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.

Sponsor:	Helsinn Healthcare SA Via Pian Scairolo 9 6912 Lugano/Pazzallo Switzerland Telephone: +41 91 985 2121 Fax: +41 91 993 2122
Sponsor's Responsible Medical Expert	[redacted]
Sponsor's Study Coordinator	[redacted]
Study/Protocol No.:	NETU-08-18
EudraCT No.:	2009-016775-30
Study Drug/Product Name:	Netupitant/palonosetron
Development Phase:	III
Indication:	Prevention of moderately emetogenic chemotherapy-induced nausea and vomiting
Study Drug Dose	300 mg netupitant/0.50 mg palonosetron
Duration of Treatment	Single dose per chemotherapy cycle
Date of First Enrollment:	21 April 2011
Date of Last Patient Completed:	06 November 2012
Date of Report:	12 June 2013

The study was conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

2. CLINICAL STUDY SYNOPSIS

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Title of Study:
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.

Protocol Number: NETU-08-18

Study Period: **Phase of Development:** III
Date of first enrollment: 21 April 2011
Date of last completed: 06 November 2012

Study Centers: A total of 177 study sites in 15 countries participated in the study.

Publication: Aapro M, Rossi G, Rizzi G, Palmas M and Grunberg S. Phase 3 study of NEPA, a fixed-dose combination of netupitant (NETU) and palonosetron (PALO), versus PALO for prevention of chemotherapy-induced nausea and vomiting (CINV) following moderately emetogenic chemotherapy (MEC). Abstract LBA9514, ASCO 2013.

Objectives:
The primary objective of the study was to compare the efficacy of a single oral dose of a fixed combination of netupitant/palonosetron (300 mg/0.50 mg) with oral dexamethasone versus oral palonosetron 0.50 mg with oral dexamethasone in terms of Complete Response (CR) in the delayed phase (25-120 hours) at cycle 1.
Secondary objectives were:

- To compare the efficacy, safety and tolerability of a single oral dose of a Fixed-Dose Combination (FDC) of netupitant/palonosetron (300 mg/0.50 mg) with oral dexamethasone to oral palonosetron 0.50 mg with oral dexamethasone for the prevention of moderately emetogenic chemotherapy (MEC)-induced nausea and vomiting in initial and repeat cycles.
- To assess the population pharmacokinetics (PK) and pharmacodynamics (PD) of netupitant (and its metabolites M1, M2 and M3) and palonosetron in patients that have received the combination product.

Study Design:

This was a phase III, multicenter, multinational, randomized, double-blind, double-dummy, parallel group, stratified study assessing the efficacy and safety of oral netupitant administered in combination with palonosetron and dexamethasone compared to oral palonosetron and dexamethasone in patients receiving Moderately Emetogenic Chemotherapy (MEC). The stratification criteria were region (United States, Latin America including Mexico, Europe, Commonwealth of Independent States [i.e., former Soviet Republics], and Asia) and age class (<55 years and ≥55 years).

Patients were randomized to receive either the oral netupitant/palonosetron (300 mg/0.50 mg) FDC with oral dexamethasone 12 mg or oral palonosetron 0.50 mg with oral dexamethasone 20 mg preceding the administration of MEC on the first day of cycle 1. After cycle 1, patients could continue in a multiple-cycle extension phase, i.e., they could participate in consecutive repeated chemotherapy cycles (at least 21 days apart from each other) as long as they continued to fulfill the inclusion/exclusion criteria. On Day 1 of each repeat cycle, the patients received the same study drugs as in cycle 1.

During cycle 1, patients participated in the study for a maximum of 37 days (including an up to 14 days screening period, one day of treatment, and a follow-up visit or a telephone call 21±2 days after Day 1). In the multiple-cycle extension, patients participated for a maximum of 30 days in every repeat cycle (including an up to 7 days screening period, one day of treatment, and a follow-up visit or a telephone call 21±2 days after Day 1).

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Number of Patients (planned and analyzed): In this study a total of 1460 patients were planned to be randomized and treated. Patients were planned to be equally distributed (1:1 randomization ratio) in 2 treatment groups of 730 patients each.
The number of patients analyzed (netupitant/palonosetron FDC group vs. palonosetron group) split by study phase and analysis population were:
Cycle 1:

Patient populations	Netupitant/palonosetron FDC	Palonosetron	Overall
Randomized	726 (100.0)	729 (100.0)	1455 (100.0)
Full analysis set (FAS)	724 (99.7)	725 (99.5)	1449 (99.6)
Per-protocol (PP) population	676 (93.1)	684 (93.8)	1360 (93.5)
Safety population	725 (99.9)	725 (99.5)	1450 (99.7)
Multiple-cycle extension:			
Full analysis set (FAS)	635 (87.5)	651 (89.3)	1286 (88.4)
Safety population	636 (87.6)	651 (89.3)	1286 (88.4)

Of the 1455 patients randomized, 5 did not receive study drugs and 39 (2.7%) discontinued from the study prematurely and 498 (34.2%) completed a cycle but did not continue in further cycles. A total of 1438 (98.8%) patients completed cycle 1.

Diagnosis and Main Criteria for Inclusion:

The study population consisted of adult (≥18 years of age) chemotherapy-naïve male or female patients scheduled to receive their first course of an anthracycline and cyclophosphamide MEC regimen for the treatment of a solid malignant tumor. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, fulfill criteria indicating a hematologic and metabolic status adequate for receiving a MEC regimen, and to be able to understand/follow study procedures and complete the patient diary. Female patients of childbearing potential were required to have a negative pregnancy test within 24 hours prior to the first dose of study drugs on Day 1 and to practice an acceptable method of contraception during the study.

Patients could not participate in the study if they experienced vomiting, retching, or mild nausea within 24 hours prior to Day 1, if they were currently using illicit drugs or abusing alcohol, were scheduled to receive any highly emetogenic chemotherapy (HEC) from Day 1 to Day 5 or MEC from Day 2 to Day 5 following the allowed MEC regimen, received (within 1 week prior to Day 1) or were scheduled to receive (between Days 1 to 5 of cycle 1) radiation therapy to the abdomen or pelvis, had symptomatic primary or metastatic central nervous system malignancy or any uncontrolled medical condition that, in the opinion of the investigator, may have confounded the results of the study or posed unwarranted risk in administering the study medication. Females could not be pregnant or lactating.

For inclusion in the multiple-cycle extension, participation had to be considered appropriate by the investigator and could not pose unwarranted risk to the patient. In addition, the patient had to have demonstrated satisfactory study compliance in the preceding chemotherapy cycles and study procedures. Patients entered the multiple cycle extension if receiving the same chemotherapy regimen as at cycle 1 and if they had an adequate metabolic status. Patients could not participate in the multiple-cycle extension if they had an active infection or uncontrolled disease except for malignancy, had started any restricted medications, or had vomiting, retching, or mild nausea within 24 hours prior to Day 1. Females could not be pregnant or lactating.

Test Product, Dose and Mode of Administration, and Lot Number(s):

Netupitant/palonosetron (300 mg/0.50 mg) Fixed-Dose Combination hard gelatin capsules for oral administration; Batch No. (expiry date): [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted])

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Reference Therapy, Dose and Mode of Administration, and Lot Numbers:
Palonosetron 0.50 mg soft gelatin capsules for oral administration; Batch No. (expiry date): [redacted]

Additional Study Drug:
Dexamethasone 4 mg tablets for oral administration; Batch No. (expiry date): [redacted]

Placebo:
For blinding of the study medication in a double-dummy fashion, the following were used:
Placebo hard gelatin capsules matching netupitant/palonosetron hard gelatin capsules for oral administration; Batch No. (expiry date): [redacted]
Placebo soft gelatin capsules matching palonosetron soft gelatin capsules for oral administration; Batch No. (expiry date): [redacted]
Placebo tablets matching dexamethasone tablets 4 mg for oral administration; Batch No. (expiry date): [redacted]

Timing and Duration of Treatment:
For each cycle, oral netupitant/palonosetron (and placebo for oral palonosetron) or oral palonosetron (and placebo for oral netupitant/palonosetron) were administered 60 minutes prior to the start of chemotherapy on Day 1 of each cycle. Oral dexamethasone/placebo tablets were administered 30 minutes prior to the start of chemotherapy on Day 1 of each cycle.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the proportion of patients with CR (defined as no emesis, no rescue medication) in the delayed phase (time interval 25-120 hours after the start of the MEC administration) at cycle 1.

Key secondary efficacy endpoints were defined at cycle 1 as the proportion of patients with:

- CR during the acute phase (0-24 hours).
- CR during the overall phase (0-120 hours).

Other secondary efficacy endpoints were defined at cycle 1 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 (Visual Analogue Scale [VAS] <25 mm) during the delayed, acute, and overall phase.
- No nausea (VAS <5 mm) during the delayed, acute, and overall phase.
- Complete protection (no emesis, no rescue medication and no significant nausea [maximum nausea VAS <25 mm]) during the delayed, acute, and overall phase.
- Total control (no emesis, no rescue medication and no nausea [maximum VAS <5 mm]) during the delayed, acute, and overall phase.

Other efficacy endpoints at cycle 1 were defined as follows:

- 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, and time to treatment failure (based on time to the first emetic episode or time to the first rescue medication intake, whichever occurs first).
- Impact on patients' daily life activities for the first 120 hours following the administration of MEC as assessed by the Functional Living Index-Emesis (FLIE) questionnaire.

Secondary efficacy endpoints evaluated during the multiple-cycle extension were the proportion of patients with:

- CR during the delayed, acute, and overall phase following subsequent cycles of MEC.
- No significant nausea during the delayed, acute, and overall phase following subsequent MEC cycles.

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Safety: Safety assessments included physical examination, vital signs, 12-lead electrocardiogram (ECG), Left Ventricular Ejection Fraction (LVEF), cardiac Troponin I (cTnI) levels, laboratory tests (hematology, blood chemistry, urinalysis) and Adverse Events (AEs).

Population pharmacokinetics and pharmacodynamics: Details on the population PK and PD of netupitant (and its metabolites M1, M2 and M3) and palonosetron are described in a separate study report (NETU-10-02).

Statistical Methods:

Efficacy: The number and percentage of patients with CR by treatment group and the difference in response rate between the treatment groups was summarized. The 95% Confidence Interval (CI) for the response rate (using the Wilson score method) and for the difference in response rate (using Newcombe-Wilson's method) were also provided. The primary analysis was performed on the FAS using a 2-sided stratum adjusted Cochran Mantel Haenszel (CMH) test including treatment, age class and region as strata. All missing data were imputed as treatment failures, following the worst case principle. The null hypothesis of no difference between treatments was to be rejected, and the superiority of the fixed combination versus oral palonosetron alone 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. The ORs and the 2-sided 95% CI for the ORs from the CMH test were presented.

Key and other secondary efficacy endpoints were analyzed in the same way. To avoid type I error inflation, a hierarchical approach to testing was used. Once the null hypothesis of no treatment difference for the primary efficacy endpoint was rejected (i.e., primary study objective was met), further confirmatory statistical tests were performed on key secondary efficacy endpoints in the following order: CR in the acute phase, followed by CR in the overall phase (tested only if the fixed oral combination was superior to oral palonosetron for CR in the acute phase).

The other secondary efficacy endpoints (no emesis, no rescue medication intake, no nausea, no significant nausea, complete protection and total control) were grouped together into families by phase (delayed, acute, and overall). Each family was tested only if the fixed combination demonstrated superiority versus oral palonosetron for CR for that phase. Results of analyses for other efficacy endpoints were interpreted descriptively with nominal p-values.

Safety: All safety analyses were performed for the safety population for cycle 1 and the multiple-cycle extension. The incidence of Treatment-Emergent Adverse Events (TEAEs), defined as an AE that begins or worsens in severity after the start of the first administration of the study drug, in each treatment group was presented overall, by system organ class and preferred term, and additionally grouped by severity and relationship to the study drug. TEAE relationship was summarized separately for events related to study drugs (netupitant/palonosetron, palonosetron), events related to dexamethasone, and overall (i.e., related to study drugs or dexamethasone). The number of patients with serious TEAEs and the number of patients with TEAEs leading to discontinuation of study were summarized. All AEs were listed.

Laboratory data were summarized as follows: descriptive statistics for observed values and change from baseline (and the same cycle 'screening' for cycle 2 onwards), shift tables from baseline (and the same cycle 'screening' for cycle 2 onwards) with respect to normal ranges, and tabulation of the number of patients with at least one marked abnormality (National Cancer Institute Common Toxicology criteria [NCI CTC] grade ≥3) for selected hematology and blood chemistry parameters with respect to normal ranges. All data were listed.

cTnI levels were summarized for each visit by treatment for cycle 1 and the multiple cycle extension using descriptive statistics. All troponin levels were listed.

ECG data were summarized highlighting differences from baseline (and the same cycle 'pre-dose reference value' for cycle 2 onwards) for quantitative variables and frequencies of treatment-emergent abnormalities. An outlier analysis was performed to show the number of patients who met pre-specified criteria. Physical examination, vital signs and left ventricular ejection fraction data were summarized using descriptive statistics, in addition to being listed.

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Efficacy Results:

This study demonstrated the superiority of the netupitant/palonosetron (300 mg/0.50 mg) FDC over palonosetron alone with respect to the primary, CR in the delayed phase, and both key secondary, CR in the acute and overall phases after the administration of moderately emetogenic chemotherapy during the first chemotherapy cycle.

Cycle 1 Results

During the first chemotherapy cycle, the CR rate in the delayed phase was 7.4% higher (76.9% vs. 69.5%) in the netupitant/palonosetron FDC group than in the palonosetron alone group (from CMH test: OR: 1.48, p=0.001). The results of the PP population supported these results. For the key secondary endpoints, the proportion of patients with CR in the acute phase was 3.4% higher in the netupitant/palonosetron FDC than in the palonosetron alone group (88.4% vs. 85.0%; from CMH test: OR: 1.37, p=0.047) and in the overall phase the CR rate was 7.7% higher in the netupitant/palonosetron FDC than in the palonosetron alone group (74.3% vs. 66.6%; from CMH test: OR: 1.47, p=0.001).

Table 1 Complete Response Rate for the Delayed, Acute and Overall Phases of Cycle 1 – FAS

	NETU/PALO FDC (N=724)	PALO alone (N=725)
Delayed		
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[a]	0.001	
Acute		
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[a]	0.047	
Overall		
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[a]	0.001	

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

In general, the results of the secondary endpoints consistently supported those of the primary and key secondary endpoints for the delayed and overall phases.

In particular, a statistically significantly greater proportion of patients in the netupitant/palonosetron FDC group compared with the palonosetron alone group had no emesis in the delayed (81.8% vs. 75.6%; p=0.004), acute (90.9% vs. 87.3%; p=0.025) and overall (79.8% vs. 72.1%; p<0.001) phases. There was a statistically significantly greater proportion of patients in the netupitant/palonosetron FDC group compared with the palonosetron alone group who did not take rescue medication in the delayed (85.8% vs. 80.6%; p=0.007) and overall (84.0% vs. 79.0%; p=0.014) phases, but this difference was not significant in the acute phase.

Although a slightly higher proportion of patients had no nausea in the netupitant/palonosetron FDC group in the delayed, acute and overall phases, there was no statistically significant difference between the netupitant/palonosetron and the palonosetron groups. However, there was a statistically significantly greater proportion of patients in the netupitant/palonosetron FDC group than in the palonosetron alone group with no significant nausea in the delayed (76.9% vs. 71.3%; p=0.014) and overall (74.6% vs. 69.1%; p=0.020) phases.

Complete protection rates were statistically significantly higher in the netupitant/palonosetron group compared to the palonosetron group in the delayed (67.3% vs. 60.3%; p=0.005) and overall (63.8% vs. 57.9%; p=0.020) phases, but not in the acute phase. Total control rates were higher in the

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netupitant/palonosetron group than the palonosetron group for the delayed (51.5% vs. 46.9%; p=0.077) and overall (48.3% vs. 44.0%; p=0.095) phases but the test failed to reach statistical significance.

The results of the other efficacy endpoints corroborated the overall results of the study.

Multiple Cycle Extension Results

During the multiple-cycle extension, the CR rates were consistently higher for the netupitant/palonosetron FDC than for palonosetron alone in each phase up to cycle 6. Similarly, the percentage of patients with no significant nausea was higher in the netupitant/palonosetron group than the palonosetron group in each phase and each cycle up to cycle 6.

Safety Results:

For each parameter data are presented for cycle 1 and then for multiple cycle extension.

In cycle 1, the proportion of patients with at least one TEAE was 76.0% in the netupitant/palonosetron group compared with 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 FDC 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 overall were alopecia (34.9%) and neutropenia (24.5%) in cycle 1 and in the multiple-cycle extension (23.6% and 36.1%, respectively). These unpleasant effects, observed in the framework of cancer patients on treatment with cytotoxic agents, are expected and do not raise any particular safety concern.

The most frequent TEAEs reported as related to study drugs were constipation (in 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).

Two patients died during the study, both in the palonosetron group. One patient experienced 2 serious TEAEs resulting in death in cycle 1: acute cardiac failure and acute respiratory failure. One patient in the multiple-cycle extension died due to progression of metastatic breast cancer during cycle 3. These events were not related to study drugs or dexamethasone.

The overall proportion of patients experiencing serious TEAEs was low in both the netupitant/palonosetron and palonosetron alone groups in cycle 1 (1.8% vs. 1.7%) and in the multiple-cycle extension (3.6% vs. 2.3%), with similar rates observed in both treatment groups. In cycle 1, none of the serious TEAEs were assessed by the investigator as being related to study drugs or to dexamethasone, while in the multiple-cycle extension none was related to study drugs and four events were considered related to dexamethasone.

The overall proportion of patients who experienced TEAEs leading to discontinuation was low in cycle 1 (0.8%); for two of these patients, both in the palonosetron group, events were assessed as related to study drug and to dexamethasone, respectively. The proportion of patients who experienced TEAEs leading to discontinuation also remained low in the multiple-cycle extension (1.8%), as well as the number of patients experiencing events that were assessed as being related to study drugs and or to dexamethasone (overall 4 patients, all in the palonosetron group).

Upon regulatory request, particular attention was paid to a number cardiac, CNS and psychiatric adverse events, defined as ‘events of special interest’ in the present document. Medical review of the cardiovascular events, identified based on pre-defined standard MedDRA Queries (SMQs) and considered of special interest, resulted in a total of 23 non-serious related AEs in 12 patients (1.7% of all patients) in the netupitant/palonosetron FDC group, whereas 6 non-serious related AEs were reported in 5 patients (0.7% of all patients) in the palonosetron alone group. In both treatment groups the majority of these events were ECG findings judged to be of mild intensity. None was considered severe in intensity and most resolved

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spontaneously without specific therapy. The evaluation of any adverse event indicative of a potential drug abuse resulted in the identification of two TEAEs experienced by two patients (0.1%), both in the netupitant/palonosetron FDC group: one was the occurrence of visual hallucination, one of mood alteration. Besides these two cases, based on the pre-defined SMQs for identification of potential CNS or psychiatric events of special interest, no additional medical condition or cluster of events was indicative of any abuse potential of the netupitant/palonosetron FDC.

Across all cycles results of hematology and blood chemistry parameters do not point to particular safety issues. The spectrum of laboratory changes observed during the study is typical of the complications following exposure to chemotherapy. As expected the proportion of patients with anemia, neutropenia, leucopenia, thrombocytopenia throughout the study was comparable in both treatment groups. Hyperglycemia related to dexamethasone was also reported in a similar percentage of patients.

Analysis of vital signs did not reveal any clinical concerns.

Central review of the ECG data indicated that most patients had QTc interval values within normal limits. Overall, the mean QT/QTc, QTcB and QTcF changes at 5 and 24 hours versus pre-dose were comparable in both treatment groups. These prolongations were transient and all values returned to pre-dose measurement or even below within 120 hours post-dosing across all cycles. An outlier analysis showed that the proportion of patients with QTcF increases from same cycle pre-dose to >500 ms was low in the netupitant/palonosetron and palonosetron groups from cycle 1 (one patient in each treatment group [0.1%]) through to cycle 6 (1 [0.5%] vs. 2 [1.0%]). Moreover, the proportion of patients with QTcF increases of >60 ms from same cycle pre-dose was also low in both the netupitant/palonosetron FDC group and in the palonosetron alone group at cycle 1 (5 [0.7%] vs. 6 [1.1%]) and through cycle 6 (3 [1.5%] vs. 5 [2.6%]). In cycle 1, the most frequently reported treatment emergent ECG abnormalities were flat T waves (12.6% vs. 12.1%), followed by ST depression (6.5% vs. 6.5%). Only 1 (0.1%) patient in the netupitant/palonosetron FDC group had a new abnormal U wave. In the multiple cycle extension, the most frequently reported treatment emergent ECG abnormalities were flat T waves (33.5% vs. 30.3%), followed by sinus tachycardia (24.7% vs. 20.9%). Only 5 patients, 3 (0.5%) in the netupitant/palonosetron FDC group and 2 (0.3%) in the palonosetron group, had new abnormal U waves. Recommended assessment criteria that could indicate a potential safety signal include a change in QTcF from baseline to >500 ms in more than 5% of patients and from baseline of >60 ms in more than 15% of patients. Hence, the above results, together with the very low proportion of patients with new abnormal U waves across treatment cycles indicate a satisfactory cardiac safety profile for the netupitant/palonosetron FDC.

Overall there were 48 patients with post-dose high troponin values; 26 (3.5%) in the netupitant/palonosetron FDC group and 22 (3.0%) in the palonosetron alone group. In the majority of cases, high troponin values developed after several cycles of anthracycline-cyclophosphamide based chemotherapy (cycle 5 and 6). Mean LVEF (assessed by ECHO) changes from screening to end of study were negligible and comparable between treatment groups.

The results obtained in this study demonstrated that the netupitant/palonosetron FDC capsule, given with dexamethasone to cancer patients before receiving anthracycline/cyclophosphamide based emetogenic chemotherapy, has a favorable safety profile in cycle 1 and over repeated cycles of chemotherapy.

The fixed dose combination represents a valid and safe therapeutic option for patients prior to receiving moderately emetogenic chemotherapy.

Conclusions:

This study demonstrated the superiority of the netupitant/palonosetron (300 mg/0.50 mg) FDC over palonosetron alone with respect to the primary, CR in the delayed phase, and both key secondary endpoints, CR in the acute and overall phases after the administration of moderately emetogenic chemotherapy during the first chemotherapy cycle.

These findings are well supported by the analyses of the secondary and other efficacy endpoints.

The difference in efficacy between treatment groups in favour of the netupitant/palonosetron FDC was maintained across multiple consecutive treatment cycles up to cycle 6.

The safety profile observed in this study was as expected due to TEAEs in the context of cancer patients

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receiving treatment with cytotoxic chemotherapy, with the most common TEAEs being neutropenia and alopecia. 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.

For neither of the 2 (0.3%) patients who died during the study death was related to study drugs or dexamethasone. Serious TEAEs were rare and none were related to the study drugs.

Based on the evaluation of CNS and psychiatric events, no clustering 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.

The safety results in this study demonstrated that the netupitant/palonosetron FDC capsule, given with dexamethasone to cancer patients before receiving moderately emetogenic chemotherapy, is generally safe with no worsening of the safety profile when patients are exposed to multiple cycle treatment.

Date of Report: 12 June 2013