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.

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Sponsor's Responsible Medical Expert:	[redacted], [redacted]
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Study/Protocol No.:	NETU-10-29
EudraCT Number:	2010-023297-39
Study Drug or Product Name:	Netupitant/palonosetron
Development Phase:	III
Indication:	Prevention of highly or 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:	20 July 2011
Date of Last Patient Completed:	12 September 2012
Date of Report:	05 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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Name of Active Ingredients: **Netupitant/Palonosetron Fixed-Dose Combination**	
Title of Study: 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.	
Protocol Number: NETU-10-29	
Study Period:	**Phase of Development:** III
Date of first enrollment: 20 July 2011	
Date of last completed: 12 September 2012	
Study Centers: A total of 72 study sites in 10 countries participated in the study.	
Publications: 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 assess the safety and tolerability of a single oral dose of a Fixed-Dose Combination of netupitant and palonosetron (300 mg/0.50 mg) in initial and repeated cycles of chemotherapy. The secondary objective of the study was: • To describe the efficacy of a single oral dose of a fixed dose combination of netupitant and palonosetron (300 mg/0.50 mg) with oral dexamethasone during the acute (0-24 hours), delayed (25-120 hours) and overall (0-120 hours) phases of initial and repeated cycles of chemotherapy.	
Study Design: This was a multicenter, multinational, randomized, active-controlled, double-blind, double-dummy, unbalanced (3:1), parallel group, stratified study assessing the safety and describing the efficacy of a single oral dose of a fixed dose combination (FDC) of netupitant and palonosetron (300 mg/0.50 mg) given with oral dexamethasone versus the antiemetic regimen with aprepitant, palonosetron and dexamethasone prior to repeated cycles of highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC). Although no formal comparison was planned with the randomized control group of oral aprepitant 125 mg, palonosetron 0.5 mg and dexamethasone, the presence of a concurrent control group in the same patient population was included in the study to help interpreting any unexpected safety finding that might have emerged in fixed combination group. For the same reason variables were minimized by choosing the same 5-HT3 receptor antagonist in both study groups. The stratification criteria were chemotherapy emetogenicity (MEC, HEC) and gender (male, female). Patients were randomized in an unbalanced ratio (3:1) on Day 1 of their first chemotherapy cycle before administration of MEC or HEC to one of the following treatment groups: • Oral netupitant/palonosetron FDC (300 mg/0.50 mg) and dexamethasone 12 mg on Day 1 of each cycle, followed by dexamethasone 8 mg on Days 2-4 (HEC patients only). • Oral aprepitant 125 mg, palonosetron 0.50 mg and dexamethasone 12 mg on Day 1 of each cycle, followed by aprepitant 80 mg on Days 2-3, and dexamethasone 8 mg on Days 2-4 (HEC patients only). There was no limit in the number of repeat consecutive cycles for each patient. The study was to be closed after the last patient enrolled had completed his/her last scheduled chemotherapy cycle. During each cycle, patients participated in the study for a maximum of 2-5 weeks according to chemotherapy schedule, including a screening period of up to 14 days, an evaluation period of 6 (+2) days of which 3 (if administered with MEC) to 4 days (if administered with HEC) were on active treatment, and a follow-up visit or a telephone call 14 (-3) to 21 (+2) days after Day 1, based on the schedule of the subsequent chemotherapy cycle.	

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Number of Patients (planned and analyzed): The study planned to randomize a total of 400 patients. According to a randomization ratio of 3:1, 300 patients (approximately 225 MEC patients and 75 HEC patients) were to be treated with netupitant/palonosetron FDC and 100 patients (approximately 75 MEC patients and 25 HEC patients) with the aprepitant+palonosetron regimen.
The number of patients analyzed (netupitant/palonosetron FDC group and aprepitant+palonosetron group) is provided below:

Patient Populations	Netupitant/palonosetron FDC	Aprepitant+ Palonosetron	Overall
Randomized	309 (100.0)	104 (100.0)	413 (100.0)
Full analysis set (FAS)	309 (100.0)	103 (99.0)	412 (99.8)
Safety population	308 (99.7)	104 (100.0)	412 (99.8)

Of the 413 patients randomized, one patient randomized to the aprepitant+palonosetron group did not receive study treatment and was excluded from the FAS and safety population.
A total of 413 patients were randomized into two treatment groups, of whom 412 patients (312 MEC and 100 HEC patients) were treated with study medication, 405 (98.1%) completed cycle 1 and 165 (40.0%; 122 patients in the netupitant/palonosetron FDC group) completed cycle 6.

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 repeated consecutive courses of HEC (any single intravenous dose of one or more of the following agents: cisplatin, mechlorethamine, streptozocin, cyclophosphamide ≥1500 mg/m^2, carmustine, dacarbazine) or MEC (any single intravenous dose of one or more of the following agents: oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin, cyclophosphamide I.V. <1500 mg/m^2, cytarabine I.V. >1 g/m^2, azacidine, alemtuzumab, bendamustine, or clofarabine) for the treatment of a 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 ch emotherapy regimen, and to be able to read, understand and 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 drug on Day 1 of each cycle and to practice an acceptable method of contraception during the study.
Patients could not participate in the study if they were currently using illicit drugs or abusing alcohol, were scheduled to receive cyclophosphamide I.V. (500 to 1500 mg/m^2) in combination with doxorubicin (≥40 mg/m^2) or epirubicin (≥60 mg/m^2), or any MEC or HEC from Day 2 to D ay 5 following Day 1 chemotherapy administration, had previously received a Neurokinin 1 receptor antagonist, had a history or predisposition to cardiac conduction abnormalities (except for incomplete right bundle branch block) or risk factors for Torsade de Point, had any uncontrolled medical condition that may have confounded the results of the study or posed unwarranted risks in administering the study medication. Females could not be pregnant or lactating.

Test Product, Dose and Mode of Administration, and Lot Number(s):
Netupitant/palonosetron fixed dose combination (300 mg/0.50 mg) hard gelatin capsules for oral administration; Batch No. (expiry date): [redacted].
Reference Therapy, Dose and Mode of Administration, and Lot Number(s):
Aprepitant 125 mg and 80 mg hard gelatin capsules for oral administration; Batch No. (expiry date): [redacted].
Palonosetron 0.50 mg soft gelatin capsules for oral administration; Batch No. (expiry date): [redacted].

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Additional Study Drug:
Dexamethasone 4 mg tablets for oral administration; Batch No. (expiry date): [redacted] ([redacted] and [redacted]), [redacted] ([redacted]), [redacted] ([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] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]).
Placebo hard gelatin capsules matching aprepitant soft gelatin capsules for oral administration; Batch No. (expiry date): [redacted] ([redacted] and [redacted]), [redacted] ([redacted]).
Placebo soft gelatin capsules matching palonosetron soft gelatin capsules for oral administration; Batch No. (expiry date): [redacted] ([redacted] and [redacted]), [redacted] ([redacted]) [redacted] ([redacted]).

Timing and Duration of Treatment: Oral netupitant/palonosetron (and placebo for oral aprepitant and palonosetron) or oral aprepitant 125 mg and palonosetron (and placebo for oral netupitant/palonosetron) (a total of 3 capsules in each treatment group) were administered 60 minutes prior to the start of chemotherapy on Day 1 of each cycle. Oral dexamethasone tablets (3 tablets) were administered 30 minutes prior to the start of chemotherapy on Day 1 of each cycle. One capsule of 80 mg aprepitant or placebo was taken in the morning on Days 2 and 3. Two 4 mg dexamethasone tablets were to be taken on Days 2, 3 and 4 in the morning by HEC patients only.
The overall duration of study participation for each patient was 2-5 weeks per cycle according to chemotherapy schedule.

Criteria for Evaluation:
Efficacy: Efficacy endpoints were defined as the proportion of patients with:
- Complete Response (CR) during the delayed, acute, and overall phase.
- No significant nausea during the delayed, acute, and overall phase.

Safety: Safety was primarily assessed by means of adverse events (AEs). Additional safety assessments included physical examination, vital signs, 12-lead Electrocardiogram (ECG), Left Ventricular Ejection Fraction (LVEF), Cardiac Troponin I (cTnI) levels, and laboratory tests (hematology, blood chemistry, urinalysis).

Statistical Methods:
Efficacy: The assessment of efficacy was a secondary objective of the study. Only descriptive statistics were planned for the efficacy endpoints. The efficacy analyses were performed on the Full Analysis Set (FAS) population. The number and percentage of patients with CR and no significant nausea in each phase (delayed, acute and overall) by treatment group and chemotherapy emetogenicity 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) was also provided.
The data were also summarized by treatment and gender. A frequency table for patients taking rescue antiemetic medications was provided by treatment.
Safety: All safety analyses were performed for the safety population. Safety analyses are presented by treatment and chemotherapy emetogenicity and additionally by treatment and gender for the whole study and for each cycle. 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 treatment. The number of patients with serious TEAEs and the number of patients with TEAEs leading to discontinuation of study drug were summarized. All AEs were listed.

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Laboratory data were summarized as follows: descriptive statistics for observed values and change from baseline (and same cycle screening for cycle 2 onwards), shift tables from baseline (or 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. All data were listed. ECG data were summarized highlighting differences from baseline (and 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 depict 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.

Efficacy Results:

In cycle 1, the proportion of patients with CR was numerically higher for the netupitant/palonosetron FDC group than in the aprepitant+palonosetron group in the delayed (83.2% vs.77.7%) and overall phases (80.6% vs.75.7%), with differences of 5.5% and 4.9%, respectively, while the CR rates were similar between these treatment groups in the acute phase (92.9% vs.94.2%, difference of -1.3%). The proportion of patients with no significant nausea in the netupitant/palonosetron FDC and in the aprepitant+palonosetron group was generally similar in the delayed (85.1% vs. 81.6%), overall (84.1% vs. 80.6%) and acute (90.6% vs. 93.2%) phases, with a difference between treatment groups of 3.6% both in the delayed and overall phases and of -2.6% in the acute phase.

Efficacy based on CR and no significant nausea was maintained throughout all study cycles at levels similar to that observed in cycle 1. In cycles 2 to 6, the proportion of patients with CR was consistently numerically higher for the netupitant/palonosetron FDC group than the aprepitant+palonosetron group in the delayed and overall phases. Results in the acute phase were more similar between groups. The same trend was also observed for no significant nausea in cycles 3 to 6, while in cycle 2 the values were more similar in all phases between treatment groups.

In summary, the netupitant/palonosetron FDC combined with dexamethasone shows high response rates in the prevention of nausea and vomiting, in the delayed, acute and overall phases of initial and repeated cycles of chemotherapy.

Safety Results:

The two treatment groups were comparable with respect to demographic and other baseline characteristics, except for a higher percentage of patients with lung and respiratory tract cancers (39.6% vs. 30.8%) and with metastatic cancers (51.9% and 43.3%) in the netupitant/palonosetron FDC compared with the aprepitant+palonosetron group. Moreover, the proportion of patients with concomitant diseases during the study was higher in the netupitant/palonosetron FDC group (78.2%) than in the aprepitant+palonosetron group (61.5%).

During cycle 1, 75.7% of patients overall received MEC, with carboplatin and oxaliplatin being the most common chemotherapeutic agent in both groups, and 24.3% of patients received HEC, with cisplatin being the most common chemotherapeutic agent in both treatment groups. There were no notable differences between the two treatment groups for any chemotherapy, in any cycle.

Throughout the study, the percentage of patients with at least one TEAE was 86.0% in the netupitant/palonosetron FDC group and 91.3% in the aprepitant+palonosetron group. The proportion of patients with TEAEs related to study drugs was relatively low in both treatment groups (10.1% in the netupitant/palonosetron FDC group and 5.8% in the aprepitant+palonosetron group). TEAEs assessed as being related to dexamethasone were 11.7% in the netupitant/palonosetron FDC and 14.4% in the aprepitant+ palonosetron group.

The type, frequency and intensity of TEAEs were comparable across treatment groups throughout the

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study.

The percentage of patients who experienced at least one TEAE tended to decrease over the first 6 cycles, from 63.8% (cycle 1) to 34.1% (cycle 6). This could be potentially attributable to the worsening of patients' clinical condition, subsequent discontinuation of chemotherapy and a relatively better health condition in patients qualifying for study continuation and finally to the reporting of less TEAE. s. Similarly, there was a decrease in the percentage of patients in the netupitant/palonosetron FDC and aprepitant+palonosetron groups with events related to study drugs (4.6% to 1.2%) and to dexamethasone (8.0% to 1.8%) from cycle 1 to 6.

Overall, for all cycles, blood and lymphatic system disorders, gastrointestinal disorders, skin and subcutaneous tissue disorders, general disorders and administration site conditions were the most commonly reported SOCs. The most commonly reported TEAEs overall were neutropenia (30.1%), alopecia (26.5%), anaemia (20.4%) and leukopenia (17.7%). These unpleasant effects are expected in the framework of cancer patients on treatment with cytotoxic agents .

The most frequent TEAE reported as related to study drugs was constipation, which was observed in 2.3% of patients in cycle 1 and in 2.5% of patients in cycle 2 in the netupitant/palonosetron FDC group.

Seventeen (4.1%) patients died during the study. None of the deaths was related to study drugs. Sixteen (5.2%) patients in the netupitant/palonosetron FDC group and one (1.0%) patient in the aprepitant+palonosetron group experienced TEAEs leading to death or discontinued the study due to death, with the most common reason being disease progression. Therefore, the number of deaths observed in the netupitant/palonosetron FDC group is likely attributable to the greater proportion of patients with lung and respiratory cancers as well as metastatic cancers in this group.

The incidence of serious TEAEs was comparable between the two treatment groups (16.2% and 18.3%) and the majority of the events were associated with the patients' underlying medical conditions or were complications following exposure to chemotherapeutic agents. Only two patients in the netupitant/palonosetron FDC group experienced serious TEAEs that were related to study drug: ventricular extrasystoles and acute psychosis (which was assessed by the investigator to be related to study drug and to dexamethasone). The overall proportion of patients who experienced TEAEs leading to discontinuation was similar between the two treatment groups, and only two (0.6%) patients in the netupitant/palonosetron FDC group experienced any drug-related TEAEs leading to discontinuation.

Particular attention was paid to selected CNS, psychiatric and cardiac adverse events, defined as 'events of special interest'. This was not done due to specific safety concerns, rather to fulfill a r egulatory requirement. The assessment of CNS and psychiatric adverse events, aimed at detecting signals of any abuse potential, as well as of cardiac adverse events does not raise any safety concern for the netupitant/palonosetron FDC.

The analysis of abnormalities in hematology and blood chemistry parameters did not reveal any unexpected trends and did not raise safety concerns. The spectrum of laboratory changes observed during the study is generally consistent with the side effects of chemotherapy.

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 FDC and in the aprepitant+palonosetron groups from cycle 1 (1 [0.3%] patient in the netupitant/palonosetron FDC group) through to cycle 6 (one [0.3%] patient each in cycle 3 and 4 in the netupitant/palonosetron FDC group and one [2.3%] patient in in cycle 6 t he aprepitant+palonosetron

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group). Moreover, the proportion of patients with QTcF increases of >60 ms from same cycle pre dose was also low both in the netupitant/palonosetron FDC group and in the aprepitant+palonosetron group at cycle 1 (1 [0.3%] vs. 1 [1.0%]) and through cycle 5 (1 [0.6%] patient in the netupitant/palonosetron FDC group); no patients had an increase of >60 ms in cycle 6. Overall the most frequently reported treatment emergent ECG abnormalities in the netupitant/palonosetron FDC and aprepitant+palonosetron groups were flat T waves (in 16.9% and 13.5%, respectively), followed by ST depression (11.7% vs. 16.3%). Only 2 (0.6%) patients in the netupitant/palonosetron FDC group and 1 (1.0%) patient in the aprepitant+palonosetron group had a new abnormal U wave. There was little change in either treatment group in the number of patients with outliers at subsequent treatment cycles. 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 to 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.

In total, 10 patients had cardiac troponin (cTnI) values ≥0.12 ng/mL and were eligible to enter a cardiovascular safety follow-up, 7 (2.3%) in the netupitant/palonosetron FDC and 3 (2.9%) in the aprepitant+palonosetron group; of these, only 3 patients (two (0.6%) in the netupitant/palonosetron FDC group and one (1.0%) in the aprepitant+palonosetron group) had cTnI levels ≥0.50 ng/mL. Of the patients entering the within-study cardiovascular follow-up, LVEF (assessed by ECHO) ranged from 46% to 65% and was comparable between treatment groups.

Overall, the safety data from this study demonstrated that administration of a single oral dose of the netupitant/palonosetron (300 mg/0.50 mg) FDC to cancer patients in initial and repeated cycles of emetogenic chemotherapy is generally safe and well tolerated.

Conclusions: The safety profile observed in this study was as expected in the context of patients receiving treatment with cytotoxic chemotherapy. The results support the conclusion that a fixed combination of netupitant and palonosetron is safe and well tolerated in patients undergoing initial and repeat cycles of MEC or HEC. In addition, netupitant/palonosetron FDC had high CR rates in the delayed, acute and overall phases of initial and repeated cycles of chemotherapy, with a similar efficacy to aprepitant+palonosetron in the prevention of CINV.

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