4 patients in cycle 1 with non-fatal but serious treatment-related TEAEs, 1 patient in the netupitant-palonosetron group had a serious TEAE before her 6th cycle of chemotherapy. The patient (patient 9310703) was a 60-year-old female with nasopharyngeal carcinoma treated with **carboplatin, cisplatin, and fluorouracil**. On the day that she received study drug prior to chemotherapy with cisplatin, a post-dose ECG recorded a rhythm abnormality with ventricular bigeminy, and the patient, though asymptomatic, was admitted to the hospital for observation. Premature ventricular complex had been observed at the screening visit (pretreatment); but this finding did not

preclude treatment. The same abnormality was again detected prior to each subsequent cycle up to cycle 6, which was the last course of planned chemotherapy. Further clinical investigation revealed an LVEF of 44% that subsequently increased to 55%, aortic valve sclerosis, and Grade 1 diastolic dysfunction. The SAE of ventricular extra-systoles was considered probably related to the study drug.

Most SAEs occurred during cycle 1. As with deaths, repeated treatments with Akynzeo across chemotherapy cycles did not seem to increase the frequency of SAEs. The most common SAEs across all cycles were febrile neutropenia (1.2%), neutropenia (0.7%), vomiting (0.4%), anemia (0.4%), and leukopenia (0.3%). In the netupitant-palonosetron and palonosetron groups, febrile neutropenia was the most frequently reported SAE (1.5% [16/1033] and 0.8% [6/725], respectively), while anemia was the most frequently reported SAE among patients in the aprepitant+palonosetron group (2.9%; 3/104).

*Medical Officer's Comment:*

*Overall, there was a low incidence of non-fatal SAEs reported across treatment groups. The most commonly reported SAEs were hematologic, and expected with cytotoxic chemotherapy.*

### **7.3.3 Dropouts and/or Discontinuations**

Taking into account all patients who received at least one dose of netupitant/palonosetron, or one of its components, 834 of 4331 (19.3%) discontinued from the study. The main reasons for discontinuation were "other" (8.8%), withdrawal by subject (3.8%), and AE (1.8%). The "other" reason was given when patients discontinued the study due to trial closure (i.e. they completed their ongoing cycle but did not enter the following cycle). The Phase 3 protocols were designed to close when the last patient enrolled had completed her/his final chemotherapy cycle. As seen in Table 77 30% of patients completed a cycle but did not continue to the next cycle.

**Table 77 Disposition Subjects Phase 2/3 Cancer Patients**

	Netupitant-Palonosetron (mg)			Total (N=1442) n (%)
	100/0.50 (N=135) n (%)	200/0.50 (N=138) n (%)	300/0.50 (N=1169) n (%)	
Completed planned/unplanned chemotherapy cycles	134 (99.3)	137 (99.3)	770 (65.9)	1041 (72.2)
Completed planned/unplanned chemotherapy cycles but discontinued during additional unplanned cycle	-	-	2 (0.2)	2 (0.1)
Other	-	-	1 (0.1)	1 (0.1)
Completed a cycle but not continuing in the next planned cycle	-	-	365 (31.2)	365 (25.3)
Adverse event	-	-	27 (2.3)	27 (1.9)
Death	-	-	4 (0.3)	4 (0.3)
Protocol violation	-	-	7 (0.6)	7 (0.5)
Lost to follow-up	-	-	5 (0.4)	5 (0.3)
Withdrawal by subject	-	-	69 (5.9)	69 (4.8)
Lack of efficacy	-	-	1 (0.1)	1 (0.1)
Sponsor decision	-	-	1 (0.1)	1 (0.1)
Other	-	-	198 (16.9)	198 (13.7)
Multicycle screen failure	-	-	53 (4.5)	53 (3.7)

Ref: Summary Clinical Safety, Table 7, p.43.

The main adverse event leading to discontinuation in patients receiving Akynzeo during cycle 1 was neutropenia. For patients receiving Palonosetron the main reason was nausea. Most AEs leading to discontinuation were experienced in only 1-2 subjects.

**Table 78 Most Frequent TEAE leading to withdrawal (all cycles)**

Preferred Term	NETU/PALO	PALO	Comparator	TOTAL
	300/0.50 mg (N=1033) n (%)	0.50 mg (N=725) n (%)	Aprepitant + PALO (N=104) n (%)	(N=1862) n (%)
Number of patients with TEAEs leading to discontinuation	43 (4.2)	18 (2.5)	13 (12.5)	74 (4.0)
Neutropenia	5 (0.5)	2 (0.3)	1 (1.0)	8 (0.4)
Neoplasm progression	5 (0.5)	1 (0.1)	-	6 (0.3)
Neoplasm malignant	4 (0.4)	-	2 (1.9)	6 (0.3)
Febrile neutropenia	2 (0.2)	-	1 (1.0)	3 (0.2)
Leukopenia	2 (0.2)	1 (0.1)	-	3 (0.2)
Thrombocytopenia	1 (0.1)	-	2 (1.9)	3 (0.2)
Peritonitis	1 (0.1)	-	2 (1.9)	3 (0.2)
Troponin increased	1 (0.1)	2 (0.3)	-	3 (0.2)
Nausea	-	3 (0.4)	-	3 (0.2)
Stomatitis	2 (0.2)	-	-	2 (0.1)
Alanine aminotransferase increased	2 (0.2)	-	-	2 (0.1)
Platelet count decreased	2 (0.2)	-	-	2 (0.1)
Angina pectoris	1 (0.1)	1 (0.1)	-	2 (0.1)
Myocardial ischaemia	1 (0.1)	-	1 (1.0)	2 (0.1)
Creatinine renal clearance decreased	1 (0.1)	-	1 (1.0)	2 (0.1)
Ileus	-	-	2 (1.9)	2 (0.1)
Blood creatinine increased	-	-	2 (1.9)	2 (0.1)

NETU = netupitant; PALO = palonosetron; TEAE = treatment-emergent adverse event

Source: Modified from Module 5.3.5.3, ISS Table 2.10.3

Ref: Summary Clinical Safety, Table 25, p.100

**Medical Officer's Comment:**

*Failure to continue to a subsequent cycle would not be surprising in this patient population. The largest number comes from the "other" category, described above.*

**7.3.4 Significant Adverse Events**

See section 7.3.3

**7.3.5 Submission Specific Primary Safety Concerns**

Adverse events of special interest were divided into two categories; cardiac and CNS and psychiatric. Standardized MedRA queries (SMQs) were developed to identify TEAEs in these areas.

SMQs relating to cardiac events included: cardiac arrhythmias, cardiac failure, cardiomyopathy, embolic and thrombotic events, ischemic heart disease, and Torsade de Pointes-QT prolongation. In addition, the MedDRA preferred terms blood pressure

increased, hypotension, hypertension, and pre-syncope have been considered. Table 79 shows serious cardiac TEAE of special interest.

**Table 79 Serious Cardiac TEAE of Special Interest - all cycles**

	Netupitant-Palonosetron (mg)				Palonosetron (mg)			Comparators			All Patients (N=3280)
	100/0.50 (N=135)	200/0.50 (N=138)	300/0.50 (N=1169)	Total (N=1442)	IV 0.25 (N=369)	Oral 0.50 (N=1231)	Total (N=1600)	Aprepitant plus:		Total (N=238)	
								Palonosetron (N=104)	Ondansetron (N=134)		
Number of patients with any cardiac TEAE of special interest	0	1 (0.7)	13 (1.1)	14 (1.0)	8 (2.2)	20 (1.6)	28 (1.8)	3 (2.9)	0	3 (1.3)	45 (1.4)
Cardiac disorders	0	0	7 (0.6)	7 (0.5)	5 (1.4)	6 (0.5)	11 (0.7)	1 (1.0)	0	1 (0.4)	19 (0.6)
Acute myocardial infarction	0	0	0	0	1 (0.3)	0	1 (0.1)	0	0	0	1 (0.0)
Angina unstable	0	0	0	0	1 (0.3)	0	1 (0.1)	0	0	0	1 (0.0)
Arteriosclerosis coronary artery	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	1 (0.0)
Arteriospasm coronary	0	0	0	0	1 (0.3)	0	1 (0.1)	0	0	0	1 (0.0)
Atrial fibrillation	0	0	0	0	0	3 (0.2)	3 (0.2)	0	0	0	3 (0.1)
Cardiac arrest	0	0	1 (0.1)	1 (0.1)	0	0	0	0	0	0	1 (0.0)
Cardiac failure acute	0	0	0	0	2 (0.5)	1 (0.1)	3 (0.2)	0	0	0	3 (0.1)
Cardiopulmonary failure	0	0	3 (0.3)	3 (0.2)	1 (0.3)	0	1 (0.1)	0	0	0	4 (0.1)
Cytotoxic cardiomyopathy	0	0	1 (0.1)	1 (0.1)	0	0	0	0	0	0	1 (0.0)
Long QT syndrome	0	0	1 (0.1)	1 (0.1)	0	0	0	0	0	0	1 (0.0)
Myocardial infarction	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	1 (0.0)
Myocardial ischaemia	0	0	0	0	0	1 (0.1)	1 (0.1)	1 (1.0)	0	1 (0.4)	2 (0.1)
Ventricular extrasystoles	0	0	1 (0.1)	1 (0.1)	0	0	0	0	0	0	1 (0.0)
General disorders and administration site conditions	0	0	0	0	1 (0.3)	0	1 (0.1)	0	0	0	1 (0.0)
Chest pain	0	0	0	0	1 (0.3)	0	1 (0.1)	0	0	0	1 (0.0)
Nervous system disorders	0	1 (0.7)	2 (0.2)	3 (0.2)	2 (0.5)	5 (0.4)	7 (0.4)	0	0	0	10 (0.3)
Cerebral infarction	0	0	0	0	1 (0.3)	0	1 (0.1)	0	0	0	1 (0.0)
Cerebral ischaemia	0	0	1 (0.1)	1 (0.1)	0	0	0	0	0	0	1 (0.0)
Cerebrovascular accident	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	1 (0.0)
Ischaemic stroke	0	0	1 (0.1)	1 (0.1)	0	2 (0.2)	2 (0.1)	0	0	0	3 (0.1)
Loss of consciousness	0	1 (0.7)	0	1 (0.1)	0	2 (0.2)	2 (0.1)	0	0	0	3 (0.1)
Syncope	0	0	0	0	1 (0.3)	0	1 (0.1)	0	0	0	1 (0.0)

	Netupitant-Palonosetron (mg)				Palonosetron (mg)			Comparators			All Patients (N=3280)
	100/0.50 (N=135)	200/0.50 (N=138)	300/0.50 (N=1169)	Total (N=1442)	IV 0.25 (N=369)	Oral 0.50 (N=1231)	Total (N=1600)	Aprepitant plus:		Total (N=238)	
								Palonosetron (N=104)	Ondansetron (N=134)		
Respiratory, thoracic and mediastinal disorders	0	0	3 (0.3)	3 (0.2)	1 (0.3)	3 (0.2)	4 (0.3)	1 (1.0)	0	1 (0.4)	8 (0.2)
Dyspnoea	0	0	1 (0.1)	1 (0.1)	1 (0.3)	1 (0.1)	2 (0.1)	0	0	0	3 (0.1)
Pulmonary embolism	0	0	2 (0.2)	2 (0.1)	0	2 (0.2)	2 (0.1)	1 (1.0)	0	1 (0.4)	5 (0.2)
Surgical and medical procedures	0	0	0	0	0	2 (0.2)	2 (0.1)	0	0	0	2 (0.1)
Catheterization venous	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	1 (0.0)
Central venous catheterization	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	1 (0.0)
Vascular disorders	0	0	2 (0.2)	2 (0.1)	1 (0.3)	6 (0.5)	7 (0.4)	1 (1.0)	0	1 (0.4)	10 (0.3)
Arterial thrombosis limb	0	0	1 (0.1)	1 (0.1)	0	0	0	0	0	0	1 (0.0)
Deep vein thrombosis	0	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	1 (1.0)	0	1 (0.4)	3 (0.1)
Femoral artery embolism	0	0	0	0	1 (0.3)	0	1 (0.1)	0	0	0	1 (0.0)
Thrombophlebitis	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	1 (0.0)
Thrombosis	0	0	0	0	0	2 (0.2)	2 (0.1)	0	0	0	2 (0.1)
Venous recanalization	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	1 (0.0)
Venous thrombosis	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	1 (0.0)

TEAE = treatment-emergent adverse event  
 Source: Modified from Module 5.3.5.3, ISS Table 2.11.7.1, Table 2.11.7.2, Table 2.11.7.3, and Table 2.11.7.4

SMQs to evaluate CNS events included: anticholinergic syndrome, convulsions, dementia, depression and suicide, self-injury, extrapyramidal syndrome, hostility-aggression, neuroleptic malignant syndrome, non-infectious encephalitis, non-infectious

encephalopathy-delirium, non-infectious meningitis, psychosis, and psychotic disorders. Special attention was also paid to CNS and psychiatric events that could be consistent with drug abuse.

With all cycles combined, there were 533 patients out of 3280 (16.3%) who had CNS TEAEs of special interest. The SOCs with the highest incidence were general disorders (3.3%; 107/3280), nervous system disorders (3.3%; 108/3280), and psychiatric disorders (3.2%; 106/3280). Table 80 shows serious CNS TEAEs of special interest.

**Table 80 Serious CNS TEAEs of Special Interest (all cycles)**

	Netupitant–Palonosetron (mg)				Palonosetron (mg)			Comparators			All Patients (N=3280)
	100/0.50 (N=135)	200/0.50 (N=138)	300/0.50 (N=1169)	Total (N=1442)	IV 0.25 (N=369)	Oral 0.50 (N=1231)	Total (N=1600)	Aprepitant plus:		Total (N=238)	
								Palonosetron (N=104)	Ondansetron (N=134)		
Number of patients with any TEAE	–	1 (0.7)	5 (0.4)	6 (0.4)	1 (0.3)	3 (0.2)	4 (0.3)	1 (1.0)	–	1 (0.4)	11 (0.3)
General disorders and administration site conditions	–	–	2 (0.2)	2 (0.1)	–	–	–	–	–	–	2 (0.1)
Pyrexia	–	–	2 (0.2)	2 (0.1)	–	–	–	–	–	–	2 (0.1)
Musculoskeletal and connective tissue disorders	–	–	–	–	–	1 (0.1)	1 (0.1)	–	–	–	1 (0.0)
Muscular weakness	–	–	–	–	–	1 (0.1)	1 (0.1)	–	–	–	1 (0.0)
Nervous system disorders	–	1 (0.7)	1 (0.1)	2 (0.1)	–	2 (0.2)	2 (0.1)	1 (1.0)	–	1 (0.4)	5 (0.2)
Convulsion	–	–	1 (0.1)	1 (0.1)	–	–	–	1 (1.0)	–	1 (0.4)	2 (0.1)
Loss of consciousness	–	1 (0.7)	–	1 (0.1)	–	2 (0.2)	2 (0.1)	–	–	–	3 (0.1)
Psychiatric disorders	–	–	2 (0.2)	2 (0.1)	–	–	–	–	–	–	2 (0.1)
Acute psychosis	–	–	1 (0.1)	1 (0.1)	–	–	–	–	–	–	1 (0.0)
Confusional state	–	–	1 (0.1)	1 (0.1)	–	–	–	–	–	–	1 (0.0)
Vascular disorders	–	–	–	–	1 (0.3)	1 (0.1)	2 (0.1)	–	–	–	2 (0.1)
Hypertension	–	–	–	–	–	1 (0.1)	1 (0.1)	–	–	–	1 (0.0)
Hypotension	–	–	–	–	1 (0.3)	–	1 (0.1)	–	–	–	1 (0.0)

TEAE = treatment-emergent adverse event

Source: Modified from Module 5.3.5.3, ISS Tables 2.12.7.1 through Table 2.12.7.4

The following are narratives of patients experiencing series TEAEs of special interest in the cardiac and CNS category.

### Netupitant/Palonosetron

- **Patient 8520401** was a 53 yo female scheduled to receive her first course of chemotherapy for invasive ductal breast cancer. During the visit at day 6 (visit 4) of the fifth cycle the measurement of troponin showed a value of 0.12 ng/mL. The subsequent clinical and instrumental cardiovascular tests (physical exam, ECG, ECHO) did not show any abnormalities. Therefore the patient was considered eligible to receive the study drug and the sixth cycle of chemotherapy. An elevation in troponin value (0.19ng/mL) was reported again, and another assessment of the cardiovascular function was performed: ECHO performed on 7 days after the last administration of study drug showed an LVEF of 50%, myocardial aneurysm in proximal part of inferior cardiac wall, and hypocontractility of inferior and septal region. The patient was hospitalized to

perform a coronarography, the results of which excluded any coronary artery disease. The final diagnosis was toxic cardiomyopathy due to anthracyclines (doxorubicin). Treatment for the event included acetylsalicylic acid. A follow-up ECHO showed persistent depression of systolic function (ejection fraction 46%) and elevated NT-proBNP (N-terminal pro b-type natriuretic peptide) 247 pg/mL (normal range: < 125 pg/mL). The outcome of the event was reported as not recovered. The event of cytotoxic cardiomyopathy was assessed by the Investigator as serious, of mild intensity, unlikely related the study drug, and not related to dexamethasone. Chemotherapeutic agent doxorubicin and previous arterial hypertension were deemed to be the most likely causes of the event.

- **Patient 8530103** was a 55-year-old white, chemotherapy naïve female scheduled to receive her first course of chemotherapy for invasive ductal breast cancer. The study drug (netupitant/palonosetron FDC) and dexamethasone were administered 60 minutes and 30 minutes before chemotherapy, respectively. 13 days after the last administration of study drug the patient developed swelling of the right upper limb and was hospitalized because of a thrombosis involving the right vena axillaris, vena subclavia and vena brachialis. The patient's port device was removed and Ampicillin and tinzaparin were administered. The patient was discharged on the following day and the outcome of the event was reported as unknown since the patient's recovery from the venous thrombosis of the upper limb could not be predicted. The event was assessed by the Investigator as serious, of moderate severity, not related to the study drug and possibly related to dexamethasone.

### Palonosetron

- Patient 8540113 was a 77-year-old chemotherapy naïve female scheduled to receive the first course of chemotherapy for invasive ductal breast cancer. There was only one administration of study drug before the AE onset. The patient's medical history was significant for atrial fibrillation, hypertension, and hyperlipidemia. 18 days after the administration of study drug the patient was hospitalized due to worsening of atrial fibrillation and underwent cardioversion. Additionally, Metoprolol was initiated as remedial treatment. The event was assessed by the Investigator as serious, of mild intensity, and not related to the study drug or to dexamethasone. The known history of atrial fibrillation likely provides a reasonable explanation for the event onset.
- **Patient 8540321** was a 69-year-old white female, chemotherapy naïve scheduled to receive the first course of chemotherapy for invasive ductal breast cancer. 21 days after the last administration of study drug the end-of-study echocardiogram showed atrial fibrillation. The patient was asymptomatic, but was hospitalized on the same day to perform cardioversion, which was successful. Additional treatment for the event included carvedilol and enoxaparin sodium.

The outcome of the event was reported as. The event was assessed by the Investigator as serious, of moderate intensity, unlikely related to the study drug, and not related to dexamethasone. Concomitant diseases – ischemic heart disease and high blood pressure were considered the mostly likely causes implicated in the event occurrence. The sponsor agreed with the Investigator’s assessment.

- **Patient 8571303** was a 56-year-old white female, chemotherapy naive scheduled to receive the first course of chemotherapy for invasive ductal breast cancer. A blood culture test showed the presence of *Stenotrophomonas maltophilia*. The events of chills, thrombosis, and neutropenia were assessed by the Investigator as serious, chills and neutropenia of mild intensity and thrombosis of moderate intensity. All SAEs were considered not related to the study drug or to dexamethasone. Bacterial infection was deemed the possible cause of shivers, chemotherapy of neutropenia, and intravenous device had plausibly determined the development of the right arm thrombosis. The sponsor agreed with the Investigator’s assessment.

*Medical Officer’s Comment:*

*In many of these cases patients were pre-disposed to the event through previous medical history. None appear study drug related.*

## 7.4 Supportive Safety Results

### Thorough QT Study NETU-07-20

The sponsor conducted a tQT study which showed no significant QTcF prolongation effect of netupitant/palonosetron (therapeutic dose 200 mg/0.50 mg, suprathapeutic dose 600 mg/1.50 mg). Two hundred subjects (106 men and 94 women), 18-45 yrs. of age with a normal baseline ECG were enrolled into the treatment phase of the study. Five subjects (#307,332,335,391,394) discontinued the study prematurely, withdrawing their consent. Three of the five withdrew consent before administration of study drug and were not dosed. The other two patients (#307 and 335) received investigational product, and there is no information to suggest that they withdrew consent due to adverse events. A total of 195 subjects completed the study. Table 81 shows adverse events during the study.

**Table 81 TEAEs tQT study NETU-07-20**

<b>System organ class preferred term [investigator's term]</b>	<b>b<sub>1</sub> (N=50)</b>			<b>b<sub>2</sub> (N=49)</b>			<b>b<sub>3</sub> (N=49)</b>			<b>b<sub>4</sub> (N=49)</b>		
	<b>n</b>	<b>%</b>	<b>f</b>									
<b>Cardiac disorders</b>	-			-			<b>1</b>	<b>2.0</b>	<b>1</b>	-		
- Palpitations [palpitations]	-			-			1	2.0	1	-		
<b>Gastrointestinal disorders</b>	<b>4</b>	<b>8.0</b>	<b>4</b>	<b>5</b>	<b>10.2</b>	<b>5</b>	<b>7</b>	<b>14.3</b>	<b>8</b>	<b>1</b>	<b>2.0</b>	<b>1</b>
- Abdominal pain [abdominal pain]	-			-			1	2.0	1	-		
- Abdominal pain upper [gastric pain, stomach ache]	-			2	4.1	2	-			-		
- Constipation [constipation]	-			3	6.1	3	4	8.2	4	-		
- Diarrhea [diarrhea]	-			-			1	2.0	1	-		
- Dry mouth [dry mouth]	2	4.0	2	-			1	2.0	1	-		
- Dyspepsia [heartburn]	1	2.0	1	-			-			-		
- Flatulence [meteorism]	1	2.0	1	-			-			-		
- Nausea [nausea]	-			-			-			1	2.0	1
- Toothache [toothache]	-			-			1	2.0	1	-		
<b>General disorders and administration site conditions</b>	-			<b>1</b>	<b>2.0</b>	<b>1</b>	-			<b>2</b>	<b>4.1</b>	<b>2</b>
- Fatigue [tiredness]	-			1	2.0	1	-			1	2.0	1
- Thirst [increased thirst]	-			-			-			1	2.0	1
<b>Infections and infestations</b>	<b>1</b>	<b>2.0</b>	<b>1</b>	<b>1</b>	<b>2.0</b>	<b>1</b>	-			<b>2</b>	<b>4.1</b>	<b>2</b>
- Nasopharyngitis [common cold]	1	2.0	1	1	2.0	1	-			2	4.1	2
<b>Injury, poisoning and procedural complications</b>	-			<b>1</b>	<b>2.0</b>	<b>1</b>	-			-		
- Injury [contusion of upper spine, hip, and left elbow]	-			1	2.0	1	-			-		
<b>Musculoskeletal and connective tissue disorders</b>	<b>2</b>	<b>4.0</b>	<b>2</b>	-			<b>1</b>	<b>2.0</b>	<b>1</b>	-		
- Muscle twitching [fasciculations muscle left upper leg]	1	2.0	1	-			-			-		
- Pain in extremity [pain in the legs]	-			-			1	2.0	1	-		
- Sensation of heaviness [heavy legs]	1	2.0	1	-			-			-		
<b>Nervous system disorders</b>	<b>8</b>	<b>16.0</b>	<b>9</b>	<b>2</b>	<b>4.1</b>	<b>2</b>	<b>8</b>	<b>16.3</b>	<b>9</b>	<b>5</b>	<b>10.2</b>	<b>5</b>
- Dizziness [dizziness, lightheadedness]	1	2.0	1	-			1	2.0	1	3	6.1	3
- Headache [headache, head pressure]	7	14.0	7	2	4.1	2	7	14.3	7	2	4.1	2
- Somnolence [drowsiness]	-			-			1	2.0	1	-		
- Syncope [fainting after blood drawing]	1	2.0	1	-			-			-		
<b>Psychiatric disorders</b>	-			-			<b>2</b>	<b>4.1</b>	<b>2</b>	-		
- Anxiety [anxiety]	-			-			1	2.0	1	-		
- Euphoric mood [euphoria]	-			-			1	2.0	1	-		
<b>Reproductive system and breast disorders</b>	<b>1</b>	<b>2.0</b>	<b>2</b>	-			-			-		
- Dysmenorrhoea [painful menstrual bleeding]	1	2.0	2	-			-			-		
<b>Skin and subcutaneous tissue disorders</b>	<b>1</b>	<b>2.0</b>	<b>1</b>	-			-			-		
- Hyperhidrosis [sweating]	1	2.0	1	-			-			-		
<b>Total</b>	<b>12</b>	<b>24.0</b>	<b>19</b>	<b>10</b>	<b>20.4</b>	<b>10</b>	<b>17</b>	<b>34.7</b>	<b>21</b>	<b>10</b>	<b>20.4</b>	<b>10</b>

b<sub>1</sub>: placebo to netupitant and placebo to palonosetron  
b<sub>2</sub>: 200 mg netupitant (50 mg + 150 mg) + 0.50 mg palonosetron (1 x 0.50 mg)  
b<sub>3</sub>: 600 mg netupitant (4 x 150 mg) + 1.50 mg palonosetron (3 x 0.50 mg)  
b<sub>4</sub>: 400 mg moxifloxacin (Avalox<sup>®</sup>, Bayer)  
f = number of adverse events, n = number of subjects with adverse events  
Source: Table 14.3.1.2

A total of 60 adverse events were reported by 49 of the 200 subjects. Except for 1 severe AE (syncope after blood drawing) which was assessed as unlikely related to the study drug, all AEs were of mild or moderate intensity. One subject (#302) had a serious adverse event (injury due to staircase fall), the event assessed as unlikely related to the study drug. This patient received 200mg Netupitant on [REDACTED] (b) (6) and experienced injury to lower back [REDACTED] (b) (6). The fall was not due to lightheadedness or syncope.

Patients receiving 200 mg netupitant and 0.50 palonosetron reported 3 events of constipation and 2 events of upper abdominal pain and headache. In the 600 mg netupitant and 1.50 mg palonosetron groups subjects reported mainly headache (5 events) followed by constipation (2 events). Subjects reported mainly dizziness (3 events) and headache (2 events) with 400 mg moxifloxacin.

The largest upper bounds of the 2-sided 90% CI for the mean difference between two netupitant/palonosetron doses and placebo groups were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

*Medical Officer's Comment:*

*As expected, more adverse events were seen in patients receiving 600mg netupitant with 1.5mg palonosetron. The event of syncope was associated temporally with phlebotomy, and not likely related to study drug. The event of falling on staircase was due to accident.*

#### **7.4.1 Common Adverse Events**

Table 82 shows TEAE by system organ class and preferred term for the TBM dose of Netu/Palo, and the two control groups, Palonosetron, and Aprepitant+PALO. The system organ classes (SOC) with the greatest number of TEAEs were blood and lymphatic, gastrointestinal, general disorders and administration site conditions, investigations, nervous system disorders, and skin and subcutaneous tissue disorders. There did not appear to be any major differences between groups.

Table 82 TEAEs with Incidence  $\geq 5\%$  All Cycles

System Organ Class/ Preferred Term	NETU	PALO	Comparator	Total
	300/0.50 mg (N=1033) n (%)	0.50 mg PO (N=725) n (%)	Aprepitant+PALO (N=104) n (%)	(N=1862) n (%)
Number of patients with any TEAE	933 (90.3)	642 (88.6)	95 (91.3)	1670 (89.7)
Blood and lymphatic system disorders	517 (50.0)	371 (51.2)	48 (46.2)	936 (50.3)
Anemia	125 (12.1)	60 (8.3)	26 (25.0)	211 (11.3)
Leukopenia	232 (22.5)	173 (23.9)	18 (17.3)	423 (22.7)
Neutropenia	390 (37.8)	317 (43.7)	29 (27.9)	736 (39.5)
Thrombocytopenia	62 (6.0)	17 (2.3)	16 (15.4)	95 (5.1)
Cardiac disorders	74 (7.2)	42 (5.8)	8 (7.7)	124 (6.7)
Gastrointestinal disorders	293 (28.4)	172 (23.7)	38 (36.5)	503 (27.0)
Constipation	75 (7.3)	55 (7.6)	9 (8.7)	139 (7.5)
Diarrhea	75 (7.3)	30 (4.1)	19 (18.3)	124 (6.7)
Nausea	64 (6.2)	53 (7.3)	11 (10.6)	128 (6.9)
Stomatitis	43 (4.2)	25 (3.4)	6 (5.8)	74 (4.0)
Gen. disorders and administration site conditions	309 (29.9)	194 (26.8)	35 (33.7)	538 (28.9)
Asthenia	138 (13.4)	91 (12.6)	12 (11.5)	241 (12.9)
Fatigue	117 (11.3)	72 (9.9)	15 (14.4)	204 (11.0)
Pyrexia	48 (4.6)	28 (3.9)	10 (9.6)	86 (4.6)
Infections and infestations	153 (14.8)	76 (10.5)	19 (18.3)	248 (13.3)
Investigations	193 (18.7)	117 (16.1)	25 (24.0)	335 (18.0)
Blood creatinine increased	12 (1.2)	4 (0.6)	6 (5.8)	22 (1.2)
Metabolism and nutrition disorders	177 (17.1)	113 (15.6)	19 (18.3)	309 (16.6)
Decreased appetite	71 (6.9)	58 (8.0)	7 (6.7)	136 (7.3)
Hyperglycemia	63 (6.1)	53 (7.3)	3 (2.9)	119 (6.4)
Musculoskeletal and connective tissue disorders	77 (7.5)	38 (5.2)	15 (14.4)	130 (7.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	36 (3.5)	6 (0.8)	7 (6.7)	49 (2.6)
Nervous system disorders	186 (18.0)	126 (17.4)	24 (23.1)	336 (18.0)
Headache	114 (11.0)	89 (12.3)	7 (6.7)	210 (11.3)
Psychiatric disorders	61 (5.9)	31 (4.3)	1 (1.0)	93 (5.0)
Renal and urinary disorders	38 (3.7)	32 (4.4)	12 (11.5)	82 (4.4)
Respiratory, thoracic and mediastinal disorders	91 (8.8)	36 (5.0)	19 (18.3)	146 (7.8)
Cough	35 (3.4)	15 (2.1)	8 (7.7)	58 (3.1)
Skin and subcutaneous tissue disorders	507 (49.1)	414 (57.1)	37 (35.6)	958 (51.5)
Alopecia	475 (46.0)	394 (54.3)	32 (30.8)	901 (48.4)
Vascular disorders	76 (7.4)	41 (5.7)	12 (11.5)	129 (6.9)

Ref: Summary Clinical Efficacy, Table 17, p.72.

Figures 6 and 7 compare the most common TEAEs from NETU-08-18 (AC MEC) and NETU-10-29 (multiple cycle extension).

Figure 3 Most common TEAEs by Treatment Group NETU-08-18

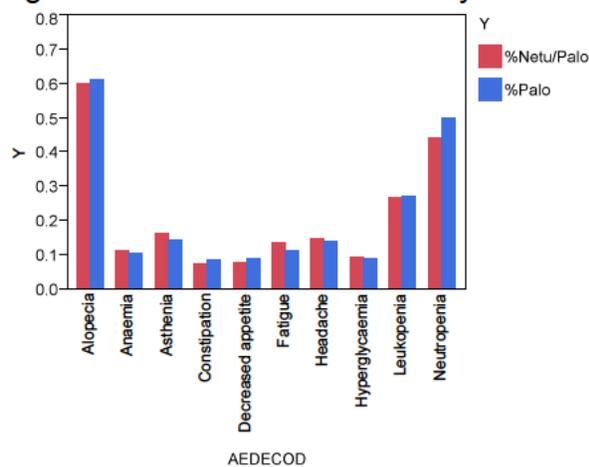
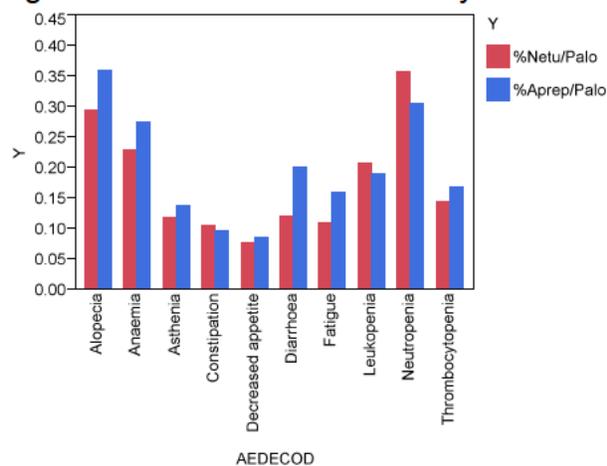


Figure 4 Most common TEAEs by Treatment Group NETU-10-29



Reviewer's tables

*Medical Officer's Comment:*

*In both trials TEAEs appear fairly well matched between the two arms. Most TEAEs listed are those known to occur with chemotherapy (i.e. alopecia, anemia, asthenia and fatigue).*

**7.4.2 Laboratory Findings**

In the Phase 3 studies there were no major differences in laboratory findings between treatment groups for hematology or chemistry, as shown in Table 83.

Table 83 Blood Chemistry New Abnormalities - All Cycles

	Netupitant/ Palonosetron 300/0.50 mg (N=1033) n (%)	Palonosetron 0.50 mg (N=725) n (%)	Aprepitant plus Palonosetron (N=104) n (%)	TOTAL (N=1862) n (%)
Number of patients with new laboratory abnormality	159 (15.4)	101 (13.9)	18 (17.3)	278 (14.9)
ALT increased	13 (1.3)	12 (1.7)	–	25 (1.3)
Grade 3	13 (1.3)	12 (1.7)	–	25 (1.3)
AST increased	9 (0.9)	5 (0.7)	–	14 (0.8)
Grade 3	8 (0.8)	5 (0.7)	–	13 (0.7)
Grade 4	1 (0.1)	–	–	1 (0.1)
Alkaline phosphatase increased	4 (0.4)	1 (0.1)	–	5 (0.3)
Grade 3	4 (0.4)	1 (0.1)	–	5 (0.3)
Creatinine increased	–	1 (0.1)	1 (1.0)	2 (0.1)
Grade 3	–	–	1 (1.0)	1 (0.1)
Grade 4	–	1 (0.1)	–	1 (0.1)
Hyperglycemia	87 (8.4)	55 (7.6)	7 (6.7)	149 (8.0)
Grade 3	81 (7.8)	53 (7.3)	7 (6.7)	141 (7.6)
Grade 4	6 (0.6)	2 (0.3)	–	8 (0.4)
Hypokalemia	18 (1.7)	5 (0.7)	5 (4.8)	28 (1.5)
Grade 3	14 (1.4)	5 (0.7)	5 (4.8)	24 (1.3)
Grade 4	4 (0.4)	–	–	4 (0.2)
Hyponatremia	57 (5.5)	46 (6.3)	7 (6.7)	110 (5.9)
Grade 3	51 (4.9)	39 (5.4)	7 (6.7)	97 (5.2)
Grade 4	6 (0.6)	7 (1.0)	–	13 (0.7)

### Hy's Law/DILI

Laboratory results for Phase 3 multicycle trials were scrutinized for Hy's Law cases or cases of drug induced liver injury (DILI). Potential Hy's law cases were defined as patients with an increase in AST or ALT (or both) more than 3x ULN and a total bilirubin value >ULN.

Five patients from NETU-08-18 (1 in Akynzeo arm and 4 in palonosetron arm) had hepatic enzyme elevations meeting these criteria. The cases were further evaluated by an expert hepatologist. After review, only 1 patient receiving palonosetron was judged to have a potential Hy's Law pattern. Two (1 palonosetron and one Akynzeo) were assessed as possible DILI. Patent narratives are provided.

### Netupitant-Palonosetron:

**Patient 8420901** had mild baseline anicteric cholestasis which was maintained throughout the study. The patient had a primary diagnosis of stomach cancer with liver and lung metastases and underwent courses of chemotherapy with fluorouracil, cyclophosphamide, and doxorubicin. Changes in liver enzyme tests suggesting a moderate liver reaction were observed during cycle 3 and cycle 4, followed by improvement. Transaminase values at baseline of cycle 5 indicated underlying injury.

The pattern of injury was assessed as “mixed” with mild severity. It was not considered a pattern consistent with Hy’s Law, although it was assessed as probable DILI due to the proximity of chemotherapy and study drug administration.

**Palonosetron:**

**Patient 8420411** was judged by the expert to have a liver reaction with a moderate, grade 2- severity with a Hy’s law pattern. The patient had a primary diagnosis of lung cancer and had received vincristine, cyclophosphamide and doxorubicin as well as antiemetic therapy with palonosetron (0.50 mg oral) and dexamethasone. After the first cycle without abnormalities, the second cycle was associated with a moderate increase in transaminases without jaundice and with a rapid recovery. The main liver event occurred during the third cycle with elevated transaminases up to 11× ULN (acute hepatocellular pattern) and an increase of bilirubin > 2× ULN on day 2 post-dose. These increases were transient, and were followed by a return to normal values on day 6. The close temporal relationship with chemotherapy and study drug suggests a possible DILI due to either chemotherapy or study treatment.

**Subject 8560647** had acute hepatocellular injury without jaundice at cycle 2. The patient had a primary diagnosis of breast cancer and had received cyclophosphamide and doxorubicin as well as antiemetic therapy with palonosetron (0.50 mg oral) and dexamethasone. The liver reaction was assessed as mild in severity (grade 1), and was considered a possible case of DILI due to time course of chemotherapy and study medication. The patient was discontinued from the study due to investigator’s decision. The other two palonosetron-exposed patients were considered unlikely to have DILI.

**Subject 8420902** had mild cholestasis on day 6 of the third cycle but no relapse during the following 3 cycles. **Subject 8570609** had a mild hepatocellular event on cycle 2 and an isolated mild increase of bilirubin during cycle 4. Table 84 summarizes these cases.

Table 84 Potential Cases of Liver Injury

Patient ID/ Gender/Age (years)	Laboratory Value								
	AST (IU/L)		ALT (IU/L)		Total Bilirubin (umol/L)		ALP (IU/L)		
Cycle/ Day	Netupitant-Palonosetron FDC								
<b>8420901/M/61</b>									
Cycle 3/ day 2	95	2.3×ULN	normal		normal		256	2.0×ULN	
Cycle 3/ day 6	137	3.3×ULN	83	1.8×ULN	28	1.3×ULN	229	1.8×ULN	
Cycle 4/ baseline	normal		normal		normal		normal		
Cycle 4/ day 2	306	7.5×ULN	333	7.4×ULN	32	1.5×ULN	303	2.4×ULN	
Cycle 4/ day 6	142	3.5×ULN	248	5.5×ULN	42	2.0×ULN	233	1.8×ULN	
Cycle 5/ baseline	119	2.9×ULN	63	1.4×ULN	normal		202	1.6×ULN	
	Palonosetron 0.50 mg PO								
<b>8420411/M/67</b>									
Cycle 2/ day 2	normal		normal		22	1.1×ULN	179	1.4×ULN	
Cycle 2/ day 6	139	3.4×ULN	352	7.8×ULN	25	1.2×ULN	160	1.2×ULN	
Cycle 3/ baseline	normal		normal		normal		normal		
Cycle 3/ day 2	400	9.8×ULN	597	13.3×ULN	57	2.7×ULN	243	1.9×ULN	
Cycle 3/ day 6	normal		normal		normal		normal		
<b>8420902/F/70</b>									
Cycle 3/ day 2	normal		normal		normal		normal		
Cycle 3/ day 6	134	3.3×ULN	81	1.8×ULN	27	1.3×ULN	221	2.1×ULN	
Cycle 4/ baseline	normal		normal		normal		normal		
<b>8560647/F/47</b>									
Cycle 2/ day 2	normal		normal		normal		126	1.2×ULN	
Cycle 2/ day 6	ND		332	7.4×ULN	25	1.2×ULN	115	1.1×ULN	
No further data									
<b>8570609/F/69</b>									
Cycle 2/ day 2	normal		normal		normal		normal		
Cycle 2/ day 6	55	1.3×ULN	139	3.1×ULN	24	1.1×ULN	67	normal	
Cycle 3/ baseline	normal		normal		normal		normal		

Ref: Summary Clinical Safety, Table 30, p.120.

Nine additional cases from NETU-07-07 and PALO-10-01 were reviewed by an independent expert, but none were regarded as potential Hy's Law cases.

**Medical Officer's Comment:**

*Based on the patient narratives and assessment by an independent expert, potential Hy's Law cases were reviewed and rejected. In the few cases where DILI was a possibility the co-administration of cytotoxic chemotherapy makes attribution difficult. This review agrees with the assessments provided by the applicant.*

**Cardiovascular Monitoring**

Based on concerns of cardiotoxicity seen in another drug of the NK-1 RA class, the sponsor was required to maintain increased cardiovascular monitoring. In Phase 3 multicycle studies NETU-08-18 and NETU-10-29 cardiac troponin (cTnI) levels were obtained during screening for cycle 1, and on day 2 (24 hours after study drug administration) and on day 6 of each cycle. Patients with cTnI levels ≥ 0.12 ng/mL (but <0.50 ng/mL) were to enter a cardiovascular follow-up, either within the study or following discontinuation, but were permitted to continue in the study at the

investigator's discretion. Patients with cTnI values  $\geq 0.50$  ng/mL also entered a cardiovascular follow-up for functional assessment, but were withdrawn from the study. Cardiovascular follow-up included the monitoring of LVEF by 2D-Echo or MUGA scan, and cardiac assessments, including New York Heart Association (NYHA) classification, vital signs, 12-lead ECG, assessment of cardiotoxic medications, and cardiac-specific concomitant medication.

The following table shows patients with elevated troponin across all cycles.

**Patients with Elevated Troponin- All Cycles**

Troponin	NETU/PALO 300/0.5mg N=1033 n (%)	PALO 0.05mg N=725	Aprepitant+Palo N=104	Total
$\geq 0.12$ ng/mL and < 0.5 ng/mL	28 (2.7)	17 (2.3)	2 (1.9)	47 (2.5)
$\geq 0.5$ ng/mL	5 (0.5)	5 (0.7)	1 (1.0)	11 (0.6)

Ref: Summary Clinical Safety, Table 31, p.129.

Patients with elevated troponin were entered into the cardiovascular follow-up study to have assessment of LV function. Most patients with elevated troponin did not have significant changes in cardiac function (i.e. most had change from baseline <10). The table below shows that in NETU-08-18 four patients in the Netupitant/Palo group had significant changes in LVEF ranging from -10 to -39. Two patients in the Palonosetron group had a decline in cardiac function ranging from -14 to -22, and one patient participating in NETU-10-29 and receiving aprepitant + palonosetron had a change in cardiac function of -25.

**Patients with Elevated Troponin and Change in LVEF of >10**

Study	Arm	Cycle	Measured value (%)	Change from B/L
NETU-08-18	NETU/PALO FDC	6	21	-39
NETU-08-18	NETU/PALO FDC	6	56	-10
NETU-08-18	NETU/PALO FDC	6	50	-20
NETU-08-18	Palo alone	5	47	-22
NETU-08-18	Palo alone	5	54	-14
NETU-08-18	NETU/PALO FDC	Post withdrawal	56	-13
NETU-10-29	Aprep/Palo	Post withdrawal	30	-25

Ref: Reviewer's table

*Medical Officer's Comment:*

*Most patients with elevated troponin levels were from NETU-08-18, and all patients had elevations during later chemotherapy cycles. Six had notable changes in cardiac function, as determined by echocardiogram. Four received Akynzeo and two received Palonosetron. Patients in NETU-08-18 received the chemotherapy agent anthracycline, which is known to be cardiotoxic. Overall these results do not seem to be a cause for concern about the cardiac safety of Akynzeo.*

### 7.4.3 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) were measured at screening of each cycle. After screening they were obtained before dosing at each cycle, and at 5, 24, and 120 hours post-dose. After the start of chemotherapy blood pressures were slightly lower in all treatment groups, but not of clinical concern.

Mean changes from baseline in systolic blood pressure among patients in the netupitant-palonosetron, palonosetron, and aprepitant+5-HT3 groups were respectively -0.3, +0.8, and +0.5 mmHg at 5 hours post-dose; -2.1, -1.0, and -1.4 mmHg at 24 hours post-dose; and -3.0, -3.6, and -2.8 mmHg at 120 hours post-dose.

Mean changes from baseline in pulse rate among patients in the netupitant-palonosetron, palonosetron, and aprepitant+5-HT3 groups were respectively +0.7, +2.1, and +0.7 bpm at 5 hours post-dose; -1.3, -0.7, and -1.6 bpm at 24 hours post-dose; and -1.4, -0.1, -1.3 bpm at 120 hours post-dose.

During the Multicycle studies there were no patterns observed over time, and no changes of clinical concern. Mean changes from baseline (i.e., last measurement before treatment in cycle 1) in systolic blood pressure across all cycles ranged from -3.7 to -0.6 mmHg in the netupitant-palonosetron group (baseline: 127.1 mmHg); -5.8 to -0.8 mmHg in the palonosetron group (baseline: 128.2 mmHg); and from -6.1 to +0.5 mmHg in the aprepitant+palonosetron group (baseline: 127.7 mmHg).

Mean changes from baseline in pulse rate were generally small across all cycles (netupitant-palonosetron: -1.2 to +1.5 bpm; palonosetron: -0.7 to +2.8 bpm; aprepitant+palonosetron: -4.6 to +1.4 bpm), and similar between treatment groups at each time point. The exception was during cycle 6, when patients treated with netupitant-palonosetron or with palonosetron generally had small mean increases from baseline in pulse rate (greatest mean increases of 1.1 bpm and 2.1 bpm, respectively), while patients treated with aprepitant+palonosetron had decreases from baseline (nadir of -4.6 bpm).

#### *Medical Reviewer's Comment:*

*For the most part, changes in vital signs were clinically insignificant. Significant changes in vital signs or heart rhythm, requiring intervention, were listed as treatment emergent adverse events.*

### 7.4.4 Electrocardiograms (ECGs)

Descriptive summaries are given for changes from baseline in ECG parameters. As Table 85 shows, at 5 hours post dose there was an increase for all treatment arms in the QT interval. By 120 hours all had returned to baseline.

Table 85 ECG Descriptive Summary QTcF Interval Cycle 1

QTcF (ms) Time point, Statistic	Netupitant- Palonosetron Combination (N=1442)	Palonosetron (N=1600)	Comparator Aprepitant+5HT3 (N=238)	Total (N=3280)
Baseline reference value				
n	1441	1600	238	3279
Mean (SD)	409.2 (19.86)	410.5 (20.26)	409.1 (20.71)	409.8 (20.12)
Day 1: 5 hours postdose				
n	1433	1585	237	3255
Mean (SD)	420.8 (21.53)	421.5 (21.07)	418.0 (22.54)	420.9 (21.39)
Change from baseline				
Mean (SD)	11.5 (16.78)	11.0 (16.76)	9.2 (16.63)	11.1 (16.76)
Day 2: 24 hours postdose				
n	1430	1584	237	3251
Mean (SD)	419.8 (22.74)	419.0 (21.79)	416.0 (21.31)	419.1 (22.19)
Change from baseline				
Mean (SD)	10.6 (18.85)	8.6 (18.52)	7.2 (16.05)	9.4 (18.53)
Day 6: 120 hours postdose				
n	1420	1556	235	3211
Mean (SD)	407.3 (20.56)	410.4 (21.08)	406.5 (20.41)	408.8 (20.86)
Change from baseline				
Mean (SD)	-1.9 (17.15)	-0.2 (18.68)	-2.3 (16.92)	-1.1 (17.91)

Ref: Summary-clin-safety, Table 32, p.136.

As Table 86 shows, new ECG abnormalities were seen in all treatment arms; 37.5% for Netu/Palo FDC, 37.4% for Palo alone, and 39.1% for Aprepitant+5-HT3. Even in subcategories such as Atrial Fibrillation, or QTcB prolongation>500ms, the proportion of patients experiencing these abnormalities was low, and shared by all treatments. The overall number of patients in the Akynzeo and Palonosetron arms was about 6 times higher than the number of patients receiving aprepitant, thus making it more difficult to discern a safety signal in the ECG parameters of patients receiving aprepitant.

Table 86 Patients with new ECG abnormalities - cycle 1

Grouped Term Abnormality, n (%)	Netupitant- Palonosetron FDC (N=1442)	Palonosetron (N=1600)	Comparator Aprepitant+5HT3 (N=238)	Total (N=3280)
Number of patients with new ECG Abnormalities	541 (37.5)	599 (37.4)	93 (39.1)	1233 (37.6)
Conduction Evaluation	101 (7.0)	84 (5.3)	13 (5.5)	198 (6.0)
1st Degree AV Block	50 (3.5)	42 (2.6)	7 (2.9)	99 (3.0)
Incomplete Right Bundle Branch Block	2 (0.1)	3 (0.2)	0	5 (0.2)
Intraventricular Conduction Delay, Nonspecific	17 (1.2)	11 (0.7)	1 (0.4)	29 (0.9)
Left Anterior Fascicular Block	14 (1.0)	12 (0.8)	3 (1.3)	29 (0.9)
Prolonged QTc	3 (0.2)	2 (0.1)	1 (0.4)	6 (0.2)
QTcB Prolongation > 500 ms	16 (1.1)	19 (1.2)	1 (0.4)	36 (1.1)
QTcF Prolongation > 500 ms	2 (0.1)	1 (0.1)	0	3 (0.1)
Right Bundle Branch Block	1 (0.1)	1 (0.1)	0	2 (0.1)
Other	0	2 (0.1)	0	2 (0.1)
Ectopy Evaluation	93 (6.4)	130 (8.1)	27 (11.3)	250 (7.6)
Frequent Atrial Premature Complexes (>3)	2 (0.1)	1 (0.1)	2 (0.8)	5 (0.2)
Frequent Ventricular Premature Complexes (>2)	0	0	2 (0.8)	2 (0.1)
Premature Atrial Complexes	57 (4.0)	81 (5.1)	16 (6.7)	154 (4.7)
Premature Ventricular Complexes	40 (2.8)	54 (3.4)	14 (5.9)	108 (3.3)
Other	1 (0.1)	4 (0.3)	0	5 (0.2)
Morphology Evaluation	3 (0.2)	9 (0.6)	0	12 (0.4)
Left Atrial Enlargement	2 (0.1)	3 (0.2)	0	5 (0.2)
Left Ventricular Hypertrophy	1 (0.1)	0	0	1 (0.0)
Low QRS Voltage	0	3 (0.2)	0	3 (0.1)
Low Voltage	1 (0.1)	1 (0.1)	0	2 (0.1)
Right Atrial Abnormality	0	4 (0.3)	0	4 (0.1)
Other Rhythm Evaluation	0	0	1 (0.4)	1 (0.0)
Intermittent Ectopic Supraventricular Rhythm	0	0	1 (0.4)	1 (0.0)
Rhythm Evaluation	151 (10.5)	192 (12.0)	26 (10.9)	369 (11.3)
Atrial Fibrillation	5 (0.3)	6 (0.4)	0	11 (0.3)
Atrial Flutter	0	1 (0.1)	0	1 (0.0)
Ectopic Supraventricular Rhythm	4 (0.3)	7 (0.4)	1 (0.4)	12 (0.4)
Junctional Rhythm	0	1 (0.1)	0	1 (0.0)
Sinus Bradycardia	20 (1.4)	20 (1.3)	3 (1.3)	43 (1.3)
Sinus Tachycardia	120 (8.3)	159 (9.9)	22 (9.2)	301 (9.2)
Supraventricular Tachycardia	3 (0.2)	0	0	3 (0.1)
Other	7 (0.5)	6 (0.4)	0	13 (0.4)

Grouped Term Abnormality, n (%)	Netupitant- Palonosetron FDC (N=1442)	Palonosetron (N=1600)	Comparator Aprepitant+5HT3 (N=238)	Total (N=3280)
ST Segment Evaluation	80 (5.5)	86 (5.4)	12 (5.0)	178 (5.4)
ST Depression	78 (5.4)	84 (5.3)	11 (4.6)	173 (5.3)
ST Elevation	2 (0.1)	2 (0.1)	0	4 (0.1)
Other	1 (0.1)	1 (0.1)	1 (0.4)	3 (0.1)
T Wave Evaluation	249 (17.3)	262 (16.4)	34 (14.3)	545 (16.6)
T Wave Inversion	93 (6.4)	79 (4.9)	12 (5.0)	184 (5.6)
T Waves Biphasic	23 (1.6)	18 (1.1)	6 (2.5)	47 (1.4)
T Waves Flat	164 (11.4)	188 (11.8)	17 (7.1)	369 (11.3)
Other	0	0	1 (0.4)	1 (0.0)
U Wave Evaluation	2 (0.1)	0	1 (0.4)	3 (0.1)
U Waves	2 (0.1)	0	1 (0.4)	3 (0.1)

Ref: Summary-clin-safety, Table 34, p.140.

Table 87 shows QTcF outliers in the multi-cycle extension studies.

Table 87 ECG outliers QTcF - all cycles

	Netupitant- Palonosetron	Palonosetron	Comparator	Total
QTcF	300/0.50 mg (N=1033) n (%)	0.50 mg PO (N=725) n (%)	Aprepitant + Palonosetron (N=104) n (%)	(N=1862) n (%)
Change from baseline or same cycle predose				
New values > 450 ms	376 (36.4)	306 (42.2)	27 (26.0)	709 (38.1)
New values > 480 ms	48 (4.6)	32 (4.4)	4 (3.8)	84 (4.5)
New values > 500 ms	11 (1.1)	6 (0.8)	1 (1.0)	18 (1.0)
Increase by > 30 and ≤ 60 ms	602 (58.3)	444 (61.2)	47 (45.2)	1093 (58.7)
Increase by > 60 ms	99 (9.6)	72 (9.9)	5 (4.8)	176 (9.5)

Note: New value is defined as a change vs predose condition where baseline is defined as last measurement before first treatment in cycle 1 and where predose is defined as the last measurement before the first treatment in the specific cycle.

Source: [Module 5.3.5.3, ISS Tables 5.2.3.22, 5.2.3.24, 5.2.3.26, 5.2.3.28](#).

Abbreviations: N= Number of patients in treatment group, n (%) = number and percentage of patients with changes in each treatment group.

Ref: summary-Clin-Safety, Table 36, p.143.

The number of patients with new ECG abnormalities in multicycle studies is similar in all treatment groups (Table 88). Although there are some differences in specific abnormalities, such as atrial fibrillation or QTc prolongation, it is difficult to interpret these in the setting of other confounding medications, electrolyte changes, and overall clinical condition.

Table 88 Patients with new ECG abnormalities from baseline - multicycle studies

Grouped Term Abnormality, n (%)	Netupitant- Palonosetron	Palonosetron	Comparator	Total
	300/0.50 mg (N=1033)	0.50 mg PO (N=725)	Aprepitant+PALO (N=104)	(N=1862)
Number of patients with new ECG abnormalities	689 (66.7)	493 (68.0)	68 (65.4)	1250 (67.1)
Conduction evaluation	148 (14.3)	94 (13.0)	14 (13.5)	256 (13.7)
1st degree AV block	66 (6.4)	36 (5.0)	6 (5.8)	108 (5.8)
Incomplete right bundle branch block	7 (0.7)	2 (0.3)	0	9 (0.5)
Intraventricular conduction delay, nonspecific	24 (2.3)	15 (2.1)	2 (1.9)	41 (2.2)
Left anterior fascicular block	16 (1.5)	12 (1.7)	1 (1.0)	29 (1.6)
Prolonged QTc	12 (1.2)	5 (0.7)	1 (1.0)	18 (1.0)
QTcB prolongation > 500 msec	47 (4.5)	37 (5.1)	4 (3.8)	88 (4.7)
QTcF prolongation > 500 msec	10 (1.0)	6 (0.8)	1 (1.0)	17 (0.9)
Right bundle branch block	5 (0.5)	0	0	5 (0.3)
Other	1 (0.1)	1 (0.1)	0	2 (0.1)
Ectopy evaluation	208 (20.1)	120 (16.6)	26 (25.0)	354 (19.0)
Premature atrial complexes	145 (14.0)	76 (10.5)	20 (19.2)	241 (12.9)
Premature ventricular complex	86 (8.3)	53 (7.3)	15 (14.4)	154 (8.3)
Other	2 (0.2)	5 (0.7)	0	7 (0.4)
Morphology Evaluation	8 (0.8)	7 (1.0)	1 (1.0)	16 (0.9)
Left atrial enlargement	3 (0.3)	0	0	3 (0.2)
Left ventricular hypertrophy	3 (0.3)	2 (0.3)	1 (1.0)	6 (0.3)
Low qrs voltage	3 (0.3)	4 (0.6)	0	7 (0.4)
Other	0	1 (0.1)	0	1 (0.1)
Rhythm evaluation	294 (28.5)	165 (22.8)	31 (29.8)	490 (26.3)
Atrial fibrillation	8 (0.8)	1 (0.1)	0	9 (0.5)
Atrial flutter	1 (0.1)	1 (0.1)	0	2 (0.1)
Ectopic supraventricular rhythm	19 (1.8)	8 (1.1)	1 (1.0)	28 (1.5)
Junctional rhythm	0	1 (0.1)	0	1 (0.1)
Sinus bradycardia	21 (2.0)	11 (1.5)	6 (5.8)	38 (2.0)
Sinus tachycardia	251 (24.3)	143 (19.7)	25 (24.0)	419 (22.5)
Supraventricular tachycardia	3 (0.3)	1 (0.1)	0	4 (0.2)
Other	11 (1.1)	4 (0.6)	0	15 (0.8)
ST segment evaluation	150 (14.5)	111 (15.3)	16 (15.4)	277 (14.9)
ST depression	149 (14.4)	110 (15.2)	15 (14.4)	274 (14.7)
ST elevation	1 (0.1)	1 (0.1)	0	2 (0.1)
Other	1 (0.1)	1 (0.1)	1 (1.0)	3 (0.2)

Grouped Term Abnormality, n (%)	Netupitant- Palonosetron	Palonosetron	Comparator	Total
	300/0.50 mg (N=1033)	0.50 mg PO (N=725)	Aprepitant+PALO (N=104)	(N=1862)
T Wave evaluation	370 (35.8)	289 (39.9)	26 (25.0)	685 (36.8)
T Wave inversion	137 (13.3)	112 (15.4)	10 (9.6)	259 (13.9)
T Waves biphasic	41 (4.0)	34 (4.7)	5 (4.8)	80 (4.3)
T Waves flat	297 (28.8)	235 (32.4)	17 (16.3)	549 (29.5)
Other	3 (0.3)	0	1 (1.0)	4 (0.2)
U Wave evaluation	6 (0.6)	2 (0.3)	1 (1.0)	9 (0.5)
U Waves	6 (0.6)	2 (0.3)	1 (1.0)	9 (0.5)
Other	0	1 (0.1)	0	1 (0.1)

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Source: Modified from Module 5.3.5.3, ISS Table 5.2.4.1

Percentages are calculated based on the number of patients with in the respective treatment group.

Abbreviations: N= number of patients in treatment group; n=number of patients in treatment group with new abnormality.  
 PALO = palonosetron; AV= Atrio Ventricular; QTcB = QT interval corrected for heart rate according to Bazett's formula  
 QTcF=QT interval corrected for heart rate according to Fridericia's formula.

**Medical Officer's Comment:**

Although there are differences in specific electrocardiographic features it is difficult to interpret these in the setting of multiple confounding factors such as medications, general clinical status, electrolytes, and overall hydration status.

#### 7.4.5 Special Safety Studies/Clinical Trials

None.

#### 7.4.6 Immunogenicity

No applicable.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

NETU-07-07 provides the best opportunity to examine dose dependency for adverse events since three doses of netupitant, given with 0.50 mg oral palonosetron were studied. Most TEAEs were mild in severity and spread among treatment arms (i.e. aprepitant+ 5HT3, netupitant 100+ palonosetron, netupitant 200 + palonosetron, netupitant 300 + palonosetron, and palonosetron alone). Table 89 shows that treatment arms were fairly well matched, particularly with respect to TEAEs that were related to study drug.

Table 89 Patients with TEAEs NETU-07-07

MedDRA SOC	Palo Alone (N=136)	PALO+ 100 NETU (N=135)	PALO+ 200 NETU (N=138)	PALO + 300 NETU (N=136)	Aprepitant (N=134)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
Any TEAE	68 (50.0%)	55 (40.7%)	71 (51.4%)	68 (50.0%)	71 (53.0%)
TEAE related to study drugs	17 (12.5%)	18 (13.3%)	24 (17.4%)	21 (15.4%)	26 (19.4%)
TEAE related to dexamethasone	15 (11.0%)	23 (17.0%)	21 (15.2%)	17 (12.5%)	24 (17.9%)
Any related TEAE	27 (19.9%)	31 (23.0%)	38 (27.5%)	34 (25.0%)	39 (29.1%)
Severe TEAE	7 ( 5.1%)	4 ( 3.0%)	8 ( 5.8%)	8 ( 5.9%)	6 (4.5%)
Severe TEAE related to study drugs	2 ( 1.5%)	0 ( 0.0%)	3 ( 2.2%)	0 ( 0.0%)	4 ( 3.0%)
Severe TEAE related to dexamethasone	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)
Any related severe TEAE	2 ( 1.5%)	0 ( 0.0%)	3 ( 2.2%)	0 ( 0.0%)	4 ( 3.0%)
Serious TEAE	3 ( 2.2%)	1 ( 0.7%)	1 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)
Serious TEAE related to study drugs	0 ( 0.0%)	0 ( 0.0%)	1 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)
Serious TEAE related to dexamethasone	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)
Any serious related TEAE	0 ( 0.0%)	0 ( 0.0%)	1 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)
Deaths	0 ( 0.0%)	1 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)
TEAE leading to study discontinuation	0 ( 0.0%)	1( 0.7%)	1 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)
TEAE related to study drugs leading to study discontinuation	0 ( 0.0%)	0 ( 0.0%)	1 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)
TEAE related to dexamethasone leading to study discontinuation	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)
Any related TEAE leading to study discontinuation	0 ( 0.0%)	0 ( 0.0%)	1 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)

Ref: NETU-07-07, Table 29, p.94.

#### 7.5.2 Time Dependency for Adverse Events

No specific analysis was done to ascertain the time dependency for adverse events.

### 7.5.3 Drug-Demographic Interactions

As noted previously, because NETU-08-18 was comprised almost exclusively of female cancer patients, the cumulative number of female patients overall is greater than male patients. The percentage of patients with at least 1 TEAE in all cycles was slightly lower in the male subgroup than the female subgroup (85.5% and 90.3%, respectively). The most commonly reported TEAEs in males and females overall generally reflected those in the overall safety population: alopecia (23.5% and 52.0%, respectively), neutropenia (26.1% and 41.5%, respectively), leukopenia (15.8% and 23.7%, respectively), asthenia (11.1% and 13.2%, respectively), anemia (17.9% and 10.4%, respectively), headache (6.4% and 12.0%, respectively), and fatigue (9.8% and 11.1%, respectively).

The multicycle Phase 3 studies included more patients < 65 years (1519/1862, 81.6%) than patients ≥ 65 years (343/1862, 18.4%). The percentage of patients with at least 1 TEAE during any cycle was comparable in the subgroups of patients < 65 years of age and patients ≥ 65 years of age overall (89.3%, 1356/1519 patients and 91.5%, 314/343 patients, respectively) and in the netupitant-palonosetron group (89.3%, 749/839 patients vs. 94.8%, 184/194 patients, respectively), with the most commonly reported TEAEs in each of the 2 age subgroups reflecting those in the overall safety population.

The Phase 3 studies included more white patients (1498/1862, 80.5%) than any other race. The second largest race subgroup is Asian patients, which included a total of 268 (14.4%) patients overall. While the netupitant-palonosetron group and the palonosetron group included small numbers of patients from the other race subgroups (total of 7 black, 84 Hispanic or Latino, 1 American Indian/Alaskan Native, 1 Pacific Islander, and 3 other patients), the aprepitant+palonosetron group comprises only white and Asian patients. There were too few patients in these subgroups to make valid comparisons and data for these subgroups are not discussed in the following sections.

### 7.5.4 Drug-Disease Interactions

The sponsor explored TEAEs and ECG results for patients with normal renal function to those in patients with mild and moderate renal impairment. Because the protocol is limited to patients with a serum creatinine ≤1.5 mg/dL or creatinine clearance ≥60 mL/min there were no patients with severe renal disease. No major differences were noted in renally impaired patients compared to patients with normal renal function.

### 7.5.5 Drug-Drug Interactions

In vitro studies have shown that netupitant and its metabolites M1 and M2 are inhibitors of CYP3A4. An in vivo study has confirmed that netupitant is a moderate inhibitor of

CYP3A4. Although netupitant inhibited CYP2C9 in an in vitro study, in vivo relevance of this interaction at the clinical dose of 300mg is not likely.

#### **Dexamethasone**

Co-administration of a single dose of netupitant (300 mg) with a dexamethasone regimen (20 mg on Day 1, followed by 8 mg twice daily from Day 2 to Day 4) significantly increased the exposure to dexamethasone in a time- and dose-dependent manner. When netupitant was co-administered on Day 1, the mean AUC of dexamethasone was increased by 1.7-fold on Day 1 and up to 2.4-fold on Day 2 and Day 4. The pharmacokinetic profile of netupitant was unchanged when administered with dexamethasone.

#### **Midazolam**

The mean C<sub>max</sub> and AUC of midazolam was increased approximately 36% and 126%, respectively, when co-administered with netupitant 300 mg.

#### **Erythromycin**

When co-administered with netupitant 300 mg, the systemic exposure to erythromycin was highly variable and the mean C<sub>max</sub> and AUC of erythromycin was increased 92 % and 56%, respectively.

#### **Oral contraceptives**

AKYNZEO, when given with a single oral dose of 60 µg ethinyl estradiol and 300 µg levonorgestrel had no significant effect on the AUC of ethinyl estradiol, and increased the AUC to levonorgestrel by 46%.

#### **Digoxin**

When a single 450mg dose of netupitant was administered with digoxin at steady-state, no significant changes in digoxin pharmacokinetics were observed. The study was not designed to show the maximal effects with the peak netupitant concentration; therefore, a potential effect on digoxin cannot be ruled out if digoxin is administered when netupitant plasma concentrations are close to the peak plasma concentration around 5 hours post-dose.

#### **Chemotherapeutic agents (docetaxel, etoposide, cyclophosphamide)**

The systemic exposure to chemotherapeutic agents that are metabolized by CYP3A4 tended to be higher when AKYNZEO was co-administered than when chemotherapeutic agents were co-administered with palonosetron only in cancer patients. When co-administered with AKYNZEO the mean C<sub>max</sub> of docetaxel and etoposide was 49% and 10% higher, and the mean AUC of docetaxel and etoposide was increased by 35 % and 28 %, respectively compared to co-administration with palonosetron alone. The mean AUC for cyclophosphamide after co-administration with AKYNZEO was 20% higher compared to when cyclophosphamide was administered with palonosetron alone.

Co-administration of docetaxel, etoposide and cyclophosphamide did not significantly affect the PK of netupitant. Co-administration of etoposide and cyclophosphamide did not significantly affect the PK of palonosetron. When docetaxel was co-administered, the AUC to palonosetron was about 65% higher than when etoposide and cyclophosphamide was co-administered.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

#### **Netupitant**

Long-term studies in animals to evaluate the carcinogenic potential of netupitant have not been performed. Netupitant was not genotoxic in the Ames test, the mouse lymphoma cell mutation test, or the in vivo rat Micronucleus test. Daily oral administration of netupitant in rats at doses up to 30 mg/kg (1.1 times the human AUC in male rats and 2 times the human AUC in female rats at the recommended human dose) had no effects on fertility or reproductive performance.

#### **Palonosetron**

Treatment with palonosetron was not tumorigenic based on results of a 104-week carcinogenicity study in CD-1 mice. The highest tested dose produced a systemic exposure to palonosetron (Plasma AUC) of about 90 to 173 times the human exposure (AUC= 49.7 ng•h/mL) at the recommended oral dose of 0.5 mg. In a 104 week carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30 and 60 mg/kg/day and 15, 45 and 90 mg/kg/day, respectively. The highest doses produced a systemic exposure to palonosetron (Plasma AUC) of 82 and 185 times the human exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the ex vivo hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronucleus test. However it was positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test. Palonosetron at oral doses up to 60 mg/kg/day (about 921 times the recommended human oral dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

See Pharm/Tox review by Dr. Ke Zhang for full details.

### **7.6.2 Human Reproduction and Pregnancy Data**

Adequate and well-controlled studies with AKYNZEO have not been conducted in pregnant women. In animal reproduction studies, no effects on embryo-fetal development were observed following daily administration of netupitant in pregnant rats during the period of organogenesis at doses up to 2.1 times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy. However, a dose-dependent increase in adverse effects on embryo-fetal development was observed following daily administration of netupitant in pregnant rabbits during the period of organogenesis with doses at least 0.1 times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy. Daily administration of netupitant in rats up to 2.1 times the human AUC at the recommended human dose during organogenesis through lactation produced no adverse effects in the offspring. In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed following oral administration during the period of organogenesis at doses up to 921 and 1841 times the recommended human oral dose in rats and rabbits, respectively. AKYNZEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Akynzeo will be given a category C

### **7.6.3 Pediatrics and Assessment of Effects on Growth**

The safety and effectiveness of Akynzeo in patients less than 18 years of age have not been established.

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

#### *Overdose*

There were no accidental overdoses that occurred during the clinical program. In clinical studies in which a higher than proposed market dose was administered adverse events appeared to increase in a dose dependent fashion and consisted of mainly constipation and headache. The risk of overdose is small since the proposed commercial package contains only one capsule.

#### *Drug Abuse Potential*

Animal abuse potential studies with palonosetron/netupitant in combination did not show rewarding properties or abuse-related behaviors. No clinical studies were requested to assess human abuse potential.

### **7.7 Additional Submissions / Safety Issues**

The sponsor has submitted a four-month safety update. No new safety findings were presented. Below are a few articles/abstracts from the safety review. The selection is not comprehensive, and intended only to provide an overview.

In an efficacy and safety study of repeated dosing of netupitant for overactive bladder, the drug did not show benefit over placebo; there were no safety concerns with daily administration of netupitant over 8 weeks.

Three PK studies were done to evaluate the potential drug-drug interaction of netupitant with palonosetron and potential interactions between NEPA (fixed dose combination of netupitant and palonosetron) with ketoconazole or rifampin, and ethinylestradiol/levonorgestrel with NEPA. The results of the studies showed no clinically relevant interactions between netupitant and palonosetron, or between NEPA and oral contraceptives. However the coadministration of NEPA with inhibitors or inducers of CYP3A4 may require dose adjustments, since ketoconazole increased netupitant AUC by 140% and C<sub>max</sub> by 25%. Rifampicin decreased netupitant AUC by 83%.

A study exploring the PK of midazolam, erythromycin and dexamethasone confirmed that netupitant is a moderate inhibitor of CYP3A4, and consequently co-administration with drugs that are substrates of CYP3A4 may require dose adjustments.

A March 2013 abstract from the Indiana University School of Medicine noted that the emetogenicity of the chemotherapeutic agents, repeated chemotherapy cycles, and patient risk factors significantly influence CINV. The use of a combination of a serotonin 5-HT<sub>3</sub> receptor antagonist, dexamethasone and a neurokinin 1 (NK1) receptor antagonist has significantly improved the control of acute and delayed emesis in single-day chemotherapy. Palonosetron, a second-generation 5-HT<sub>3</sub> receptor antagonist with a different half-life, a different binding capacity and a different mechanism of action than the first-generation 5-HT<sub>3</sub> receptor antagonists appears to be the most effective agent in its class. Aprepitant, the first and only agent clinically available in the NK1 receptor antagonist drug class has been used effectively as an additive agent to the 5-HT<sub>3</sub> receptor antagonists and dexamethasone to control CINV. Rolapitant and netupitant are other NK1 receptor antagonists that are currently in phase III clinical trials. Despite the control of emesis, nausea has not been well controlled by current agents. Olanzapine, a US-FDA approved antipsychotic, has emerged in recent trials as an effective preventative agent for CINV, as well as a very effective agent for the treatment of breakthrough emesis and nausea. Clinical trials using gabapentin, cannabinoids and ginger have not been definitive regarding their efficacy in the prevention of CINV.

Additional studies are necessary for the control of nausea and for the control of CINV in the clinical settings of multiple-day chemotherapy and bone marrow transplantation.<sup>2</sup>

## 8 Postmarket Experience

The fixed dose netupitant palonosetron combination capsule has not been marketed. Palonosetron has been marketed since 2003. No specific safety issues have occurred with the palonosetron component of the FDC.

## 9 Appendices

### 9.1 Literature Review/References

A literature search of Pub Med does not reveal any new information on the Netupitant/Palonosetron FDC.

### 9.2 Labeling Recommendations

Below is a summary of the major changes to the clinical section of the sponsor's proposed label.

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<sup>2</sup> Navari RM. Management of chemotherapy-induced nausea and vomiting: focus on newer agent and new uses for older agents. *Drugs*. 2013 Mar; 73(3):249-62.

FDA Proposed	Rationale
<p><b>Indications &amp; Usage</b>            AKYNZEO is a fixed dose combination of netupitant, a substance P/neurokinin 1 (NK<sub>1</sub>) receptor antagonist, and palonosetron, a serotonin-3 (5-HT<sub>3</sub>) receptor antagonist indicated for:            prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy including but not limited to highly emetogenic chemotherapy</p>	<p>Because of changes by ASCO reclassifying AC regimens as HEC, and because in practice a strict distinction between HEC and MEC is not observed, the division changed the I&amp;U section to combine HEC and MEC into one indication, described as "prevention of acute and delayed n&amp;v associated with initial and repeat courses of cancer chemotherapy, including highly emetogenic chemotherapy".</p>
<p><b>6 Adverse Reactions</b>  <b>6.1 Clinical Trials Experience</b></p>	
<p>In a multicycle safety study the safety profile of AKYNZEO was comparable to aprepitant and palonosetron in patients undergoing initial and repeat cycles of chemotherapy, including highly emetogenic chemotherapy.</p>	<p>NETU-10-29 was a multicycle safety study. Efficacy was exploratory. Therefore reference to the study should be in the safety section of the label and not the clinical studies section.</p>
<p><b>14. Clinical Studies</b></p> <p>Major secondary efficacy endpoints included CR for the (b) (4) (acute phase) and for the (b) (4) (delayed phase).            [Removal of (b) (4) reference]</p>	<p>(b) (4)</p>

### 9.3 Advisory Committee Meeting

None.

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