26 March 2015
EMA/236963/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Akynzeo

International non-proprietary name: netupitant / palonosetron

Procedure No. EMEA/H/C/003728/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Administrative information

Name of the medicinal product:	Akynzeo
Applicant:	Helsinn Birex Pharmaceuticals Ltd. Damastown, Mulhuddart Dublin 15 Ireland
Active substance:	netupitant / palonosetron hydrochloride
International Nonproprietary Name/Common Name:	netupitant / palonosetron
Pharmaco-therapeutic group (ATC Code):	Antiemetics and antinauseants (A04AA55)
Therapeutic indication(s):	Akynzeo is indicated in adults for the: - Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin based cancer chemotherapy. - Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.
Pharmaceutical form:	Capsule, hard
Strengths:	300 mg / 0.50 mg
Route of administration:	Oral use
Packaging:	blister (alu/alu)
Package size:	1 capsule

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List of abbreviations

5-HT	5-hydroxytryptamine, serotonin
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ASMF	Active substance master file
AST	aspartate aminotransferase (SGOT)
ATC	Anatomical-Therapeutic-Chemical classification
BCS	Biopharmaceutics Classification System
BHA	Butylated hydroxyanisole
BID	bis in diem (twice daily)
CEP	Certification of suitability of European Pharmacopoeia monographs
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human use
CVMP	Committee for Medicinal Products for Veterinary use
CI	confidence interval
CINV	chemotherapy-induced nausea and vomiting
CK	creatine kinase
CPMP	Committee for Proprietary Medicinal Products
CR	complete response
CR 0-120	complete response during 0-120 hours after cisplatin administration
CRA	clinical research associate
CRF	case report form
CRO	Contract Research Organization
CRR	Cumulative Response Rate
CTCAE	Common Terminology Criteria for Adverse Events
CTC	common toxicity criteria
CYP3A4	cytochrome P450 3A4
EC	Ethics Committee
EC	European Commission
EU	European Union
ECG	electrocardiogram
EMA	European Medicines Agency

FAS	full analysis set
FDA	Food and Drug Administration (United States)
FDC	Fixed dose combination
GC	Gas chromatography
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HEC	Highly emetogenic chemotherapy
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IP	intra-peritoneal
IR	Infrared
ISR	Incurred Sample Reanalysis
IV	intravenous
IVRS	interactive voice response system
KF	Karl Fischer titration
kg	kilogram(s)
KM	Kaplan-Meier
L	litre
MAH	Marketing authorisation holder
MASCC	Multinational Association of Supportive Care in Cancer
MCE	Multiple-cycle extension
MEC	Moderately emetogenic chemotherapy
MedDRA	Medical Dictionary for Regulatory Activities
MFAS	modified full analysis set
mg	milligram(s)
MI	myocardial infarction
mL	millilitre(s)
mmol	millimole
MS	Mass spectrometry
NCI CTC	National Cancer Institute Common Toxicity Criteria
NETU	Netupitant
NK1	Neurokinin 1

NMR	Nuclear magnetic resonance
NYHA	New York Heart Association
PALO	Palonosetron
PDCO	Paediatric Committee
PE	physical Examination
PET	positron emission tomography
Ph. Eur.	European Pharmacopoeia
PI	Principal Investigator
PK	pharmacokinetics
PKWP	Pharmacokinetic Working Party
PO	per os
PP	per protocol
QWP	Quality Working Party
RH	Relative humidity
SAE	serious adverse event
SAP	statistical analysis plan
SAWP	Scientific Advice Working Party
SOC	system organ class (MedDRA)
SOP	standard operating procedure
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event
t.i.d.	ter in die (three times daily)
TSE	Transmissible Spongiform Encephalopathy
UK	United Kingdom
US(A)	United States (of America)
USP	United States Pharmacopoeia
UV	Ultraviolet
VAS	visual analogue scale
WBC	white blood cell
WHO	World Health Organization
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Helsinn Birex Pharmaceuticals Ltd. submitted on 13 December 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Akynzeo, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 February 2013.

The applicant applied for the following indication:

AKYNZEO is indicated in adults for the:

Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.

Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) on the granting of a product-specific waiver (P/0014/2012).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance NETUPITANT contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 20 January 2011, followed-up on 20 September 2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following country: USA.

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Helsinn Birex Pharmaceuticals Ltd.
Damastown
Mulhuddart
Dublin 15
Ireland

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Salmon

Co-Rapporteur: Joseph Emmerich

- The application was received by the EMA on 13 December 2013.
- The procedure started on 22 January 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 April 2014 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 April 2014 (Annex 2). During the meeting on 22 May 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20/11/2014 (Annex 4).
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 05/01/2015 (Annex 5).
- During the CHMP meeting on 22 January 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant (Annex 6).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23/02/2015 (Annex 7)
- During the meeting on , the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Akynzeo.

2. Scientific discussion

2.1. Introduction

Problem statement

Nausea and vomiting are among the side effects associated with cancer treatment that patients and their families often fear the most. If nausea and vomiting are not controlled in a cancer patient, serious metabolic problems such as fluid and electrolyte balance disturbances and nutritional status deficiencies can develop. Psychological problems associated with nausea and vomiting may include anxiety and depression. In addition, uncontrolled nausea and vomiting may also lead to the decision by the physician to reduce chemotherapy dose intensity or to the wish by the patient to stop potentially beneficial cancer therapy.

CINV is classified as acute, occurring within the first 24h after chemotherapy, or delayed, occurring after the first 24h. The development of acute emesis is known to largely depend on serotonin (5-HT). The 5-HT_3 receptor has been demonstrated to selectively participate in the emetic response, thus providing a physiologic explanation for the demonstrated and clinically useful antiemetic effects of 5-HT_3 receptor antagonists (RAs).

The pathophysiology of delayed emesis is less understood, and multiple mechanisms may contribute, including substance P. Substance P belongs to the neurokinin (NK) family of neuropeptides and exerts its biological effects via interaction with the NK1 receptor.

Presently, a four-level classification of intravenous chemotherapy agents, based on incidence of emetogenicity (high >90%, moderate 30%-90%, low 10%-30% and minimal <10%) has been accepted by the major organizations producing recommendations on antiemetics, who recommend that patients receiving HEC regimens or MEC regimens with anthracycline combined with cyclophosphamide should be treated with a combination of a 5-HT_3 RA, NK1 RA and a systemic corticosteroid.

About the product

The proposed palonosetron-netupitant fixed combination (Combination or FDC) is composed of palonosetron - (ALOXI) - a registered 5-HT_3 RA, and the new molecular entity, NK1 RA netupitant. It is a hard gelatin capsule for oral route.

Palonosetron is a well-known potent and selective 5-HT_3 receptor antagonist with demonstrated efficacy by the intravenous (I.V.) and oral route for the prevention of nausea and vomiting associated with cancer therapy.

Palonosetron 250 mcg solution for injection (ALOXI EU/1/04/306/001) was approved via the Centralised Procedure on March 22, 2005 and is indicated in adults for:

- the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy,
- the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Palonosetron 500 mcg oral capsules (ALOXI EU/1/04/306/002-003) were approved as a line extension application on May 5, 2010 and are indicated in adults for:

- the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Netupitant is a novel, potent and selective NK1 receptor antagonist. It has been shown to be a highly effective antiemetic in a variety of pre-clinical models. In human volunteers, the antiemetic effect of netupitant was assessed using an apomorphine challenge model. Overall, netupitant appeared to reduce the incidence of emetic episodes following the apomorphine challenge in a concentration-dependent manner, with the incidence of vomiting decreasing as netupitant plasma concentration increased.

The characteristics of the two active pharmaceutical ingredients supported the development as a fixed combination, since their mechanism of action is exerted on different neuropathways (5-HT_3 receptors and NK1 receptors) and both drugs show an extended half-life (approximately 40 and 90 hours for palonosetron and netupitant, respectively).

The main advantages of the netupitant-palonosetron fixed-dose combination product are to improve patient compliance due to a simplification and convenience of therapy and to increase adherence to guidelines for administration of both a 5-HT_3 and NK1 RA.

The claimed and approved indication is:

Akynzeo is indicated in adults for the:

Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.

Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Type of Application and aspects on development

This Marketing Authorisation Application (MAA) for the combination capsule netupitant 300 mg - palonosetron 0.50 mg, for the prevention of acute and delayed nausea and vomiting associated with cancer chemotherapy in adult patients is a full application in accordance with directive 2001/83/EC as amended and regulation 726/2004.

The development program of the product to support its Marketing Authorisation Application (MAA) was agreed with CHMP during a Scientific Advice Procedure, where clinical aspects were presented together with quality, multi-disciplinarily, and non-clinical items.

With regard to clinical efficacy and safety, the CHMP agreed that the proposed netupitant/palonosetron combination is based on valid therapeutic principles, in accordance with guidance on fixed-dose combination (CPMP/EWP/240/95) and that the proposed safety and efficacy program, if successful, is suitable to support the registration of the combination in the HEC and MEC target therapeutic indication.

HEC Study NETU-07-07: the CHMP agreed that the study has the potential for consideration as the sole pivotal efficacy trial to support the HEC indication, considering the robustness of results, and provided that the similar study conducted in MEC induced CINV (NETU-08-18) is similarly positive, since the HEC and MEC diseases are closely related. The NETU-07-07 primary efficacy endpoint and analysis were considered adequate to demonstrate efficacy to support the proposed target indication in HEC.

MEC Study NETU-08-18: the CHMP judged the proposed superiority design acceptable to provide evidence of efficacy and therefore to support the proposed target indication in MEC. The choice of the

primary efficacy endpoint (i.e. proportion of patients with Complete Response in the delayed phase at cycle 1) and key secondary efficacy endpoints (i.e. proportion of patients with Complete Response in the acute and overall phases at cycle 1), including the proposed approach to address multiplicity for the primary and key secondary efficacy endpoints in the study NETU-08-18 were considered acceptable. The adoption of a 5% type I error (2-sided) was accepted for this single MEC pivotal study since the results of the HEC trial NETU-07-07 were strongly supportive. The definition of the Full Analysis Set (FAS) was considered adequate for the primary efficacy analysis in Cycle 1. For the primary efficacy analysis of the multiple cycle extension (MCE) the Party recommended to include all patients from the Cycle 1 full analysis set in the MCE full analysis set, because the proposed MCE FAS is not appropriate as patients were not re-randomised at the time of entering the MCE. The proposed primary efficacy analysis in NETU-08-18 was considered acceptable to demonstrate efficacy and the proposed patient population in NETU-08-18 adequate to support the proposed target label.

Safety HEC and MEC Study NETU-10-29: the comparator, the sample size assumption and the population (in term of represented chemotherapy regimens) were considered adequate to characterize the safety profile of the Combination in chemotherapy repeated cycles.

HEC Study PALO-10-01: As a general perspective, the CHMP considered the study probably not necessary to provide evidence of efficacy of palonosetron 0.50 mg oral capsules in the HEC setting, since the efficacy of oral palonosetron monotherapy in HEC can be inferred both from its proven efficacy in MEC and from the results of study NETU-07-07, where the monotherapy arm performed far better than a non-active treatment could possibly achieve. The CHMP considered the design of the study reasonable and the primary endpoint (proportion of patients with CR in the acute phase) acceptable. The 15% non-inferiority margin was deemed sufficiently narrow given the poor expected efficacy of placebo. The choice to set the type I error at 1% was judged even more stringent than requested; the definitions and proposed roles for populations of analyses in PALO-10-01, were considered appropriate. The proposed primary efficacy analysis in PALO-10-01 was considered acceptable to demonstrate efficacy. Finally the proposed patient population in study PALO-10-01 was adequate to support the proposed target label, in view of the proposed role of PALO-10-01 in the development program of the Combination.

In relationship to the overall characterization of the safety profile of the Combination in the global registration program, the Party considered it adequate in term of number of individuals and type of patient population and agreed on the adequateness of safety measures proposed in both clinical studies NETU-08-18 and NETU-10-29. Based on the long half-lives of both compounds, it was recommended to add additional investigations approximately 10 days after dosing.

Finally, the CHMP agreed on the adequateness of the global PK evaluation, including Population PK/PD Assessment, without performing a full PK study in cancer patients.

A full waiver for a Paediatric Investigation Plan for the Combination was obtained based on the lack of significant therapeutic benefit over existing treatments for all subsets of the paediatric population (0 to 18 years of age) in the condition of prevention of chemotherapy-induced nausea and vomiting (EMA decision P/0014/ 2012 dated January 24, 2012).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard gelatin capsules containing 300 mg of netupitant and 0.5 mg of palonosetron (as hydrochloride) as active substances.

Other ingredients found in the finished product components are:

Hard capsule contents:

Netupitant tablets: microcrystalline cellulose (E460), sucrose lauric acid esters, povidone K-30, croscarmellose sodium, colloidal hydrated silica, sodium stearyl fumarate and magnesium stearate.

Palonosetron soft capsule content: glycerol monocaprylcaproate (type I), glycerol, polyglyceryl oleate, purified water and butylated hydroxyanisole (E320).

Palonosetron soft capsule shell: gelatin, glycerol, sorbitol, 1,4-sorbitan and titanium dioxide (E171).

Hard capsules:

Shell: gelatin, titanium dioxide (E171), yellow iron oxide (E172) and red iron oxide (E172).

Printing ink: shellac glaze (partially esterified), black iron oxide (E172) and propylene glycol (E1520).

The product is available in alu/alu blisters.

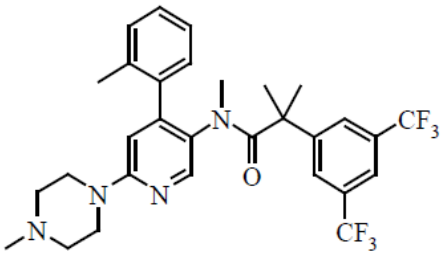
2.2.2. Active Substance

Netupitant

General information

The information on netupitant is provided according to the Active Substance Master File (ASMF) procedure.

The chemical name of netupitant is 2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethyl-*N*-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)pyridine-3-yl]propanamide and has the following structure and properties:



Molecular formula: $C_{30}H_{32}F_6N_4O$ - Relative molecular mass: 578.61 $gmol^{-1}$

The structure of netupitant was inferred from its route of synthesis and confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, mass spectrometry, elemental analysis and XRPD.

Netupitant is a white to off-white, non-hygroscopic, crystalline powder. It is very slightly soluble in water and freely soluble in a range of organic solvents such as acetone, toluene, and methanol. The active substance is milled to reduce particle size. Three physical forms are known, including unstable amorphous and solvated forms. The chosen commercial form is the most thermodynamically stable and is stable to the particle size reduction process. Netupitant is achiral.

Manufacture, characterisation and process controls

Netupitant is synthesized convergently in nine main steps using commercially available, well-defined starting materials with acceptable specifications. Five manufacturers are listed in the dossier with

responsibility for different steps in the netupitant manufacturing process, An additional two manufacturers are responsible for the subsequent micronization of the active substance.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Genotoxic impurities can potentially form at several steps of the process. The applicant provided impurity spike and purge data to demonstrate that these are removed by the process and not present in the isolated active substance. In addition the applicant will test the first three batches of netupitant synthesized from intermediates sourced from each intermediate manufacturer for genotoxins, using the relevant analytical methods, to provide further assurance of active substance safety.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification includes tests for appearance (visual inspection), identity (IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), heavy metals (USP), sulphated ash (Ph. Eur.) and particle size distribution (laser diffraction). In addition, a test for genotoxic impurities (HPLC and GC-MS) is included in the specification to be carried out on the first three batches of netupitant synthesized from intermediates from each source.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Analysis data on seven production scale batches of the active substance, using starting materials from all proposed suppliers, and milled at both proposed micronisations sites, were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on seven production scale batches of active substance from the proposed manufacturers stored in a container closure system representative of that intended for the market for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: appearance, water content, related substances and assay. The analytical methods used were the same as for release and were stability indicating. No significant changes were observed for any of the parameters tested.

Photostability testing following the ICH guideline Q1B was performed on one batch. A reduction in assay indicates that netupitant is photosensitive but it is stored away from light and so this is not of concern.

Forced degradation studies were also carried out by exposing netupitant solutions to heat, light, acid (pH 1), base (pH 11) and hydrogen peroxide. Solid netupitant was also exposed to heat. The active substance is not sensitive to heat, or the extremes of pH tested. It is however susceptible to oxidation and photo-degradation.

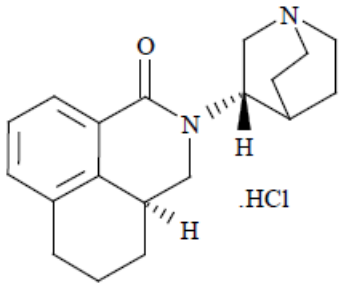
The stability results indicate that the drug substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

Palonosetron Hydrochloride

General information

The information on palonosetron hydrochloride is provided according to the Active Substance Master File (ASMF) procedure.

The chemical name of palonosetron hydrochloride is (3a*S*)-2-[(*S*)-1-azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*-benz[*de*]isoquinoline hydrochloride and it has the following structure and properties:



Molecular formula: $C_{19}H_{24}N_2O.HCl$ - Relative molecular mass: 332.87 $gmol^{-1}$

The structure of palonosetron hydrochloride was inferred from its route of synthesis and confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, mass spectrometry, elemental analysis. The absolute configuration was determined by XRPD.

Palonosetron hydrochloride is a white to off-white, non-hygroscopic, crystalline powder. It is freely soluble in water, slightly soluble in polar organic solvents, and practically insoluble in apolar organic solvents.

Palonosetron contains 2 stereocentres and is synthesized as the (*S*,*S*)-isomer. Enantiomeric purity is controlled in the specification of the starting material which contains a single chiral centre, and by specific optical rotation in the active substance. The enantiomeric and diastereomeric impurities are controlled in the active substance specification. Polymorphism has been observed for palonosetron hydrochloride but since it is in solution within the soft capsule formulation, its physical properties do not impact bioavailability and neither particle size nor polymorphic form is controlled.

Manufacture, characterisation and process controls

Palonosetron hydrochloride is synthesized by the ASMF holder in three main steps using well-defined starting materials with acceptable specifications. Palonosetron hydrochloride purity is enhanced by recrystallization.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification includes tests for appearance (visual inspection), identity (IR, UV), assay (HPLC), clarity of solution (visual inspection), pH of solution (Ph. Eur.), optical rotation (Ph. Eur.), loss on drying (Ph. Eur.), residue on ignition (Ph. Eur.), heavy metals (USP), impurities (HPLC), assay (HPLC), chloride content ($AgNO_3$ titration), residual solvents (GC), bioburden (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Analysis data for ten commercial scale batches of palonosetron hydrochloride are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three commercial scale batches of palonosetron hydrochloride from the proposed manufacturer stored in the intended commercial package for 60 months under long term conditions (25 ºC / 60% RH), for 12 months under intermediate conditions (30 ºC / 60% RH), and for 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Since the active substance is well-known and has been on the market (as Aloxi) since 2003, the intermediate conditions pre-date ICH Q1A and are thus slightly different from the current guideline conditions. The following parameters were tested: appearance; assay; impurities; loss on drying; bioburden. The analytical methods used were the same as for release and were stability indicating. There were no significant trends or changes to any measured parameter under any of the conditions.

Photostability testing following the ICH guideline Q1B on 1 batch demonstrates that palonosetron hydrochloride is not photosensitive.

Stability data generated under stressed conditions (in aqueous solution at acidic and basic pH, at high temperature, on irradiation with light, and in the presence of H_2O_2) indicate that the main degradation pathway is oxidation. Solid state studies show deliquescence and degradation at high temperatures and humidities.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of pharmaceutical development was to produce a dosage form containing fixed amounts of netupitant and palonosetron hydrochloride. Palonosetron is already authorised in the marketed product Aloxi, which is available both as a solution for injection and as soft capsules. Netupitant is a new active substance. Initial studies were focused on the compatibility of the two active substances and attempts to find a common formulation. No degradation was observed when netupitant and palonosteron were combined under a variety of conditions. However, the large difference in dose size (300 vs 0.5 mg) and differences in physicochemical properties, made co-formulation difficult. A solid form formulation of Palonosetron was tested and displayed reduced potency, and dry mixtures containing both active substances had poor content uniformity. By contrast, the relatively large dose of netupitant was insufficiently soluble in suitable liquid vehicles for softgel capsule filling. Thus, the decision was made to combine palonosetron softgel capsules with netupitant tablets inside a hard capsule.

Netupitant exhibits low aqueous solubility but high permeability (BCS class II). In order to ensure a consistent dissolution profile, it is micronized to reduce particle size. All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards or in-house specifications for non-compendial excipients. There are no novel excipients used in the finished product formulation. The tablets proposed for inclusion in the commercial formulation are round, flat and off-white. The critical quality attributes identified were appearance, identity, assay, purity, uniformity of dosage units, water content and dissolution.

A series of bioequivalence studies enabled bridging between the various netupitant formulations used clinically. The choice of dissolution method was adequately justified and its discriminatory power has been demonstrated.

Palonosetron is highly soluble and highly permeable (BCS class I). Its physicochemical properties are not important for formulation purposes as it is in solution within the softgel capsules. The development of the softgels for Akynzeo was based on the composition of Aloxi. In order to reduce the softgel capsule size to enable it to fit within the larger hard capsule, the amount of glycerol monocaprylcaproate solvent was halved. Other excipients were held at the same levels as in Aloxi, and comprise butylated hydroxyanisole to prevent oxidative degradation as well as glycerine and water to prevent capsule hardening over time. The solubility and stability of palonosetron hydrochloride in the fill solution was demonstrated. The critical quality attributes identified were appearance, identity, assay, purity, uniformity of dosage units and dissolution. Most excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. Non-pharmaceutical excipients are also used in the capsule shell but these are mixtures of well-known or pharmacopoeial excipients.

The final image of Akynzeo is white size 0 capsules with a caramel-coloured cap imprinted in black ink on the white part. Each capsule contains three netupitant tablets and one palonosetron softgel capsule. The full list of excipients is included in section 6.1 of the SmPC. The dissolution methods for the combined capsules are considered discriminatory. A switch was made late in the development programme from the white capsules with blue caps used in phase III clinical studies as the colour faded over time. Other than colour, there is no difference between the compositions of the two capsule types.

The primary packaging is alu/alu blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process of intermediate netupitant tablets consists of five main steps: mixing of netupitant with intra-granular excipients followed by high shear wet granulation; drying and milling; blending with extra-granular excipients; compression to form tablets; bulk packaging. This is considered to be a standard manufacturing process and validation will be performed before commercialisation. Acceptance limits have been defined for critical process parameters in the granulation, drying, and compression steps in order to meet the intended quality.

The manufacturing process of intermediate palonosetron softgel capsules consists of four main steps: dissolution of palonosetron and excipients in the fill solution; encapsulation into softgel capsules and lubrication; drying and washing; bulk packaging. Given the company's experience of manufacturing Aloxi softgel capsules using a similar method, this is considered to be a standard manufacturing process, and so validation will be carried out prior to commercialisation. In-process controls for the critical encapsulation step have been defined and are well justified.

For the production of Akynzeo hard capsules, three netupitant tablets and one palonosetron softgel capsule are filled into the size 0 hard capsules. Controls are in place to ensure the correct filling of each

capsule. Once sealed, the capsules are put into the primary packaging. Validation of this standard process will be performed prior to commercialisation.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and comprise tests for appearance of capsules (visual inspection), identity (HPLC, UV), assay (HPLC), impurities (HPLC), BHA content (HPLC), dissolution (Ph. Eur.) and microbial enumeration (Ph. Eur.). Given the final dosage form comprises netupitant tablets and palonosetron softgels combined in a hard capsule, certain parameters are tested in the intermediate standalone dosage forms as follows:

Netupitant tablets: appearance (visual inspection), identity (HPLC, UV), uniformity of dosage units (Ph. Eur.), impurities (HPLC), dissolution (Ph. Eur.) and loss on drying (Ph. Eur.).

Palonosetron softgels: appearance and aspect of content (visual inspection), identity (HPLC, UV), uniformity of dosage units (Ph. Eur.), impurities (HPLC), assay (HPLC), dissolution (Ph. Eur.), BHA content (HPLC), and microbial enumeration (Ph. Eur.).

The applicant committed to re-evaluate the dissolution specification as a review of the consistency of manufacturing and *in vitro* performance.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Analysis results are provided for five batches of combination capsules. Additional data on three commercial batches of a previous product format with different coloured capsules, and six batches used in clinical trials made by different manufacturers, including the commercial one, were provided as additional information and support the above conclusions.

Analysis results are also provided for intermediate netupitant tablets, (nine commercial scale batches from the commercial manufacturer and four from a previous manufacturer), and for intermediate palonosetron softgel capsules (eight commercial scale batches).

The combined provided data confirms the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on three commercial scale batches of the blue/white capsules and three commercial scale batches of the caramel/white capsules stored for up to 24 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate conditions (30 ºC / 65% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The finished product was stored in the proposed commercial container closure system and manufactured using the proposed manufacturing process by the proposed manufacturer. Samples were tested for appearance, aspect of the palonosetron softgels, assay (both active substances), impurities (from both active substances), BHA content, dissolution (both active substances) and microbial enumeration. The analytical procedures used are stability indicating. There were no significant changes to any of the measured parameters under any condition, other than the fading of the blue colour in the blue/white capsules. Some capsules from later time-points under all conditions required S2 and S3 testing to meet specification for dissolution, an observation attributed to hardening of the hard gelatin capsules over time and which is not considered an issue.

In addition, one batch of caramel/white capsules was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products indicating that Akynzeo is not affected by exposure to light.

Bulk holding times were investigated on one batch of blue/white capsules for up to 24 months and one batch of caramel/white capsules for up to 9 months. A bulk holding time of up to 24 months is acceptable, starting from the date of manufacture of whichever intermediate product is produced first.

Bulk stability study results for one batch each of intermediate netupitant tablets and palonosetron softgels were also provided. The results support bulk holding times of up to 12 months for netupitant tablets and up to 24 months for palonosetron softgels. In line with the CHMP/CVMP QWP Q&A document on "stability issues of pharmaceutical bulk products for use in manufacture of the finished product," the applicant will made a commitment (located in the post-authorisation stability section for each intermediate product) to carry out bulk stability studies on an additional batch of each intermediate following a request from CHMP.

The applicant will continue the stability studies of the caramel/white capsules up to the end of the proposed shelf life, and bulk holding time. In addition, the first three commercial batches of Akynzeo will be placed on long term stability studies.

Based on available stability data, the shelf-life as stated in the SmPC are acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEPs from the suppliers of the gelatine used in the manufacture are provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant should review the finished product dissolution specification once sufficient manufacturing experience has been gained, and tighten if appropriate.
- The applicant should carry out a bulk stability study on an additional batch of intermediate netupitant tablets and complete the ongoing stability study on the additional batch of intermediate palonosetron softgels, in line with the CHMP/CVMP QWP Q&A document on "stability issues of pharmaceutical bulk products for use in manufacture of the finished product."

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical part of this Marketing Authorization Application is consistent with the EU Guideline EMEA/CHMP/SWP/258498/2005 “Guideline on the Non-Clinical Development of Fixed Dose Combination Medicinal Products”.

Thus, this submission includes studies of orally administered netupitant and intravenously administered netupitant that investigated the pharmacology, toxicokinetics and ADME, safety pharmacology, general toxicology and genetic toxicity (in vivo and in vitro). Reproductive and developmental toxicology studies were conducted in rats and/or rabbits to assess effects on fertility, embryofetal development, and pre- and post-natal development. The toxicologic aspect of the combination of netupitant and palonosetron was evaluated by pharmacology, safety pharmacology and repeat dose studies. Full non clinical investigation on Palonostrone has been carried out for the authorisation of Aloxi (palonosetron).

The pivotal pharmacokinetic and toxicity studies were performed in accordance with GLP as claimed by the applicant.

2.3.2. Pharmacology

Tabulated overview of Pharmacology studies

Table 1: In vitro pharmacology studies with <u>netupitant and its metabolites</u>

GLP aspect	Type of study	Test system	Noteworthy Findings
no GLP	Affinity of **netupitant** for NK1 receptor	Human recombinant NK1 receptors expressed in Chinese hamster ovary (CHO) cells	Human recombinant NK1 : pKi = 9.0 => high affinity. Canine NK1 receptor : pKi = 8.6 rodent NK1 receptor : pKi = 8.1 ⇨ high affinity
no GLP	Affinity of netupitant for human NK3 receptor	**Netu** = 0.03 nM-10 µM)	Human NK3 receptor : pKi = 7.5 => low affinity when compared to the human NK1
no GLP	Receptor binding profile	**Netu** : 0.1 µM, 10 µM	Approximately 3 orders of magnitude of selectivity for the NK1 receptor.
no GLP	Affinity of netupitant	**Netu** : 0.1 µM to 30 µM in duplicate	pKi = 5.9 at the diltiazem binding site on the Ca2+ channel in rat cortical tissue.
no GLP	Receptor binding profile	**M1** at 1 µM	Interaction at the L-type Ca2+ channel for M1 at 1 µM (IC50 = 2.8 nM; Ki = 1.4 nM)
no GLP	Receptor binding profile	**M1, M2**, and **M3** = 10 µM	M1 and M3: more effect with regard to norepinephrine and dopamine uptake at 10 µM.
no GLP	Receptor binding profile	**M4** = 10 µM	- At hNK1 receptor : IC50 = 3.7 nM; Ki = 1.6 nM - At hNK3 receptor: IC50 = 8 µM ; Ki = 8 µM.

Metabolite = M, netu = netupitant

Table 2: In vivo pharmacology studies with <u>netupitant and its metabolites</u>

Type of study No of animals/dose GLP aspect	Doses (mg/kg)	Major findings
Induced Foot-Tapping in Gerbils		
Inhibition of NK1 Agonist-Induced Foot-Tapping in Gerbils M + F, number not provided No GLP	Netupitant metabolites: M1: 10, M2: 10, M3: 10 oral, ip	**Netupitant :** ED_{50} = 0.5 mg/kg p.o. and 1.5 mg/kg i.p.. M1: ED_{50} = 2.4 mg/kg p.o. and 5.4 mg/kg i.p.. M2: ED_{50} > 10 mg/kg p.o. and < 10 mg/kg i.p.. M3: ED_{50} = 1.2 mg/kg i.p.. (T½) = 48 h. **M1, M2 and M3** : all metabolites were active; the most potent being the M3 metabolite.
Emesis studies in Ferrets		
Ferrets M,number not provided No GLP	Netu : 3 Oral	Prevention of emesis induced by apomorphine (0.125 mg/kg sc), morphine (0.5 mg/kg sc), ipecacuana (1.2 mg/kg po) and copper sulphate (100 mg/kg ig).
Ferrets M,number not provided No GLP	Netu = 0, 0.03, 0.1, 0.3 oral + apomorphine or cisplatin	Inhibition of retches and vomits: ED_{50} = 0.1mg/kg po.
Ferrets Male 4-6/group No GLP	Netu 1-3 oral+ cisplatin (5mg/kg ip)	- Complete control of emesis throughout the 72h test period. - Incidences of retches and vomits were 7 at 1 mg/kg, and 0 at 3 mg/kg.
Emesis studies in Suncus murinuse		
Suncus murinuse M, number not provided No GLP	Netu 0, 0.03, 0.1, 0.3 oral	Effect of netupitant in motion-induced emesis. Netupitant produced a dose related inhibition of retches and vomits at 0.1 and 0.3 mg/kg.

Metabolite = M, netu = netupitant

Table 3: In vivo pharmacology studies with <u>netupitant / palonosetron</u>

Type of study No of animals/dose GLP aspect	Doses (mg/kg)	Major findings
Emesis studies in Ferrets		
Ferrets Emesis studies Male, 4-6/group No GLP	**Palo**: 0.03-0.1 mg/kg **and/or Netu :** (0.1- 1 mg/kg) Oral + cisplatin (5 mg/kg ip) alone or with dexamethasone (1 mg/kg i.p)	A single higher doses of Palo and Netu, antagonized the 0-72 h response, an associated improvement in food consumption was observed.
Kaolin consumption in rats		
Rat/ Wistar Kaolin Consumption Males 3-5/ group No GLP	**Palo**: 0.5 mg/kg, **and/or Netu**: 1 mg/kg **SC +** Cisplatin (6 mg/kg ip)	Cisplatin (6 mg/kg ip) induce decreases in food consumption and water consumption and increases in kaolin consumption. → No effect with netupitant and palonosetron, alone, and combined together.

netu = netupitant , palo = palonosetron

Primary pharmacodynamic studies

Netupitant is a high affinity hNK1 receptor antagonist (comparable to substance P and the selective NK1 receptor antagonist MK869) with a 1000-fold greater selectivity for hNK2 and a 34 fold greater selectivity for hNK3. While netupitant at 10 μM indicated approximately 3 orders of magnitude separation between affinity for the NK1 compared to over 50 other receptors and ion channels, interactions at the histamine (H2), adenosine (A3), DA and 5-HT reuptake sites, L-type Ca2+ channel and diltiazem binding site on the Ca2+ channel were observed.

Additional binding studies (Reports NETU-10-24, NETU-10-16 and NETU-12-13) were performed with netupitant and its metabolites (M1, M2, M3 and M4). These studies demonstrate that netupitant and all its metabolites have a high affinity for NK1. Furthermore netupitant and M4 show 10,000 fold selectivity over NK2 and NK3 receptors. Binding of M1, M2, and M3 to NK2 and NK3 have not been performed. However, based on the inhibition of foot-tapping in gerbils, netupitant and M3 showed comparable potency, whereas M1 and M3 were less potent. Therefore, it cannot be excluded that M1 and M3 contribute to the pharmacological activity of netupitant. In further binding studies, the netupitant main metabolites, M1 was shown to interact at the L-type Ca2+ channel (IC50 = 2.8 μM; Ki = 1.4 μM).

In clinical studies, an additional metabolite M4 (N-oxide, N-demethyl derivative) was detected. This metabolite showed activity on hNK1 receptor (IC50 = 3.7 nM; Ki = 1.6 nM) and on hNK3 (IC50 was 8 μM and the Ki =8 μM).

Intracerebroventricular injection of the NK1 agonist GR73632 produces a foot tapping response in gerbils which is inhibited by brain-penetrating antagonists of the NK1 receptor. This in vivo assay was employed to examine dose and time dependent effects of netupitant on foot tapping responses in gerbils. Netupitant blocked the foot-tapping response elicited by the central injection of GR73632 with an ED50 of approximately 0.5mg/kg p.o. and 1.5 mg/kg i.p. The plasma levels of netupitant necessary to achieve a robust inhibition (75%) of this effect were approximately 40ng/ml. The half-life of activity for netupitant was 48h in this test. A 60 minute pre-treatment time with netupitant (3 mg/kg) was required for complete blockade of foot-tapping. Moreover, the three main metabolites M1, M2 and M3 were also examined for activity in the gerbil foot-tapping test. These data concluded that M1 and Me are active following IP administration and M1 is active following oral administration. The PK for the M1 and M3 were not measured but given the affinity of these metabolites to the respective receptors it can be assume they are present.

Netupitant demonstrated antiemetic action in ferrets against various acute-induced and delayed models of emesis. The ED50 for oral netupitant for the prevention of emesis induced by ap cisplatin in ferrets was approximately 0.2 mg/kg. Netupitant administered orally as a single dose (3 mg/kg) was also found to completely block the acute (<24h) phase of emesis produced by cisplatin and block up to 90-95% of delayed (24-72 h) phase of emesis produced by cisplatin. Plasma levels showed that both the parent compound and M1 metabolite were detectable up to 96 hours and were functional at points up to 72 hours (90-95% inhibition of cisplatin-induced emesis).

Palonosetron is a highly specific 5-HT_3 receptor antagonist and has significantly stronger receptor binding than some other such drugs, e.g. ondansetron, granisetron. The drug is highly effective in preventing antineoplastic-induced emesis in dogs and ferrets. It has no clinically significant action on other serotonergic receptors. M4 and M9 exhibited at least 100-fold less antagonistic activity than palonosetron and their activity is not considered clinically relevant.

Palonosetron (0.1 mg/kg, p.o.) and netupitant (1 mg/kg, p.o.), alone or in combination together with dexamethasone were able to prevent emesis induced by cisplatin up to 72 hrs. The combination of

netupitant and palonosetron was thought to offer a greater therapeutic advantage versus the treatments alone in that the antiemetic action was 100% maintained for the entire 72 hr duration.

Secondary pharmacodynamic studies

No secondary pharmadynamics studies have been submitted for netupitant or netupitant / palonosetron; for alonosetron when tested against substance P-induced contractions in the isolated guinea pig ileum palonosetron caused a slight decrease in response. This less than 2-fold change was found at concentrations 1000-fold higher than required to block the $5HT_3$ receptor in this system.

Safety pharmacology programme

In a non-GLP Irwin study performed in rats, netupitant up 1000 mg/kg had no effects on gait, reflexes or other neurological signs. Furthermore, netupitant (3, 30, and 100 mg/kg p.o.) showed no signs of anti- or pro-convulsant activity in rats following an infusion with pentylenetetrazol.

In vitro, netupitant and it's metabolites (M1, M2 and M3) blocked hERG K+ channels with IC50 of 0.76, 0.84, 43 and 4.4 µM, respectively. In isolated canine ventricular mycoytes, netupitant and its metabolite M1 induced a very slight inhibition (21 ± % and 25 ± 2%, respectively) of IKr tail current whereas metabolite M3 induced 14 ± 2% and 57 ± 8% inhibition of IKr tail current at 3 and 30 µM, respectively. Netupitant was only tested to 3 µM owing to issues with solubility, m2 showed no effect up to 30 µM. In isolated canine Purkinje fibres, significant decreases in action potentials were seen with neupitant and its metabolites at concentrations >3 µM. In isolated canine papillary muscle, only the M3 metabolite was shown to induce significant increase in action potential duration at APD50, APD70 APD90.

The safety pharmacology of palonosetron including central nervous system, respiratory system, autonomic nervous system, gastrointestinal system, renal/urinary system, blood compatibility and hemodynamic and respiratory effects have been studied. Moreover, extensive investigation of cardiovascular safety was performed. In vitro studies confirmed the expected effects of palonosetron, at high concentrations. In vivo studies using several species showed effects on cardiac conduction, but no Torsades de Pointes were observed, despite the use of doses up to 1 mg/kg (which is 300-fold higher than the proposed human dose).

In vivo the combination of palonoestron and netupitant induced a slight prolongation of action potential duration in an in vivo guinea pig study and in an in vivo canine model produced decrease in atrio-ventricular conduction and ventricular depolarization rate associated with a prolongation of ventricular repolarization. Cardiovascular effects were observed in conscious dogs with netupitant and its main metabolite M1 only after repeated administration (14-day) at the highest dosages (netupitant 50 mg/kg and M1 30 mg/kg). These studies suggest that M1 is more likely to be associated with the onset of QT prolongation than netupitant – M1 exposure was also higher in the heart and with heart/plasma concentration ratio compared to netupitant (See PK section). Moreover exposure to M1 is quantitatively higher in the dog compared to human.

Netupitant had no significant effect on respiratory, renal or gastrointestinal systems at doses up to 50 mg/kg (respiratory) and 100 mg/kg (renal and gastrointestinal). Palonosetron is an approved drug with a known preclinical and clinical safety profile. While, no safety pharmacology studies investigating the respiratory, gastrointestinal and central nervous systems have reported with the netupitant/palonosetron combination, no significant effects on on GI, respiratory and CNS were reported in the 13-week rat and dog studies.

No abuse liability/dependence potential or withdrawal behaviours were observed with Netu/Palo combination at doses similar to or higher then the proposed therapeutic dose in humans (i.e. 300/0.50 mg Netu/Palo p.o.).

Pharmacodynamic drug interactions

No non clinical PD drug interactions studies have submitted for netupitant, palonosetron, netupitant / palonosetron combinaison.

2.3.3. Pharmacokinetics

The pharmacokinetics of netupitant and its major metabolites was determined following single and repeat doses in rats and dogs. Distribution was investigated by whole body autoradiography following oral and intravenous doses of [^{14}C]-netupitant, and plasma protein binding was investigated in human, rat, dog and gerbil in vitro. Metabolite profiles were determined in rat and dog. Absorption was determined following oral and intraperitoneal administration of netupitant in rats and oral administration in dogs and cynomolgous monkeys. Absorption following oral administration was moderate with T_{max} of about 3.5 hours in rats and 2-5 hours in dogs depending on the salt used. In rats following IV administration netupitant had low to moderate clearance and a long apparent terminal half life. Volume of distribution was high in all species. Oral bioavailability in each species varied substantially between animals, with 42-105%, 34-83% and 37-62% in rats, dogs, and monkeys. The large variation is most likely due to the low numbers of animals used in the studies.

Netupitant was highly bound (>99%) to plasma proteins in all species. The mean percentage of free drug was 0.33% in man, 0.22% in dog, 0.31% in rat, 0.50% in gerbil and < 1% in mouse. The in vitro plasma protein binding of the three major metabolites of netupitant, M1, M2 and M3 was also determined in man, dog (Swiss beagle) and rat. The plasma protein binding over 99% for M1 metabolite, and high for M2 metabolite were (2.3% (man), 2.2% (dog) and 0.65% (rat) free drug). For M3, plasma protein binding was 99% in rat and human and 97.5% in dog. In vivo distribution was determined by whole body autoradiography in rats. Following oral doses of 10 mg/kg netupitant, distribution was extensive. Radioactivity was seen highest (>20 fold plasma exposure) in the harderian gland, followed by lung, adrenal, spleen, pituitary, exorbital and intraorbital lachrymal glands and thyroid. Netupitant related material crossed the blood brain barrier, but was not detectable by 216 hours post-dose. The M1 metabolite was the predominant drug-related material by 24 hours, so distribution behaviour was considered to be due largely to M1. Repeated administration indicated accumulation in nasal mucosa, mandibular lymph nodes, epididymis and choroid plexus. Administration to pigmented rats showed 5-8 times greater levels in the uveal tract than in unpigmented animals. Binding was reversible, and netupitant was not phototoxic in vitro. Netupitant and its three major metabolites were shown to cross the blood brain barrier in a specific study in rats. In dogs, netupitant, M1 and M3 were measurable in the heart. At the end of the two 4 weeks toxicology studies and the telemetry study in dog M1 was on average approximately 5-fold more concentrated than netupitant in heart tissue.

In human, rat, dog, minipig and marmoset liver microsomal incubations, two major metabolites, an N-demethylation product (M1) and an N-oxidation product (M2), in addition to hydroxylation products (M3), were identified in all species. CYP3A4 was found to be responsible for the oxidation of netupitant to the same metabolites observed also in the incubations with human liver microsomes. In rats and dogs in vivo, the three major metabolites were all identified. Metabolism was extensive, with the metabolites generally reaching greater concentrations than parent drug by 24 hours. M1 and M2 exposure was similar in rat to humans, but higher in dogs, however M3 was lower in both species than in humans. In both rat and dog, excretion was predominantly by the faecal route, with over 85% of the administered dose recovered in faeces. Less that 0.5% and 2% of dose was recovered in the urine in rats and dogs respectively. In dogs administered netupitant intravenously, recovery was largely in faeces, indicative of biliary excretion. In rat and dogs, elimination was very slow. In rats excretion was not complete after 1 week following oral or IV dosing, with 6% of the oral dose remaining in the carcass. In dogs, 87.8% and 88.1% of the dose was recovered following oral and IV dosing at two weeks post-dose, and radioactivity

was detectable 1008 hours after the dose. The data indicate that drug related material is eliminated very slowly and persist in the species tested for considerable time following administration.

For Palonosetron, Protein binding was approximately 48 % in rat and 66 % in dog plasma. The moderate extent of plasma protein binding suggests that small changes would have no influence on palonosetron availability.

Palonosetron was extensively distributed, including to the brain. It did not accumulate and is rapidly cleared. No metabolites were measured in the brain, suggesting that they did not pass the blood-brain barrier or were cleared very rapidly.

Palonosetron was rapidly absorbed in rats and dogs when administered orally. Despite high absorption, oral bioavailability was low in rats and dogs (6.4% and 12.5 % respectively), attributed to a strong firstpass effect in all two species, which suggest the possibility that some animal toxicities may not be relevant to humans. A range of metabolites was identified from animal oral studies but many were not relevant to the clinical situation, being products of first-pass metabolisms. In accordance with “the guideline on the non-clinical development of fixed combinatons of medicinal products” (EMEA/CHMP/SWP/258498/2005), pharmacokinetic studies with combination netupitant/palonosetron are not required.

2.3.4. Toxicology

Single dose toxicity

Table 4: Single dose toxicity studies performed with netupitant

Study ID	Species/ Sex/Number / Group	Dose/Route	Approx. lethal dose/observed max non-lethal dose	Major findings
NETU-07-23 (GLP)	Mouse/CD-1 6 F/group	1000 & 2000 mg/kg oral gavage	1000 mg/kg None	In the 1000 and 2000 mg/kg treated groups, delayed clinical signs and body weight loss were observed. At necropsy, nodular-thickened mesenteric lymph nodes at 2000 mg/kg. Microscopically, at 1000 and 2000 mg/kg, changes were observed in multiple organs and tissues.
1009566 (GLP)	Rat/ Wistar 4/sex/group (main), 2/sex/group (TK)	0, 500, 1000, 1500 and 2000 mg/kg oral gavage	2000 mg/kg 1500 mg/kg	2000: Mortality (males), clinical signs, body weight loss, lower food consumption, phosphor-lipidosis, necrosis of the liver and mesenteric lymph nodes. 1500: thinness, piloerection, body weight loss, lower food consumption, phospholipidosis, necrosis of the liver. 1000: lower body weight gains and food consumption. 500: NOAEL

Study ID	Species/ Sex/ Number / Group	Dose/Route	Approx. lethal dose/observed max non-lethal dose	Major findings
1009567 (GLP)	Dog/ beagle 1/sex/group	0, 200, 300 & 400 mg/kg Oral	Not established >400 mg/kg	200: vomiting, ↓Body weight 300: liquid faeces and subdued behavior; ↓Body weight and food consumption 400: mg/kg, liquid faeces and signs of subdued Behavior; vomiting, ↓Body weight and food consumption. Gall bladder: microscopic signs of phospholipidosis NOAEL: 200 mg/kg
B-167720 (non-GLP)	Dog/ beagle 1/sex/group	3, 10, 30, 30, 60, 100 and 150; escalating dose design Oral	150 mg/kg None	Slight or moderate parietal cell necrosis in the glandular stomach. Minimal vacuolated macrophage infiltration in lymphoid tissues and lungs indicates minimal phospholipidosis.

Four single dose studies in mice, rats and dogs. The major toxicity findings included death, microscopic changes in multiple organs and tissues along with signs of phospolipidosis in various organs at the higher doses. Clinical observations amounted to reduced food consumption and loss of body weight and body weight gain. An NOAEL of 500 mg/kg and 200 mg/kg were established for the rat and dog, respectively. No NOAEL was determined for mice.

Palonosetron

Studies were carried out in mouse, rat and dog using intravenous and oral route of administration. Death in all species was associated with convulsions and collapse.

Single dose toxicity studies established a maximum non-lethal intravenous dosage of 10 mg/kg in rats and mice and 20 mg/kg in dogs. A maximum non-lethal oral dosage of 250 mg/kg in rats, 100 mg/kg in mice and 50 mg/kg in dogs were established. Signs seen at non-lethal dosages included inactivity, tremors, ataxia and laboured respiration

Repeat dose toxicity

A number of preliminary, non-pivotal repeated dose toxicity studies were performed in rat and dog to examine the effects of netupitant alone and in combination with palonoestron. The applicant has provided results from a series of non-pivotal repeat dose toxicity studies (<1 month) conducted in mice, rats and dogs. The majority of these studies were performed to GLP and presented preliminary/dose range finding for the pivotal studies. The main findings for netupitant alone amounted to effects on body weight and food consumption, changes in clinical chemistry parameters, increased liver and adrenal weight increases and occurred at all doses in some studies. Microscopic findings included changes in the lung, lymphoid tissues, liver, adrenal glands, kidney, stomach and trachea. Some of these changes occurring at does as low as 15 mg/kg were indicative of drug-induced phospholipidosis (foamy/vacuolated macrophage infiltration) with associated necrosis. In combination studies in rats (1 week and 28 day) dosed with palonosetron/netupitant (0/0-60/30 mg/kg) reduced body weight and/or body weight gain, reduced food consumption, changes in clinical pathology and blood parameters, increases in liver and kidney weights, minimal hepatocytic hypertrophy and syncytial macrophages in mesenteric lymph nodes were observed.

Similarly in dogs, decreases in body weight and food consumption were observed at all dose levels (10/3 and 20/15 mg/kg palonosetron/netupitant). Several clinical signs were also seen relating to CNS (tremors to severe seizure-like episodes, calm or restless behaviour, abnormal posture, uncoordinated movements, salivation, squeaking, head shaking), as well as effects on heart (prolonged ST and QT intervals) and liver (hepatocyte hypertrophy) at 15/7.5 and 20-15/15 mg/kg palonosetron/netupitant doses.

As in the non-pivotal studies, the main toxicity findings observed in rats at higher dose levels were in relation to microscopic changes in various organs (liver (hepatocellular vacuolation), lungs (infiltration by foamy macrophages), spleen (histiocytosis), mesenteric and mandibular lymph nodes (diffuse histiocytosis and histiocytic aggregates)) that were consistent with drug induced phospholipidosis. These changes were completely or at least partially in the case of liver, lung and lymph nodes reversible after an 8 week recovery period. No evidence of drug-induced lamellar inclusion bodies was observed at dose up to 450 mg. Reduced body weight, body weight gain and food consumption, changes in clinical parameters (increased protein, globulin, cholesterol levels & changes in various liver enzymes) were again observed in these studies but these were considered related treatment induced inflammatory changes in some organs and microscopic changes in the liver. Increased liver and kidney (female only) weights were also observed. NOAELs of 3 mg/kg and 1 mg/kg were established for the 13 week and the 26 week repeat-dose toxicity, respectively.

In the 13 week pivotal study in dogs, mild drug induced phospholipidosis was observed as indicated by vacuolated macrophages in lymphoid tissue in the highest dose group (10 mg/kg). However this was reversible upon the 8 week recovery period. In the 9 month study, slightly longer QT intervals (males only) and prolonged PQ intervals were noted in high dose animals but were reversible upon cessation of treatment. Increased liver weights with correlated microscopic evidence of minimal periacinar hepatocytic hypertrophy and elevated alkaline phosphatase levels in the plasma were also seen in the high dose males. As with all other studies, changes in body weight and body weight gain and reduced food consumption were also apparent. A NOAEL of 3 mg/kg was established for both studies.

In rat combination studies with palonosetron / netupitant (0, 2/1, 6/3, 18/10, 18/0, or 0/10 mg/kg), the main target organs identified were the adrenals in females and liver and mesenteric lymph node in males and females. Toxicities amounted to adrenal zona fasciculate hypertrophy at 118/10 and 0/10 mg/kg which was reversible at the end of the recovery period; reversible hepatocytic hypertrophy in high dose females at combination therapy (18/10), as well as for males and females with netupitant monotherapy (0/10) and for females with palonosetron monotherapy (18/0). These liver changes were also associated with increased liver weights. Mesenteric lymph node syncytial macrophages with increasing severity were also observed at 6/3 (females), 18/10 (males and females) and 0/10 mg/kg (males and females). These findings were not reversible at the end of the recovery period and are thought to represent a precursor to phospholipidosis which was one of the main toxicity findings seen in the repeat dose toxicity studies. Of note form the toxicokinetic studies, after single administration of the combination product some gender differences were observed where exposure in males was lower than that observed in females particularly in the 6/3 dose group. The NOAEL for this study was 2/1 mg/kg palonosetron/netupitant.

In dog combination studies with palonosetron / netupitant (0, 3/1, 5/3, or 10/10 mg/kg), the main toxicities observed were reduced body weight gain in females at 10 mg/kg, prolonged ST- and QT intervals at 10/10 mg/kg and increased liver weights that maintained in some animals until the end of the recovery period (10 mg/kg). The NOAEL concluded for this study was 5/3 mg/kg palonosetron/ netupitant.

Studies submitted for palonosetron to assess the repeated dose toxicity in mice used the oral route. The applicant's justification for performing oral studies to mimic the exposure profile during intravenous

administration in humans was considered acceptable. The CHMP assumes that, with the intended clinical human exposure being a single i.v. injection (the intended clinical i.v. dose of palenosetron (0.25mg) equates to approximately 0.004 mg/kg for a 70 kg adult), and at a dose many multiples lower than the lowest animal i.v NOAEL (7 mg/kg/day and 6 mg/kg/day for rat and dog, respectively), palenosetron, in the absence of drug interactions, is safe for the intended use in human.

Genotoxicity

Two Ames bacterial cell reverse mutation assays were performed with netupitant. Owing to precipitation and toxicity observed, concentrations from 2 to 200 µg/plate (Study No. 1004078) and from 5 to 500 µg/plate and 1 to 100 µg/plate for the plate incorporation and pre-incubation versions of the assay respectively (Study No. 1006128) were tested. Even at these concentrations, toxic effects were visible at the upper concentrations, with variation depending on strain and presence or absence of metabolic activation. Netupitant did not induce any dose related increased of the number of revertant colonies/plate in any of the five tester strains examined (Salmonella typhimuriurn: TA1535, TA97, TA98, TAl00 and TA102). Netupitant did not increase the mutant frequency in a mouse lymphoma assay in the absence (5.0 to 17.5 µg/mL (3 h treatment) and 1.0 to 7.0 µg/mL (24 h treatment)) or presence of metabolic activation (5.0 to 30.0 µg/mL (3 h treatment). No chromosome damage was detected in vivo in rat bone marrow micronucleus test at concentrations up to 1000 mg/kg.

With palonosetron in vitro bacterial mutation and mammalian cell mutation studies were negative. A chromosome aberration study in Chinese hamster ovary cells was positive without S9 mix at concentrations of 201µg/mL or more. A positive result with S9 mix at the highest concentration, 650µg/mL, was considered equivocal. An intravenous mouse micronucleus test at dosages up to 10mg/kg, and an intravenous rat liver unscheduled DNA study at dosages up to 30mg/kg, were both negative. The highest dosages were close to established lethal dosages. Treatment in the rat study was associated with clonic convulsions. Based on toxicokinetic data from other studies, high exposures can be assumed.

Carcinogenicity

No carcinogenicity studies were performed with netupitant which is considered acceptable given the short duration of treatment.

Two long-term studies assessed the carcinogenic potential of palonosetron in rat and mouse. Although the oral gavage route was used in these studies, whereas bolus intravenous is the route of administration of the proposed indication, all dosages used were multiples of the proposed human dosage and comparison of AUC0-24h values indicated large multiples, ranging from 136 to 1220-fold in males and from 61 to 706-fold in females. High doses applied daily for two years caused an increased rate of liver tumours, endocrine neoplasms (in thyroid, pituitary, pancreas, adrenal medulla) and skin tumours in rats but not in mice. The underlying mechanisms are not fully understood, but because ofthe high doses employed and since palonosetron is intended for single application in humans, these findings are not considered relevant for clinical use.

Reproduction Toxicity

In reproductive and developmental toxicity studies, higher numbers of foetuses with tarsal hyperflexion and/or pes adductus were reported in rats at 10 and 30 mg/kg/day. These limb variations were not associated with alterations in skeletal or soft tissue parts and could be considered related to restricted movement in the uterus such as caused by loss of amniotic fluid or crowded uterine horns. At the NOAEL for both maternal and developmental endpoints, there was no safety margin (exposure ratio = 0.6).

In rabbits, litter parameters were unaffected except the slight decreases foetal body weight at 30 mg/kg/day. Position anomalies of forelimbs and/or hindlimbs and forepaws were noted in dose-related manner. At 10 and 30 mg/kg/day, these effects occurred at a higher incidence than in study and historical controls.

A treatment-related increase in the number of minimally/partially fused sternebrae was observed at 10 mg/kg and 30 mg/kg (fetal incidence: 7.9% and 15.0%; litter incidence: 40% and 58.8%) in the pivotal study. This finding occurred at a higher incidence than in study and historical controls (fusion and/or abnormal shape of 2 or more sternebrae: 1.1%-8%), and is considered as a malformation in spite of the lack of reduction in inter-sternebral spaces.

Agenesis of accessory lung lobe was observed at a higher incidence at ≥ 10 mg/kg/day (25%-29%) than in study controls (10%) or in historical controls. As regards historical control data, it is limited to 5 studies (the current study being excluded). The incidence of absent accessory lung lobe ranged from 0% to 23%, with incidence exceeding 15% in only one study (0%, 0%, 9%, 14%; 23%). Overall, a treatment-related effect is considered given the increased incidence of this malformation in treated rabbits.

Palonosetron oral application to rats (one –month repeat-dose toxicity study in rat) was associed with degeneration of the seminferous epithelium, this was not observed in i.v. fertility studies, leading to the conclusion that this toxic effect might be due to metabolites. Reproductive and developmental studies conducted were overall acceptable and the NOAELs were high enough to allow a reasonable assumption of safety in human. No treatment-related teratogenic effets were seen with palonosetron. Maternal toxicity was the limiting factor in the embyo-foetal studies. Overall the reproductive and developmental studies conducted were appropriate and the NOAELs were high enough to allow a reasonable assumption of safety in human.

In accordance with “the guideline on the non-clinical development of fixed combinatons of medicinal products” (EMEA/CHMP/SWP/258498/2005), no embryo-foetal development studies with combination netupitant/palonosetron are not required.

Toxicokinetic data

Table 5: Toxicokinetics of Netupitant in rat, dog and rabbit

Study ID	Daily Dose (mg/kg)	C_{max} (ng/mL)		Steady state AUC_{24h} (ng.h/ml)		Animal:Human Exposure Multiple	
		♂	♀	♂	♀	♂	♀
Rat							
1007326 **2 week**	30	-	2510	-	52000	-	2.1
	100	-	17400	-	398000	-	15.8
	300	-	17500	-	299000	-	11.9
1003562 **4 week**	10	1100	1620	15100	-	0.6	-
	100	9750	4490	17300	-	0.7	-
1006011 **4 week**	3	593	704	9080	14100	0.4	0.6
	10	899	1350	15000	28600	0.6	1.1
	30	1490	2580	29600	54400	1.2	2.2
NETU-06-03 **4 week**	10P/3N	239	710	4358	14965	0.2	0.6
	18P/10N	707	957	13251	20112	0.5	0.8
	60P/30N	1185	1560	23430	31726	0.9	1.3
161/578S **13 week**	3	426	553	**7150**	**11100**	**0.3**	**0.4**
	10	764	1220	14000	26600	0.6	1.1
	30	1490	2080	30200	49200	1.2	2.0
	30§	1310 §	2540 §	26500 §	49400 §	1.1	2.0

Study ID	Daily Dose (mg/kg)	C_{max} (ng/mL)		Steady state AUC_{24h} (ng.h/ml)		Animal:Human Exposure Multiple	
	2P/1N	161	332	**7490**	**7500**	**0.3**	**0.3**
NETU-07-19	6P/3N	467	546	7520	12500	0.3	0.5
13 week	18P/10N	680	1190	12100	27100	0.5	1.1
	0P/10N	669	1230	13800	22600	0.5	0.9
NETU-07-21	1	126	318	**2550**	**6070**	**0.1**	**0.2**
26 week	3	458	1050	6510	17200	0.3	0.7
	10	829	1340	16000	27500	0.6	1.1
Dog							
	1	108	223	1500	2530	0.1	0.1
1006010**	3	503	296	5980	3560	0.2	0.1
4 week	5	814	855	10000	9440	0.4	0.4
	15	1610	1720	27900	28100	1.1	1.1
	50	3840	4160	78700	63900	3.1	2.5
NETU-06-05	10P/3N	300	318	3330	3784	0.1	0.2
4 week	15P/7.5N	592	572	8633	8492	0.3	0.3
	20(15#)P/15N	1866	1029	27397	16511	1.1	0.7
	1	169	137	2230	1640	0.1	0.1
1009175	3	342	324	**3970**	**3520**	**0.2**	**0.1**
13 week	10	819	420	11000	6470	0.4	0.3
	10§	1150§	1080§	14600§	14200§	0.6	0.6
NETU-07-18	3P/1N	167	154	1900	1670	0.1	0.1
13 week	5P/3N	527	374	**6760**	**4070**	**0.3**	**0.2**
	10P/10N	883	795	15300	11500	0.6	0.5
NETU-07-22	1	147	202	1880	2290	0.1	0.1
9 month	3	466	417	**6280**	**5520**	**0.2**	**0.2**
	10	1200	848	20500	12400	0.8	0.5
Rabbit (pregnant)							
1007931	3	-	57	-	816	-	<0.1
GD 17	10	-	159	-	2500	-	<0.1
	30	-	310	-	5460	-	0.2

§: following intermittent oral administration, **: data from day 29

Table 6: Toxicokinetics of Netupitant metabolites M1, M2 and M3 in rat, dog and rabbit

Study	Doses (mg/kg)	$AUC_{(0-24)}$ (h·ng/mL))	Human Exposure Multiple	$AUC_{(0-24)}$ (h·ng/mL)	Human Exposure Multiple	$AUC_{(0-24)}$ (h·ng/mL)	Human Exposure Multiple)
		M1(M/F)		**M2 (M/F)**		**M3 (M/F)**	
Rat							
1007326	30	34700	6.5	884	<1	2450	
2 week	100	165000	31	19400	10	23400	
	300	69700 ***	13	36600 ***	20	13600 ***	
1006011	1	15100/10800	2.8/2	NC/NC	<1	255/54.2	<1
4 week	3	30000/25100	5.6/4.7	NC/NC	<1	/2240	<1
	10	47200/45400	8.8/8.5	476/1610	<1	3000/3630	<1
NETU-06-03	10P/3N	6379/11659	1.2/2.2	65.5/32.6	<1	356/465	<1
4 week	18P/10N	18797/18004	3.5/3.4	602/551	<1	1188/1265	<1

Study	Doses (mg/kg)	$AUC_{(0-24)}$ (h·ng/mL))	Human Exposure Multiple	$AUC_{(0-24)}$ (h·ng/mL)	Human Exposure Multiple	$AUC_{(0-24)}$ (h·ng/mL)	Human Exposure Multiple)
	60P/30N	26425/24510	5/4.6	655/864	<1	2273/2725	<1
161/578S	**3**	**14300/12500**	**2.7/2.3**	NC	-	552/138	<1
13 week	10	25700/ 27700	4.8/5.2	NC	-	1190/1260	<1
	30	43800/36700	8.2/6.9	581/841	<1	2720/3750	<1
	30§	32700/3200	6.1/0.6	512/689	<1	2520/2610	<1
NETU-07-19	**2P/1N**	**5120/4850**	**1/0.9**	BLQ	-	BLQ	-
13 week	6P/3N	13200/12300	2.5/2.3	325/238	<1	643/529	<1
	18P/10N	22300/23400	4.2/4.4	324/495	<1	1230/1630	<1
	0P/10N	23200/17800	4.4/3.3	480/478	<1	1290/1380	<1
NETU-07-21	**1**	**4010/3960**	**0.8/0.7**	BLQ/BLQ	<1	BLQ/BLQ	-
26 week	3	13070/16900	2.5/3.2	268/346	<1	695/722	<1
	10	27100/24600	5.1/4.6	726/650	<1	1590/1860	<1
Dog							
1006010**	1	2570/3950	0.5/0.7	NC	-	NC	-
4 week	3	10900/6660	2/1.3	1260/819	<1	503/396	<1
	5	25400/22100	4.8/4.2	2240/2590	1.2	NC/NC	<1
	15	54900/64900	10.3/12.2	6080/7510	3.3/4.1	3530/3560	<1
	50	119000/133000	22.4/25	38600/34200	<20	8750/14100	1.2/2.2
NETU-06-05							<1
	10P/3N	6419/7495	1.2/1.4	1838/1156	<1	337/371	
4 week							<1
	15P/7.5N	21828/14143	4.1/2.7	4494/2338	2.4/1.2	1334/1690	
							<1
	20P/15N	48866/31968	9.2/6.0	10871/6294	6/3.4	2978/2130	
1009175	1	2910/2080	0.5/0.4	527/401	<1	BLQ/BLQ	-
13 week	**3**	**5780/5740**	**2.0/1.1**	947/892	<1	419(only F)	<1
	10	25400/15600	4.8/2.9	5310/2670	2.9/1.4	1240/878	<1
	10§	17300/20300	3.3/3.8	3570/3920	2	1390/1140	<1
NETU-07-18	3P/1N	3060/2870	0.6/0.5	548/527	<1	ND	<1
13 week	**5P/3N**	**13500/6700**	**2.5/1.3**	2310/1060	1.2/<1	636/367	<1
	10P/10N	32600/24700	6.1/4.6	4680/3720	2.5/2	1700/1480	<1
NETU-07-22	**1**	**3890/4650**	**0.7/0.9**	984/1160	<1	ND	-
9 month	3	12200/9920	2.3/1.9	1990/1630	~1	648/679	<1

Study	Doses (mg/kg)	$AUC_{(0-24)}$ (h·ng/mL))	Human Exposure Multiple	$AUC_{(0-24)}$ (h·ng/mL)	Human Exposure Multiple	$AUC_{(0-24)}$ (h·ng/mL)	Human Exposure Multiple)
	10	45400/26100	8.5/4.9	6380/4940	3.4/2.7	2470/1590	<1
Rabbit (pregnant)							
1007931	3	NC	-	NC	-	NC	-
GD 17	10	1320	0.2	1140	<1	1330	<1
	30	3320	0.6	3620	1.9	3750	<1

: data from day 29 *: data from day 5, only from male animals

Pivotal study toxicokinetics

In the 13 week study in rat, maximum plasma concentrations of netupitant were 426/553 and AUC (0-24h) values were 2550/6070 h.ng.mL (male/females) on day 91 at the NOAEL dose of 3 mg/kg/day. Plasma concentrations of netupitant in male and female rats were similar although there was a tendency to higher plasma concentrations in female than in male rats. An accumulation of netupitant was observed throughout the study. A high exposure to the main metabolite M1 was observed with AUC(0-24h) values of 14300/12500 h.ng/mL in male/female rats at the NOAEL dose. In 26 week study in rat, maximum plasma concentrations of netupitant were 126/318 and AUC (0-24h) values were 7150/11100 h.ng.mL (male/females) on at the NOAEL dose of 1 mg/kg/day. An accumulation of netupitant and metabolites M1 in week 4 compared to week 1. A high exposure to the main metabolite M1 was observed with AUC(0-24h) values of 14300/12500 h.ng/mL in male/female rats at the NOAEL dose. Palonosetron/Netupitant combination treatment did not appear to have a significant effect on exposure to netupitant or metabolite M1 compared to netupitant alone.

In the 13 week dog study maximum plasma concentrations of netupitant were 324/342 ng/mL and AUC(0-24h) were 3520/3970 h.ng/mL (female/male) on day 87. Slight to moderate accumulation was evident compared to day zero values. In all dosing groups there was a tendency for higher plasma concentrations of netupitant and all three metabolites in male than in female dogs. AUC(0-24) was 5780/5740 h.ng/mL in males/females. There was a high accumulation of M1 with mean accumulation factors ranging from 2.2 to 2.9 in females and from 2.4 to 4.3 in males, and a dose proportional increase between 1 and 10 mg/kg. TK parameters for netupitant in the 3-month combination study was approximately similar to that in the 28-day combination therapy study in dogs, although AUC levels in males apeared to be increased in 5P/3N males.

In the 9 month study maximum plasma concentrations of netupitant were 466/417and AUC (0-24h) values were 6280/5520 h.ng/mL (male/females) at the NOAEL dose. C_{max} and AUC increased generally in a dose proportional manner over the dose range of 1 to 3 mg/kg and from 3 to 10 mg/kg, with ratios for C_{max} ranging from 2.1-5.4 and 1.7-3.2 respectively. AUC ratios were 2.2-4.8 and 2.2-4.2 respectively. C_{max} and AUC increased generally in a dose proportional manner over the dose range of 1 to 3 mg/kg and from 3 to 10 mg/kg, with ratios for C_{max} ranging from 2.1-5.4 and 1.7-3.2 respectively. AUC ratios were 2.2-4.8 and 2.2-4.2 respectively. AUC values slightly increased over time in males and females at all dose levels. Netupitant and its metabolites M1, M2 and M3 was similar in males and females, and showed dose proportional kinetics. Netupitant accumulated slightly, in terms of AUC, in both sexes at all dose levels.

Local Tolerance

In an intravenous local tolerance study in rabbits, marked local non-reversible reactions along with increased neutrophils and monocytes were noted at 10 mg/kg i.v. However, netupitant was considered non-irritating and non-sensitising to eye and skin of rabbits and albino guinea pigs. The relevance of

these studies is limited owing to the proposed clinical oral indication. For palonosetron, no evidence of local tolerance toxicity was observed in the i.v. toxicology investigations. In accordance with "the guideline on the non-clinical development of fixed combinatons of medicinal products" (EMEA/CHMP/SWP/258498/2005), local tolerance studies with combination netupitant/palonosetron are not required.

Other toxicity studies

The possible phototoxic potential of netupitant was examined in vitro by the 3T3 fibroblast Neutral Red uptake assay. Netupitant absorbs UV light between 240 and 380 nm. Murine fibroblasts were incubated for 1 h with 0.75-96.0 µg/mL netupitant in the presence of UVA exposure and in the dark. Under these experimental conditions netupitant was considered to be non-phototoxic.

Neputipant was not antigenic in male guinea pigs tested for active systemic and for passive anaphylaxis (Study No. 1007385; GLP). Neputipant did not appear to be phototoxic, irritating or sensitizing and was not antigenic.

The genotoxic potential of impurities was evaluated by SARS analysis (Derek). The results of this assessment were negative. Furthermore, the specified impurities 12-NETU and 14-NETU i10 were negative in an Ames test in the absence or presence of S9 metabolism at concentrations up to 5000 µg/plate.

Given that an additional metabolite M4 was detected in clinical studies, the mutagenic potential of this metabolite was examined in an Ames assay. The M4 metabolite was considered to be non-mutagenic in the Ames assay. Moreover, an IC50 of 66.6 µg/ml for the M4 metabolite was obtained in the in vitro cytotoxicity assay in BALB/C 3T3 cells. Given that the M4 systemic exposure (AUC) is 3% of netupitant systemic exposure, the results of the in vitro studies sufficiently characterise this metabolite.

For palonosetron in *vitro* photo-cytotoxicity and photo-clastogenicity tests, and a photo-allergenicity investigation that included a preliminary single-dose photo-irritation study were conducted and no evidence of phototoxicity were observed. In accordance with "the guideline on the non-clinical development of fixed combinatons of medicinal products" (EMEA/CHMP/SWP/258498/2005), others toxicity studies with combination netupitant/palonosetron are not required.

2.3.5. Ecotoxicity / environmental risk assessment

NETUPITANT

Table 7: Ecotoxicity data of netupitant

Substance : NETUPITANT			
CAS-number : 290297-26-6			
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	**4.35 (pH= 6.5 after 48h) - 5.28 (pH= 8.5 after 48h)**	not B
Phase I			

Calculation	Value	Unit	Conclusion
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	**0.003 (0.006 in worst case)**	µg/L	> 0.01 threshold (Y)

The first test (OECD 301) is scheduled to be completed in 2014.

PALONOSETRON

Table 8: Ecotoxicity data of palonosetron

Substance : PALONOSETRON			
CAS-number : 135729-62-3			
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	**4.3 at pH 7.4**	not B
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0025	µg/L	> 0.01 threshold (Y)

Palonosetron PEC surfacewater is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore, palonosetron is not expected to pose a risk to the environment.

Netupitant PEC surfacewater is below the action limit of 0.01 µg/L but log Kow exceeds 4.5 As a result the available data do not allow to conclude definitively on the potential risk of netupitant to the environment.

The applicant has initiated a tiered risk assessment with regards to PBT in a stepwise manner:

Step 1) OECD 301 Ready Biodegradability Test;

Step 2) OECD 308 Sediment-Water Transformation Test;

Step 3) OECD 305 Bioconcentration Test with Fish;

Step 4) OECD 201 (Algae), 210 (Fish Early Life Stage) and 211 (Daphnia Reproduction).

From work completed (OECD 301 Ready Biodegradability Test), netupitant was not considered readily biodegradable.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends for further investigation: To conduct the remaining studies and submit the data upon finalisation.

2.3.6. Discussion on non-clinical aspects

In accordance with "the guideline on the non-clinical development of fixed combinations of medicinal products" (EMEA/CHMP/SWP/258498/2005), the repeat-dose and dependance studies with combination netupitant / palonosetron were performed and no other studies are required.

In the non-clinical studies the pharmacodynamic, pharmacokinetic and toxicological effects of netupitant alone and in combination with palonoestron have been sufficiently characterised.

The pharmacodynamic studies provide sufficient proof of efficacy (antineoplastic-induced emesis in ferrets & inhibition of NK1 agonist-induced foot-tapping in gerbils) for the individual actives alone as well as in combination with palonosetron.

Interactions at the histamine (H2), adenosine (A3), DA and 5-HT reuptake sites, L-type Ca2+ channel and diltiazem binding site on the Ca2+ channel were observed with netupitant. However, taking into account the protein binding for both netupitant and palonosetron, the free plasma concentration of both drugs were well below the concentrations that are reported to affect binding sites at H2, A3 receptors, DA, 5-HT reuptake and L-type and diltiazem binding sites, thus significant clinical interactions are not expected at therapeutic dose on these mechanism.

In further binding studies, the netupitant main metabolites, M1 was shown to interact at the L-type Ca2+ channel (IC50 = 2.8 µM; Ki = 1.4 µM). However, given the low systemic exposure to the M1 metabolite in human studies, the interaction of M1 with L-type Ca^{2+} channel is unlikely to have any clinical implications. This is further supported by the lack of any significant cardiovascular side effects observed in human studies.

Cardiovascular effects were observed in conscious dogs with netupitant and its main metabolite M1. Since M1 has a major role in the QT prolongation and it is present in higher concentrations in dogs than in humans, the findings obtained in animals are not considered to be directly correlated to human cardiotoxicity. This is further supported by the lack of significant changes of QT prolongation with netupitant alone and in combination with palonosetron in a thorough QT prolongation study (Study No. NETU-07-20) and in a phase I clinical studies in healthy volunteers (Study No. NP16603/1007847 & NP16601-1014020).

For palonosetron, in rats changes were mainly detected in bone, kidney, testis, adrenal zona glomerulosa and spleen. The target organs in the dogs were thymus and liver. The CHMP assumed that, with the intended clinical human exposure and at a dose many multiples lower than the lowest animal i.v NOAEL was safe for the intended use in human.

While the M3 metabolite had comparable pharmacological activity with respect to netupitant, the toxicity profile of the metabolite (outside of the well characterised cardiovascular effects) in the pivotal repeat-dose studies is unclear. However, given that M3 AUC concentrations in the 4 week dogs study following higher doses of netupitant were equivalent to the expected clinical exposure, and that patients will only receive a single dose prior to the chemotherapy cycle, it can be accepted that the lack of exposure in the pivotal toxicity studies does not pose a significant clinical safety risk.

In vitro CYP450 inhibition studies indicated a potential for clinically relevant CYP3A4 interactions, with both netupitant and metabolite M1. A concentration dependent inhibition of CYP3A4-mediated docetaxel inhibition was also seen, with an IC50 of 3.7 uM. The interaction is described in the SmPC. Induction of CYP1A2, CYP2C9, CYP2C19 or CYP3A4 was not seen in human hepatocytes. Based on the C_{max}/IC50 ratio, interaction with BCRP is considered a possibility and is highlighted in section 4.5 of the SmPC.

At higher dose levels microscopic changes in various organs (liver (hepatocellular vacuolation), lungs (infiltration by foamy macrophages), spleen (histiocytosis), mesenteric and mandibular lymph nodes (diffuse histiocytosis and histiocytic aggregates)) that were consistent with drug induced phospholipidosis were shown in rats and dogs. These changes were completely or at least partially in the case of liver, lung and lymph nodes reversible after an 8 week recovery period. Furthermore, risk of phospholipidosis induction in humans was examined in a Phase I clinical trial where peripheral lymphocytes were isolated and examined for the presence of lamellar bodies. No evidence of drug-induced lamellar inclusion bodies was observed at doses up to 450 mg.

No clinically relevant laboratory abnormalities were observed in the completed Phase I studies and review of adverse events (AEs) from the completed Phase III studies showed that overall slightly higher proportion of patients in the netupitant/palonosetron combination group had liver transaminases increased (AEs in the Investigations SOC) in comparison to palonosetron group but none of these laboratory abnormalities was assessed as a serious AE. The toxicological significance of PLD is still unclear in humans, but considering the evidence of toxicity and adverse functional changes in non-clinical studies “phospholipidosis” was included as an important potential risk in the RMP and in 5.3 of the SmPC.

Alteration of hepatic structure and function has been observed in non-clinical studies. The review of adverse events from the Phase III studies showed that overall slightly higher proportion of patients in the netupitant/palonosetron combination group had liver transaminases increased (AEs in the Investigations SOC) in comparison to palonosetron group, with no impact on hepatic function. None of these laboratory abnormalities was assessed as a serious AE, but the applicant proposed to include “liver transaminases increase” as an important potential risk in 4.8 of the SmPC and this was agreed by the CHMP.

Administration of netupitant to rabbits during the period of organogenesis was shown to increase the incidence of some foetal malformations: limb and paw positional anomalies, minimal/partial fusion of sternebrae, and agenesis of accessory lung lobe. The NOAEL for embryo-fetal development is 3 mg/kg/day. Taking into account the teratogen effect of netupitant in rabbit without a safety margin, a contraindication of AKYNZEO during pregnancy with a contraception measure for women of childbearing potential was included into the SmPC.

The applicant has initiated a tiered risk assessment with regards to PBT. From work completed (OECD 301 Ready Biodegradability Test), netupitant was not considered readily biodegradable. The remaining studies are underway or are being planned. In the context of the obligation of the MAH to take due account of technical and scientific progress full and final reports are recommended to be submitted when completed for final assessment.

2.3.7. Conclusion on the non-clinical aspects

The main toxicities observed during the non-clinical development of netupitant were in relation to phospholipidosis and QT prolongation. These toxicities were partially if not fully reversible upon cessation of treatment. Moreover, the toxicities appear to be related to continued administration and to the abundance of the M1 metabolite both in the rat and dogs. Lamellar inclusion bodies (biomarker of phospholipidosis) after single and multiple administration doses of netupitant up to 450 mg were not detected in humans while no significant changes of QT prolongation were seen in the TQT study in healthy volunteers. Appropriate information was included in section 5.3 of the product information.

In view of a number of foetoxic findings observed in the rabbit reprotoxicity studies’, a teratogenic risk of the FDC is probable. Alternative treatment options are available in this indication. Therefore Akynzeo has been contraindicated in pregnant women and it is advised in the SmPC that women of childbearing

potential must use effective contraception during therapy. The SmPC of Akynzeo in section 5.3 summarizes the foetotoxic effects seen in animal studies seen with netupitant and in combination with palonosetron such as an increased number of minimally/partially fused sternebrae, cleft palate, microphthalmia and aphakia and lobular agenesis of the lung.

Overall, the non-clinical data for the FDC are considered appropriate to support the proposed indication.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 9: Tabular overview of clinical studies

Study Number	Objective(s)	Design	Inclusion criteria	N subjects	Treatment
Bioavailability studies					
BP-17408	Comparative bioavailability of 2 different formulations per os; to evaluate the sucrose ester formulation with food	Randomised open label, 3-ways crossover	Healthy subjects	12M, 6F	Single-dose PO. Netupitant 450 mg SDS capsule formulation or SE capsule formulation
NETU-11-23	Comparative bioavailability of Netupitant as 3 formulations	Randomised, open-label, 3-treatments, 6-sequence, 3-period crossover	Healthy subjects	24M	Single-dose PO. Netupitant/Palonosetron 300 mg/0.5 mg FDC standard capsule, Netupitant/Palonosetron 300 mg/0.5 mg FDC slow-dissolution capsule, and extemporaneous netuputant 300 mg suspension + Palonosetron 0.5 mg softgel
NETU-08-12	Pilot bioequivalence of FDC capsule (phase III formulation) vs. extemporaneous combination	Randomised, open-label, 2-period, 2-sequence crossover pilot study.	Healthy subjects	8M	Single-dose PO. Netupitant/Palonosetron 300 mg/0.5 mg FDC capsule, and extemporaneous Netupitant 2*150 mg capsules+ Palonosetron 0.5 mg softgel
NETU-09-07	Bioequivalence of FDC capsule (Phase 3 formulation) vs. extemporaneous combination	Randomised, open-label, 4-period, 2-sequence replicate crossover	Healthy subjects	26M, 24F.	Single-dose PO. Netupitant/Palonosetron 300 mg/0.5 mg FDC capsule, and extemporaneous Netupitant 2*150 mg capsules+ Palonosetron 0.5 mg softgel

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NETU-09-07	Bioequivalence of FDC capsule (Phase 3 formulation) vs. extemporaneous combination	Randomised, open-label, 4-period, 2-sequence replicate crossover	Healthy subjects	26M, 24F.	Single-dose PO. Netupitant/Palonosetron 300 mg/0.5 mg FDC capsule, and extemporaneous Netupitant 2*150 mg capsules+ Palonosetron 0.5 mg softgel

NETU-11-02	Bioequivalence between FDC capsules by 2 different manufacturers: Phase 3 and late Phase 1.	Randomised, open-label, 4-period, 2-sequence, 2-treatment, replicate crossover	Healthy subjects	19F, 69M	Single-dose PO. Netupitant/Palonosetron 300 mg/0.5 mg FDC capsules Nerpharma vs. HBP
PK Studies					
1007847/ NP16603	Assess PK and PD of Netupitant after single oral ascending doses	Randomised, double-blind, placebo-controlled, single centre	Healthy subjects	30M	Single-dose PO. Netupitant 10, 30, 100, 300 and 450 mg
1014020/ NP16601	Assess tolerability, safety and PK of Netupitant after 1 week daily oral dosing in ascending fashion	Randomised, double-blind, placebo-controlled, ascending dose	Healthy subjects	33M (including 3 E)	PO once daily for 7 days, Netupitant 100, 300, 450 mg
1014816/ BP17085	Assess tolerability, safety and preliminary PK of ascending dose of Netupitant IV	Randomised, double-blind, placebo-controlled, single ascending dose	Healthy subjects	19M	IV Netupitant 3, 10, 30 mg
NETU-09-21	Mass-balance study for Netupitant	Non-randomised, open-label	Healthy subjects	6M	Single dose PO ^{14}C-Netupitant 300 mg
NETU-11-01	Investigate safety and tolerability of ascending doses of IV Netupitant, select the IV dose of Netupitant providing PK similar to 300 mg oral Netupitant, and evaluate PK of metabolites	Sequential-cohort, placebo-controlled, double-blind, unbalanced single ascending dose	Healthy subjects	16M, 16F	Single IV Netupitant 25, 50, 75, 100 mg
PK studies in target population					
NETU-10-02	Population PK-PD modelling of Netupitant (and metabolites M1, M2, M3) and Palonosetron	Population PK-PD design	Samples from Phase II trial NETU-08-18	117 subjects, 571 concentrations	Single and multiple dose, Netupitant/Palonosetron FDC 300/0.5 mg
NETU-10-09	Drug-drug interaction with Docetaxel, Etoposide, Cyclophosphamide	Randomised, open-label; 2-periods crossover	Cancer patients	Docetaxel: 15M 2F Etoposide: 14M 1F Cyclophosphamide : 1M 9F	Single dose PO Netupitant/Palonosetron FDC 300/0.5 mg
Special populations					
1007929 Protocol 16600	Food and age effect for Netupitant, in 2 parts	1: randomised open-label crossover (fast vs. fed) 2: Randomised double-blind placebo-control in fed state	Healthy subjects	Food : 12M Age effet12: 6 E	Single dose PO. Food: Netupitant 300 mg, age: Netupitant 100 mg

NETU-10-12	Food and age effect	Randomised open-label 2-way crossover	Healthy subjects	22M, 14F Including 12 E	Single dose, Netupitant/Palonosetron FDC 300/0.5 mg
NETU-10-10	Effect of hepatic impairment on Netupitant and Palonosetron	Single centre, open-label, 1 period	Hepatic impaired patients and healthy subjects	26 M, 10F	Single dose, Netupitant/Palonosetron FDC 300/0.5 mg
Drug interaction studies					
1012084/ NP16599	PK and safety evaluation of interaction with midazolam and erythromycin	Randomised, partially blind, 3-way crossover	Healthy subjects	20M	Single dose PO Netupitant 300 mg
NETU-06-06	PK interaction between Netupitant and Palonosetron	Randomised, open-label, 3-period	Healthy subjects	9M, 9F	Single dose PO, Netupitant 150 mg, Palonosetron 0.75 mg
NETU-06-07	PK and safety evaluation of interaction with Dexamethazone	Randomised, open-label, 3-period crossover incomplete latin square design	Healthy subjects	14M, 11F treated	Netupitant 100, 300, 450 mg
NETU-06-27	PK interaction between Netupitant and Palonosetron	Randomised, open-label, 3-period crossover	Healthy subjects	9M, 9F	Single dose PO, Netupitant 450 mg, Palonosetron 0.75 mg
NETU-07-01	PK interaction between Netupitant and Digoxine at steady state	Open-label 1 way	Healthy subjects	8M, 8F	Netupitant 450 mg on Day 8
NETU-10-08	PK interaction between Netupitant/Palonosetron and Ethinylestradiol / Levonorgestrel	Randomised, open-label, 2-way crossover	Healthy subjects	24F	Single dose, Netupitant/Palonosetron FDC 300/0.5 mg
NETU-10-11	PK interaction between Netupitant/Palonosetron with Ketoconazole and Rifampicine	Randomised, open-label, 2-group, 2-way crossover	Healthy subjects	Ketoconazole: 11M, 6F Rifampicine: 10M, 8F	Single dose, Netupitant/Palonosetron FDC 300/0.5 mg
PD studies					
1009726 NP16602	Apomorphine challenge	Randomised double-blind, placebo controlled, 4-group, single ascending dose	Healthy subjects	30M, 2F	Single PO , Netupitant 100, 300, 450 mg
NETU-06-08	PET study to investigate the degree of occupancy of NK1 receptors in the brain	Randomised, open-label, single dose PET study	Healthy subjects	6M	Single PO , Netupitant 100, 300, 450 mg

NETU-10-12	Food and age effect	Randomised open-label 2-way crossover	Healthy subjects	22M, 14F Including 12 E	Single dose, Netupitant/Palonosetron FDC 300/0.5 mg
NETU-10-10	Effect of hepatic impairment on Netupitant and Palonosetron	Single centre, open-label, 1 period	Hepatic impaired patients and healthy subjects	26 M, 10F	Single dose, Netupitant/Palonosetron FDC 300/0.5 mg
Drug interaction studies					
1012084/ NP16599	PK and safety evaluation of interaction with midazolam and erythromycin	Randomised, partially blind, 3-way crossover	Healthy subjects	20M	Single dose PO Netupitant 300 mg
NETU-06-06	PK interaction between Netupitant and Palonosetron	Randomised, open-label, 3-period	Healthy subjects	9M, 9F	Single dose PO, Netupitant 150 mg, Palonosetron 0.75 mg
NETU-06-07	PK and safety evaluation of interaction with Dexamethazone	Randomised, open-label, 3-period crossover incomplete latin square design	Healthy subjects	14M, 11F treated	Netupitant 100, 300, 450 mg
NETU-06-27	PK interaction between Netupitant and Palonosetron	Randomised, open-label, 3-period crossover	Healthy subjects	9M, 9F	Single dose PO, Netupitant 450 mg, Palonosetron 0.75 mg
NETU-07-01	PK interaction between Netupitant and Digoxine at steady state	Open-label 1 way	Healthy subjects	8M, 8F	Netupitant 450 mg on Day 8
NETU-10-08	PK interaction between Netupitant/Palonosetron and Ethinylestradiol / Levonorgestrel	Randomised, open-label, 2-way crossover	Healthy subjects	24F	Single dose, Netupitant/Palonosetron FDC 300/0.5 mg
NETU-10-11	PK interaction between Netupitant/Palonosetron with Ketoconazole and Rifampicine	Randomised, open-label, 2-group, 2-way crossover	Healthy subjects	Ketoconazole: 11M, 6F Rifampicine: 10M, 8F	Single dose, Netupitant/Palonosetron FDC 300/0.5 mg
PD studies					
1009726 NP16602	Apomorphine challenge	Randomised double-blind, placebo controlled, 4-group, single ascending dose	Healthy subjects	30M, 2F	Single PO , Netupitant 100, 300, 450 mg
NETU-06-08	PET study to investigate the degree of occupancy of NK1 receptors in the brain	Randomised, open-label, single dose PET study	Healthy subjects	6M	Single PO , Netupitant 100, 300, 450 mg

2.4.2. Pharmacokinetics

As the pharmacokinetics of palonosetron are already well characterised, this section will focus predominantly on the pharmacokinetics of netupitant. More than one fixed dose formulation of the fixed dose formulations has been investigated in PK studies as well as extemporaneous combinations of palonsetron and netupitant which were used in the earlier PK studies.

Overall 23 PK studies were submitted in the dossier including five bioequivalent studies. Proposed analytical methods were adequate and had been satisfactorily validated.

Absorption

- **Bioavailability**

Netupitant

Bioequivalence studies were presented to investigate the PK of the formulation to be used commercially. Absolute bioavailability studies with the palonseteron/netupitant combination were not carried out in humans. Based on two studies with IV netupitant (BP17085 and NETU-11-01) the oral bioavailability in humans was greater than 60%.

A number of studies were undertaken which enable the characterisation of the extent of absorption in healthy volunteers (NETU-11-23, NETU-08-12, NETU-09-07 and NETU-11-02).

Overall measurable plasma netupitant concentrations were detected between 15 minutes and 3 hours after dosing in single dose oral studies. After this lag time, plasma concentrations followed a first order absorption process and reached C_{max} in approximately 4-5 hours. Netupitant is eliminated from the body in a multi-exponential fashion, with an apparent mean elimination half-life ranging from 30 to approximately 100 hours (across all studies for doses of 30 mg to 450 mg) with a few longer outliers.

Palonosetron

After single oral doses using buffered solution mean maximum palonosetron concentrations (C_{max}) and area under the concentration-time curve (AUC0-∞) were dose proportional over the dose range of 3.0 to 80 µg/kg in healthy subjects.

In 36 healthy male and female subjects given a single oral dose of 500 mcg palonosetron, maximum plasma palonosetron concentration (C_{max}) was 0.81 ± 1.66 ng/mL (mean ± SD) and time to maximum concentration (T_{max}) was 5.1 ± 1.7 hours. In female subjects (n=18), the mean AUC was 35% higher and the mean C_{max} was 26% higher than in male subjects (n=18). In 12 cancer patients given a single oral dose of palonosetron 500 mcg one hour prior to chemotherapy, C_{max} was 0.93 ± 0.34 ng/mL and T_{max} was 5.1 ± 5.9 hours. The AUC was 30% higher in cancer patients than in healthy subjects.

- **Influence of food**

The influence of food was investigated in two PK studies an older study conducted by Roche in 2002 (NP16600D) and a more recent one conducted by Helsinn Birex in 2010 (NETU-10-12).

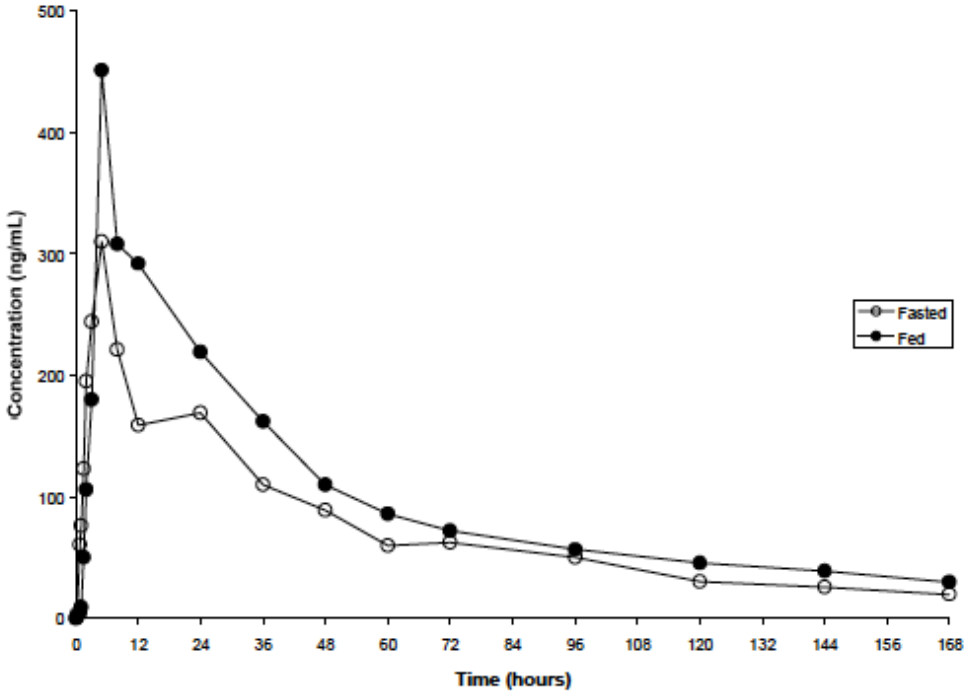
NP 16600 was an open labelled randomised cross over study with 12 healthy volunteers (aged 18-45 years of age) who received a single oral dose of 300mg Ro-67 3189 (netupitant) on two occasions under fasting and fed conditions. There was a minimum of a two week washout period between

treatments. Blood samples for PK assessment were taken pre-dose, 15 minutes and 45 minutes post-dose and 1, 1.5, 2, 3, 5, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144 and 168 hours post-dose. One subject was withdrawn from the study.

Following oral administration of 300 mg of the study drug, the plasma concentration of RO0673189 increased in a first order fashion. The relative exposure and 95% confidence intervals for treatment under fed conditions compared to fasting treatment were determined based on the results from ANOVA on log-transformed parameters. The plasma exposure, judged by peak plasma concentration and AUC of the parent compound, increased by between 69% (C_{max}) and 47% (AUC_{last}), in the fed compared to the fasted state.

Amongst healthy subjects, the impact of food on the bioavailability of RO0673189 ranged from no effect to > 3-fold increase.

Figure 1: Mean RO0673189 Plasma Concentration-Time Profiles Following Administration under Fasted and Fed Conditions



NETU-10-12 was an open, randomised, two-way, cross-over study in 24 healthy male and female adult volunteers (aged 22 to 45 years) to investigate the effect of food on the PK of netupitant and palonosetron of a single dose of a fixed dose oral combination netupitant and palonosetron (300mg/0.5mg).

Blood samples for netupitant and its metabolites were taken on D1 for each period at pre-dose as well as 1, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 12, 24, 48, 72, 96, 120, 144, 192, and 240 hours post-dose

Two subjects in the cross-over part were excluded from the statistical analysis of pharmacokinetic data as they did not have two evaluable treatment periods for pharmacokinetics:

Table 10: Pharmacokinetic parameters of netupitant after single dose administration of the FDC

Pharmacokinetic characteristic [unit] of Netupitant		T	R
AUC_{0-tz} [h·µg/L]	N	22	22
	Geo. Mean (Geo. SD)	18862 (1.27)	16002 (1.50)
	Mean ± SD (CV)	19406±4919 (25.4)	17150±6122 (35.7)
	Min. - Max.	12472-30622	4946-33403
$AUC_{0-\infty}$□ [h·µg/L]	N	22	22
	Geo. Mean (Geo. SD)	21271 (1.36)	18344 (1.57)
	Mean ± SD (CV)	22391±8650 (38.6)	20039±8396 (41.9)
	Min. - Max.	13442-53872	5308-39739
$AUC_{tz-\infty}$□ [%]	N	22	22
	Geo. Mean (Geo. SD)	9.08 (1.79)	10.3 (1.78)
	Mean ± SD (CV)	10.9±8.36 (77.0)	12.2±8.80 (71.9)
	Min. - Max.	2.71-44.5	2.72-47.1
C_{max} [µg/L]	N	22	22
	Geo. Mean (Geo. SD)	635.0 (1.25)	539.3 (1.66)
	Mean ± SD (CV)	649.8±141.6 (21.8)	596.4±233.0 (39.1)
	Min. - Max.	377.8-952.4	135.1-959.8
t_{max} [h]	N	22	22
	Median	5.50	5.04
	Min. - Max.	4.00-8.00	4.00-8.00
$t_{1/2,\lambda z}$ [h]	N	22	22
	Geo. Mean (Geo. SD)	80.7 (1.41)	91.4 (1.56)
	Mean ± SD (CV)	86.3±39.9 (46.2)	101.2±52.8 (52.2)
	Min. - Max.	49.3-244.0	38.2-285.6

T: one capsule of 300 mg netupitant and 0.5 mg palonosetron in fed state (Test)
R: one capsule of 300 mg netupitant and 0.5 mg palonosetron in fasted state (Reference)
SD: Standard deviation, CV: Coefficient of variation

Table 11: Pharmacokinetic parameters of palonosetron after single dose administration of the FDC

Pharmacokinetic characteristic [unit] of Palonosetron		T	R
AUC_{0-tz} [h·ng/L]	N	22	22
	Geo. Mean (Geo. SD)	28989 (1.28)	29198 (1.34)
	Mean ± SD (CV)	29760±6539 (22.0)	30371±8416 (27.7)
	Min. - Max.	14519-40953	12592-47893
$AUC_{0-\infty}$□ [h·ng/L]	N	22	22
	Geo. Mean (Geo. SD)	32442 (1.25)	32445 (1.33)
	Mean ± SD (CV)	33199±6945 (20.9)	33645±8974 (26.7)
	Min. - Max.	17023-44880	14402-51459
$AUC_{tz-\infty}$□ [%]	N	22	22
	Geo. Mean (Geo. SD)	10.3 (1.25)	9.70 (1.28)
	Mean ± SD (CV)	10.6±2.50 (23.5)	9.98±2.41 (24.1)
	Min. - Max.	7.27-16.2	6.66-13.8
C_{max} [ng/L]	N	22	22
	Geo. Mean (Geo. SD)	752.5 (1.23)	760.1 (1.29)
	Mean ± SD (CV)	767.9±159.2 (20.7)	785.6±223.5 (28.4)
	Min. - Max.	506.2-1106	477.0-1514
t_{max} [h]	N	22	22
	Median	5.50	4.50
	Min. - Max.	1.00-6.02	2.00-5.50
$t_{1/2,\lambda z}$ [h]	N	22	22
	Geo. Mean (Geo. SD)	37.6 (1.29)	35.9 (1.26)
	Mean ± SD (CV)	38.9±11.3 (29.1)	36.9±8.70 (23.6)
	Min. - Max.	26.1-76.5	22.4-53.7

T: one capsule of 300 mg netupitant and 0.5 mg palonosetron in fed state (Test)
R: one capsule of 300 mg netupitant and 0.5 mg palonosetron in fasted state (Reference)
SD: Standard deviation, CV: Coefficient of variation

Table 12: Analysis of variance on netupitant pharmacokinetics (effect of food)

Pharmacokinetic Parameter for Netupitant	ANOVA CV [%]	Ratio	Point estimate [%]	90% Confidence interval [%]
AUC_{0-tz} [h·µg/L]	19.41	T/R	117.88	106.66 - 130.27
$AUC_{0-\infty}$□ [h·µg/L]	20.13	T/R	115.96	104.54 - 128.62
C_{max} [µg/L]	30.87	T/R	117.74	100.65 - 137.74

T: one capsule of 300 mg netupitant and 0.5 mg palonosetron in fed state (Test)
R: one capsule of 300 mg netupitant and 0.5 mg palonosetron in fasted state (Reference)
ANOVA = Analysis of variance, CV = coefficient of variation
Source: Table 14.2.6.1

Table 13: Analysis of variance on palonosetron pharmacokinetics (effect of food)

Pharmacokinetic Parameter for Palonosetron	ANOVA CV [%]	Ratio	Point estimate [%]	90% Confidence interval [%]
AUC_{0-tz} [h·ng/L]	9.50	T/R	99.29	94.51 - 104.30
$AUC_{0-\infty}$□ [h·ng/L]	9.04	T/R	99.99	95.41 - 104.79
C_{max} [ng/L]	11.96	T/R	99.00	93.05 - 105.33

T: one capsule of 300 mg netupitant and 0.5 mg palonosetron in fed state (Test)
R: one capsule of 300 mg netupitant and 0.5 mg palonosetron in fasted state (Reference)
ANOVA = Analysis of variance, CV = coefficient of variation
Source: Table 14.2.6.2

For netupitant, the ANOVA point estimates and 90% CI for the treatment ratios T (high fat breakfast)/R (fasted) for AUC0-tz, AUC0-∞, and C_{max} were 117.88% (106,66%, 130,27%) 115.96% (104.54%; 128.62%) and 117.74% (100.65%; 137.74%), respectively. The upper limits of the 90% CIs were above the no-effect limit of 125% for all three parameters. The lower limits of the 90% CI were within the no-effect limits of 80% to 125%. However, the lower limits were above 100.00%. A statistically significant treatment effect was observed for AUC0-tz and

AUC0-∞ (p = 0.0102, and p = 0.0230, Table 12). A significant period or sequence effect was not seen (p>0.05) for any of the three parameters. The ANOVA CV was higher for C_{max} (30.87%) than for AUC0-tz and AUC0-∞ (19.41% and 20.13%).

For palonosetron, the ANOVA point estimates and 90% CI for the treatment ratios T/R for AUC0-tz, AUC0-∞, and C_{max} were 99.29% (94.51%; 104.30%), 99.99% (95.41%; 104.79), and 99.00% (93.05%; 105.33%), respectively. The limits of the 90% CIs were within the no-effect limits of 80% to 125% for all three parameters. No significant effects of treatment, period or sequence were seen (p>0.05, Table 13). There is no food effect for palonosetron.

Distribution

The mean Vd for netupitant in humans generally ranged from approximately 850 L to over 2000 L, indicating substantial distribution to tissues. Nonclinical data also show that netupitant is extensively distributed to

tissues following single or multiple (7 days) oral dosing in the rat. The drug is highly bound to plasma proteins (> 99%) with apparently no large differences in free fraction between healthy subjects and patients with hepatic failure.

Palonosetron at the recommended doses is widely distributed in the body (volume of distribution of approximately 8.3±2.5 L/kg) and approximately 62% is found as bound to human-plasma proteins.

- Distribution in cancer chemotherapy patients

Data on distribution in cancer chemotherapy patients comes from the a population PK analysis (NETU-10-02), performed in association with the Phase 3 study NETU-08-18.

Netupitant disposition was characterized by a 2-compartment model with an estimated median systemic CL of 20.5 L/h and a large volume of the central (486 L) and peripheral compartments (1170 L), respectively. These estimates for CL and volume indicated that the drug was extensively distributed in body tissues and the plasma elimination was rapid.

Elimination

- **Excretion**

Netupitant is primarily excreted via hepatic/biliary routes, with renal clearance (CLr) accounting for less than 5% of CL. In early studies, 3 active metabolites were identified (M1, M2 and M3). In plasma from humans who were administered oral netupitant, netupitant and its 3 major metabolites were extensively bound (> 97%) to plasma protein at concentrations ranging from 10 to 1500 ng/mL.

In an open label label, single dose study (NETU-09-21) in 6 healthy males designed to assess the mass balance recovery, PK, metabolic profile and metabolic identification of 300mg [14C]-netupitant, approximately half the administered dose of radioactivity was recovered within 120 h of dosing. However, for all subjects, insufficient radioactivity data (ie <90%) was recovered by 336 h. Therefore, subjects were required to collect faeces samples for a 24 h period (456 to 480 h) at home, and both faeces and urine samples for an additional 24 h period (672 to 696 h) in the clinic.

Based on the total radioactivity recovered in all samples, including the additional collection periods, total radioactivity from the urine accounted for 3.95% (range 2.2% to 4.6%) of the dose and total radioactivity from the faeces accounted for 70.7% (range 62.1% to 75.2%) of the dose at 696 h post-dose. These data indicate that the hepatic/biliary route, rather than renal clearance, is the major elimination route for drug-related entities.

The mean recovery from subjects after the second additional 24 h collection was subsequently estimated to be approximately 90% (based on the assumption that the excretion was proceeding at a steadily decreasing rate). Including the extrapolated values for the periods 336 to 456 h and 480 to 672 h, the total drug-related material to have been excreted by 696 h post-dose via the faeces was estimated to be 86.49%; a mean of 4.75% of drug-related material was estimated to have been excreted in the urine for the same time period.

Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites.

Following administration of a single oral 0.75 mg dose of [14C] palonosetron to six healthy subjects, 85% to 93% of the total radioactivity was excreted in urine, and 5% to 8% was eliminated in faeces. The amount of unchanged palonosetron excreted in the urine represented approximately 40% of the administered dose. In healthy subjects given palonosetron capsules 500 mcg, the terminal elimination half-life (t½) of palonosetron

was 37 ± 12 hours (mean ± SD), and in cancer patients, t½ was 48 ± 19 hours. After a single dose of approximately 0.75 mg intravenous palonosetron, the total body clearance of palonosetron in healthy subjects was 160 ± 35 mL/h/kg (mean ± SD) and renal clearance was 66.5± 18.2 mL/h/kg.

- **Metabolism**

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. M4 was identified as a minor metabolite (< 10% exposure of the parent) late in the development process in study NETU-09-21.

In NETU-09-21 netupitant was shown to undergo extensive metabolism, forming both phase I and phase II metabolites. Phase I metabolites observed included those formed through N-demethylation (mono and bis), mono and di-hydroxylation, N-oxidation, desaturation, N-formylation, oxidation and reduction to a keto group, and oxidation to an acid (including oxidation of the toluene methyl group to an acid). Intermediate metabolites in the 1-methylpiperazine degradation pathway to the further oxidised 6-amino-pyridinyl derivatives were also observed. Phase II metabolites included those formed by glucuronidation and conjugation to a hexose (C6 sugar) group. A glucuronic acid conjugate of the acid-half molecule of netupitant was also observed in urine.

Analysis of the plasma samples for the metabolites M1, M2, and M3 indicated that based on the AUC0-t values, metabolites M1, M2 and M3 represented 9.8%, 4.8% and 11.3% of the total radioactivity exposure and netupitant represented 34.0% of the total radioactivity exposure. Exposure to M1, M2 and M3 as a percentage of netupitant exposure (based on AUC0-t values) was approximately 29%, 14% and 33%, respectively.

These results confirm that M1, M2, and M3 are all major metabolites of netupitant and account for >10% of parent drug exposure. A fourth metabolite, M4 (N-oxide, N-demethyl derivative, see Figure 10) was discovered during this study, having a peak at the same location as the parent. M4 had a C_{max} <7% of the parent. (M4 PK parameters were confirmed in study NETU-11-23, showing a systemic exposure of approximately 3% compared to the parent).

M1, M2 and M3 were all shown to be pharmacologically active in in a gerbil foot tapping NK1 assay. M3 was the most potent and M2 the least active.

- Pharmacokinetics of metabolites

Pharmacokinetic data for metabolites from Study NP16603 are shown in Table 14. Additional data for M4 Study NETU-09-21 is shown in Table 15.

Table 14: Mean Exposure Parameters of Netupitant, M1, M2 and M3 Metabolites in Humans (Study NP16603)

	10mg	30mg	100mg	300mg	450mg
Netupitant					
C_{max} (ng/mL)	8.8 (32.4)	36.0 (15.9)	168.2 (22.1)	746.5 (26.8)	1134 (30.8)
$AUC_{0-\infty}$ (h.ng/mL)	232.2 (20.3)	994.7 (55.8)	4795 (27.3)	25232 (24.9)	43676 (19.5)
M1 metabolite					
C_{max} (ng/mL)	NC	3.9 (11.3)	14.2 (22.9)	46.1 (12.4)	64.1 (8.9)
$AUC_{0-\infty}$ (h.ng/mL)	NC	497.4 (58.0)	1174 (15.5)	5317 (26.4)	12687 (51.9)
M2 metabolite					
C_{max} (ng/mL)	NC	14.2*	34.9 (21.2)	112.5 (14.5)	175.2 (20.0)
$AUC_{0-\infty}$ (h.ng/mL)	NC	NC	500 (23.2)	1829 (36.0)	2530 (46.0)
M3 metabolite					
C_{max} (ng/mL)	NC	7.81 (16.7)	25.2 (24.2)	85.7 (20.0)	116.5 (7.9)
$AUC_{0-\infty}$ (h.ng/mL)	NC	NC	1571 (27.6)	6555 (25.2)	11548 (10.0)

*M2 metabolite detected in only one subject after dosing with 30mg
NC = not calculated (insufficient data)
Values are of arithmetic means and coefficient of variation (CV%)

Table 15: Summary of Mean PK parameters for netupitant metabolites (NETU-09-21) – N = 6, dose 300mg [14C]-Netupitant oral suspension

	C_{max}		T_{max}		$AUC_{0-\infty}$		$T_{1/2}$	
	Ng/ml	% CV	h	% CV	Ng.h/ml	% CV	h	% CV
M1	39	25	13.58	61.3	4449	20%	66.68	27
M2	198	45	2.33	35	1901	51	17.78	32
M3	71	25	20.92	36.1	4325.5	22.4	42.28	23.1
M4	20.1	5.8 -29.7	4.8	4-6	NC	NC	NC	NC

- **Consequences of possible genetic polymorphism**

Netupitant is primarily metabolized via hepatic cytochrome P450 3A4. In general, genetic polymorphism of CYP3A4 results in a decrease in enzyme activity, but occurs in a small proportion of the population across all of the affected alleles and are not expected to lead to clinical relevant increase in netupitant exposure. Specific studies to evaluate effect of genetic polymorphism of CYP3A4 on netupitant disposition were not conducted.

Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron M9 and 6-hydroxy-palonosetron M4. These metabolites each have less

than 1% of the 5-HT_3 receptor antagonist activity of palonosetron. The N-oxide metabolite M9 (08-PALO-D1), accounted for approximately 13% of the IV and oral dose, and metabolite M4 (08-PALO-M4), represented approximately 11% of the dose after IV administration and approximately 17% after oral administration. In vitro metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates (PALO-99-39). Moreover, in vitro testing indicated that palonosetron does not inhibit or induce cytochrome P450 isozymes at clinically relevant concentrations. Palonosetron is almost exclusively metabolised by cytochrome P450, primarily via CYP2D6 and, to a lesser extent, by CYP3A and CYP1A2. Small amounts of M9 were present in the plasma relative to the parent compound in all studies. Exposure, as measured by AUC, to M9 was generally less than 10% after both oral and IV administration in healthy volunteers and CINV patients. Plasma concentrations of palonosetron generally increased with increasing doses, similar to what was observed with IV dosing. Dose proportionality of M9 was generally observed. Exposure to M4 was measured in cancer patients. At 0.50 mg and 0.75 mg dose of palonosetron, when M4 concentrations were measurable, there was high variability between patients. Overall mean exposure ranged from 9-16% compared to the parent.

Dose proportionality and time dependencies

- **Dose proportionality**

A double-blind placebo controlled single ascending oral dose study (NP16603) was conducted in 2003 to assess the tolerability, safety, PK, and PD of netupitant (RO0673189)after single oral ascending doses in healthy male volunteers. Five dose levels were investigated 10, 30, 100, 300 and 450. For each dose group four subjects were randomly assigned to netupitant and 2 to placebo. Blood samples for pharmacokinetic analysis were collected pre-dose and at 15 and 45 min and 1, 1.5, 2, 3, 5, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144 and 168 h post-dose.

Following a lag time of up to 3 hours, netupitant was absorbed in a first-order fashion, with C_{max} being reached at approximately 5 hours post-dose (see Table 4). For doses up to 300 mg, there was a statistically significant over-proportional increase with dose in C_{max}, AUC_{last} and AUC0-∞ for netupitant. Dose-proportionality was observed between the 300 mg and 450 mg doses, with ratios being close to one.

RO0673189 (netupitant) showed a statistically significant over-proportional increase with dose for C_{max} ($p=0.0001$), AUC_{last} ($p=0.0002$) and AUC_{inf} ($p<0.0001$) for doses up to 300 mg. The measures of deviation from dose-proportionality between the 100 mg and 300 mg doses are 1.48, 1.77 and 1.75 respectively for C_{max}, AUC_{inf} and AUC_{last}. For the 300 mg and 450 mg doses, the increase in exposure appears to be dose-proportional, with ratios for C_{max}, AUC_{last} and AUC_{inf} all being close to one.

Metabolites RO0681133 (M1), RO0713001 (M2) and RO0731519 (M3) were measured in plasma for the 30mg doses of netupitant upwards. Exposure to metabolites was considerably lower than to parent compound, with C_{max} values of one tenth to one fifth of parent levels and AUC values between one twentieth and one third of the parent compound.

Metabolite RO0681133 (M1), was dose proportional for C_{max}but not AUC_{last}. The increase in AUC_{last} was over proportional for doses from 10mg to 300mg but not from 300 mg to 450 mg. For RO0713001 (M2), none of the parameters showed a statistically significant deviation from dose-proportionality. For RO0731519 (M3) there was an over-proportional increase in AUC_{last} but a dose proportional increase in $C_{max}$with increasing doses of netupitant.

Figure 2: Mean RO0673189 Plasma Concentrations by Dose

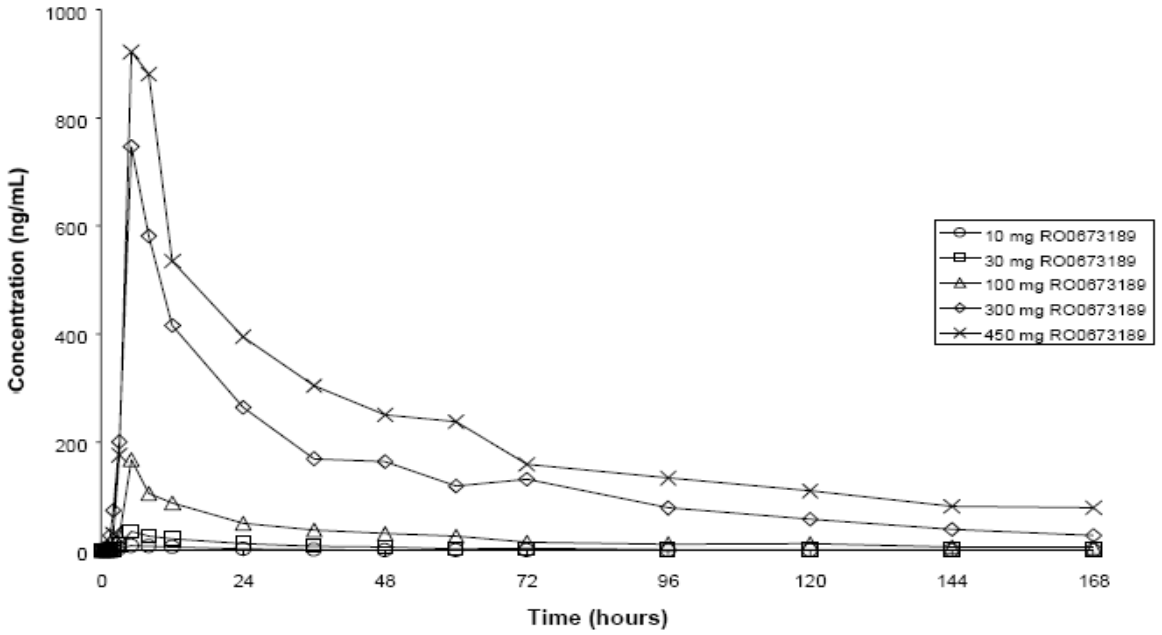


Table 16: Summary of Mean (CV%) Metabolites to Parent Ratios

	10 mg Mean	(CV%)	30 mg Mean	(CV%)	100 mg Mean	(CV%)	300 mg Mean	(CV%)	450 mg Mean	(CV%)
RO0681133/RO0673189										
C_{max}	0	(-)	0.111	(18.2)	0.085	(8.2)	0.065	(26.7)	0.059	(21.6)
AUC_{last}	0	(-)	0.188	(25.2)	0.224	(6.4)	0.200	(22.9)	0.191	(19.3)
AUC_{inf}	-	(-)	0.385	(0.6)	0.251	(12.7)	0.215	(20.9)	0.296	(57.1)
RO0713001/RO0673189										
C_{max}	0	(-)	0.106	(200)	0.211	(21.2)	0.156	(21.0)	0.166	(31.8)
AUC_{last}	0	(-)	0.032	(200)	0.066	(51.6)	0.054	(17.8)	0.060	(38.6)
AUC_{inf}	-	(-)	-	(-)	0.108	(19.5)	0.073	(25.2)	0.059	(38.8)
RO0731519/RO0673189										
C_{max}	0	(-)	0.221	(23.3)	0.151	(20.8)	0.122	(32.0)	0.109	(26.8)
AUC_{last}	0	(-)	0.189	(24.2)	0.293	(12.4)	0.269	(26.4)	0.272	(13.9)
AUC_{inf}	-	(-)	-	(-)	0.327	(1.7)	0.269	(27.8)	0.270	(17.2)

Palonosetron

After single oral doses using buffered solution mean maximum Palonosetron concentrations (Cmax) and area under the concentration-time curve (AUC0-∞) were dose proportional over the dose range of 3.0 to 80 µg/kg in healthy subjects.

Dose proportionality in multiple ascending doses of netupitant

A fed study (NP16601) was undertaken to assess the tolerability, safety, and pharmacokinetics of netupitant following one week daily oral dosing in ascending fashion in healthy volunteers. The study also included 3 elderly volunteers, however only two completed the study. Results are presented for the non-elderly population only as a full plasma concentration profile was only available for one elderly person..

Exposure to netupitant showed a slightly greater than proportional increase with dose. For Day 1, there was statistically significant evidence against dose proportionality for $AUC_{(0-23.5)}$ and C_{max}. After 7 doses, there was statistically significant evidence against dose proportionality for $AUC_{(0-23.5)}$ but for C_{max} the results were of borderline significance (p=0.062). For both parameters, the results for the 300 mg and 450 mg doses were higher on days 1 and 7 than would be expected if dose proportionality held.

In keeping with its long estimated half-life, these data showed increase in netupitant exposure of approximately 3-fold after 7 days' dosing. Results of the ANOVA confirmed that the accumulation of netupitant by Day 7 was statistically significant for both $AUC_{(0-23.5)}$ and C_{max}.

Overall the PK data showed an increase in netupitant exposure of approximately 3-fold after 7 days of dosing. This is consistent with the long t1/2 of the compound. Mean maximum plasma concentrations and AUC (0-23.5) values recorded on Days 1 and 7 of dosing with 100, 300 or 450 mg of netupitant are shown in Table 17. Exposure netupitant showed a slightly greater than proportional increase with dose. The small magnitude of this effect is considered unlikely to have any clinical relevance.

Table 17: Mean Exposures on Day 1 and Day 7 following Daily Dosing with Netupitant for Seven Days

Dose	Day 1		Day 7	
	C_{max} (ng/mL)	$AUC_{(0-23.5)}$ (h.ng/mL)	C_{max} (ng/mL)	$AUC_{(0-23.5)}$ (h.ng/mL)
100mg	111 (23.1)	1360 (21.6)	269 (19.4)	4160 (24.0)
300mg	599 (38.0)	6400 (26.5)	1060 (19.0)	17100 (16.6)
450mg	720 (35.4)	9670 (34.9)	1790 (43.1)	28800(45.1)

Values are arithmetic means and coefficient of variation (CV%)

- **Time dependency**

Netupitant

In a multiple ascending dose study (NP16601), after oral daily administration of 300mg netupitant for 7 days, systemic exposure on Day 7 increased 2.7-fold as compared to Day 1, as expected on the basis of the long drug half-life. Assuming that on Day 7 netupitant plasma levels approach steady state, the PK parameters CL/F, Vz/F and t1/2 were calculated from AUC0-23.5 values determined on Day 7. These parameters remain substantially unchanged on Day 7 as compared to findings of single dose studies (e.g., NP16599, NETU-10-11, NETU-10-12). Hence, time-dependent pharmacokinetics of netupitant is unlikely.

Table 18: Mean PK parameters for 300 mg oral netupitant in single (SD) and multiple dose (MD) clinical studies

Study	Dose (mg)	Treatment Group	N	C_{max}		$AUC_{0-23.5}$		t_{max}		$t_{1/2}$		CL/F		Vz/F	
				ng/mL	CV%	ng.h/mL	CV%	h	CV%	h	CV%	L/h	CV%	L	CV%
NP16601	300	SD (Day1)	8	599	38.0	6400	26.5	5.50	51.4	-	-	-	-	-	-
	300	MD (Day7)	8	1060	19.0	17100	16.6	5.44	53.9	82.5	27.3	17.8	19.5	2090	28.8
NP16599	300	SD	10	479	25.0	-	-	4.90	37.0	67.03	41.6	17.3	30.5	1630	44.3
		SD	10	384	29.7	-	-	5.20	27.0	61.83	54.8	20.1	32.2	1960	98.3
NETU-10-11	300	SD	17	546.0	44.1	-	-	5.27	15.3	86.6	25.7	18.4	33.5	2342	45.8
		SD	18	498.1	45.3	-	-	5.12	10.4	87.6	53.1	19.9	38.2	2540	76.4
NETU-10-12	300	SD, Fasted	22	596.4	39.1	-	-	5.14	17.3	101.2	52.2	20.5	52.7	2851	57.3

Palonosetron

In study PALO-02-12, the PK profile of palonosetron was studied after IV administration of 0.25 mg daily doses for 3 consecutive days. A 2-fold increase in systemic exposure was estimated on Day 3 as compared to Day 1, which is consistent with the long plasma elimination half-life of palonosetron. The main PK parameters for palonosetron are summarized in the following table.

Table 19: Mean PK parameters for 0.25 mg oral palonosetron in single (SD) and multiple dose (MD) clinical studies

Study	Dose	Treatment Group	N	C_{max}		AUC_{0-24}		$t_{1/2}$		CL		Vz	
				ng/L	CV%	ng.h/L	CV%	h	CV%	L/h	CV%	L	CV%
PALO-02-12	0.25 mg	SD (Day 1)	12	1130	61	8900	22	-	-	-	-	-	-
		MD (Day3)		2430	47	18200	19	42.8	25	14.21	21	878	32
2092	10 µg/kg*	SD	12	3530	48	26200	17	35.0	25	0.16 (L/h/kg)	23	7.83 (L/kg)	23
PALO-04-21	0.25 mg	SD	11	1650	60	8884	23	33.3	30	12.5	21	553.8	30

*Note: 10 µg/kg is approximately 0.25 mg

Assuming that on Day 3 palonosetron plasma levels approach steady state, CL, Vz and t1/2 were calculated from the AUC0-24 estimates on Day 3. These PK parameters did not change following multiple dosing as compared to the CL, Vz and t1/2 values observed after single IV dose studies (e.g., studies 2091 and PALO-04-21). Therefore, time-dependent pharmacokinetics of palonosetron appears to be unlikely.

Inter-individual variability

Netupitant

No clear patterns between inter-individual variability and dose emerged e.g. CV% for the 30mg single dose in NP 16603 was 55.83% and for the 300mg dose was 24.9%. In NP16601 CV% for the 300mg dose on day 1 was 26.5% similar to that for NP16603 (these were both fed studies). Inter-individual variation appeared to be higher in fasted studies (49.05% in those in the fasted study of NP16600 and 41.9% in those in the fasted study in NETU-10-12).

Inter-subject variability was higher for those in the hepatic impairment PK trial from 54.8, 55.2 and 63.8% respectively for mild, moderate and severe hepatic impairment respectively (NETU-10-10), in some interaction studies e.g netupitant and etoposide (49.05%) and in the elderly (NETU-10-12) where inter-subject variability was 54.4%. The inter subject variability of palonosetron was lower, with a variability of 20 to 29%.

Pharmacokinetics in target population

- ***PK in cancer patients***

The PK of netupitant and its metabolites were evaluated in a drug interaction study (NETU-10-09) and population PK study NETU-10-02 (performed in association with the Phase 3 study NETU-08-18.

In study NETU-10-09, male and female cancer patients were treated with the netupitant/palonosetron FDC and docetaxel, etoposide, or cyclophosphamide alone or in combination with other chemotherapy agents, provided they were not inhibitors, inducers or substrates of CYP3A4. Overall, exposure to netupitant and its metabolites in terms of C_{max}, AUC0-t and AUC0-∞ values were consistent with previous data reported in healthy subjects and generally appeared to be independent of the chemotherapeutic regimen administered. Variability was high (50 to 70%) for C_{max} and moderate for other parameters. Mean t1/2 ranged from approximately 70 h to 90 h, consistent with the known profile of netupitant, and were not different across the 3 treatment groups. Exposure to netupitant metabolite M1 and M3 relative to netupitant was 8 to 14% for C_{max} and approximately 30 to 35% for AUC0-t. Exposure to netupitant metabolite M2 relative to netupitant ranged from approximately 45 to 70% for C_{max} and from 20 to 30% for AUC0-t. These data are also consistent with previous data in healthy subjects.

Overall, mean PK parameters of palonosetron in cancer patients from Study NETU-10-09 with the FDC were consistent with its known PK profile and support previous studies in both healthy volunteers and cancer patients. Mean palonosetron PK variables from this study indicated a slightly higher exposure (C_{max} and AUC0-∞) and longer t1/2 in patients receiving docetaxel, compared to etoposide or cyclophosphamide, with moderate variability.

In the population PK analysis (NETU-10-02), netupitant disposition was characterized by a 2-compartment model with an estimated median systemic CL of 20.5 L/h and a large volume of the central (486 L) and peripheral compartments (1170 L), respectively. These estimates for CL and volume indicated that the drug was extensively distributed in body tissues and the plasma elimination was rapid. Based on the PK model parameter estimates, the median t1/2 for netupitant was calculated as 88 hours. None of the covariates (body mass index [BMI], age, gender, race, chemotherapy regimen, rescue medication, smoking status, doxorubicin, epirubicin and flororuacil, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, albumin, bilirubin, Eastern Cooperative Oncology Group [ECOG]status and neutrophil count) had a significant impact on the disposition of netupitant. Metabolites M1 and M3 showed a large Vd and a slower elimination compared to the parent compound (CL accounted for 20% and 30% of the parent, respectively). A 3-compartment model was used to describe the concentration data of M2 due to the multiple exponential decay and flat elimination phase. The estimated parameters indicated that CL (1.24 L/hr) was approximately 6% of the parent.

Palonosetron estimates from the population PK analysis (NETU-10-02)were consistent with a previous analysis with regard to CL and Vd (median palonosetron CL was estimated to be 7.61 L/h; estimated median volume of the central compartment was 367 L). Palonosetron CL was influenced by creatinine clearance but this reduction (approximately 29%) would not result in a significant change in palonosetron exposure and would not necessitate a dosing reduction.

Special populations

- **Impaired renal function**

No specific studies were performed to evaluate netupitant in patients with renal impairment. In the ADME trial, less than 5% of all drug-related material was excreted in urine (NETU-09-21) and less than 1% of the netupitant dose was eliminated unchanged in the urine (NETU-06-27) and therefore any accumulation of netupitant or metabolites after a single dose would be negligible. The population PK study showed no correlation between PK parameters of netupitant and markers of renal dysfunction. In this study, patients with a reduced creatinine clearance (CLCR) also had a reduced palonosetron CL, but this reduction would not result in a significant change in palonosetron exposure (NETU-10-02).

- **Impaired hepatic function**

In NETU 10—10 maximum and total exposure of netupitant was increased in subjects with mild (Child Pugh 5-6) , moderate (Child Pugh 7-9) , and severe (Child Pugh 10-15) hepatic impairment compared to matching healthy subjects, although there was pronounced individual variability in both hepatically-impaired and healthy subjects. There were eight subjects in each in the mild and moderate hepatic impairment groups with matching controls and only 2 with severe hepatic impairment. Exposure to netupitant (C_{max}, AUC0-t and AUC0-∞) compared to matched healthy subjects was 11%, 28% and 19% higher in mild and 70%, 88% and 143% higher in moderate hepatically-impaired subjects, respectively. PK parameter increases in the severe hepatically-impaired subjects were similar to the moderately- impaired group, however there were only 2 subjects in this group so no conclusions can be drawn.

Total palonosetron exposure was also increased in subjects with mild and moderate hepatic impairment compared to matched healthy subjects. In study NETU-10-10 exposure to palonosetron (C_{max}, AUC0-t and AUC0-∞) compared to matched healthy subjects was 14%, 35% and 33% higher in mild and 1% lower, 60% and 62% higher in moderate hepatically-impaired subjects, respectively. A numerical decrease of palonosetron exposure was observed in the subjects with severe hepatic impairment compared to matching healthy subjects, which was not statistically significant.

The population PK study showed no correlation between PK parameters and markers of hepatic dysfunction including AST, ALT, alkaline phosphatase, albumin and bilirubin .

- **Gender**

A pooled analysis using data from 3 Phase 1 single-dose studies (NETU-11-02, NETU-09-07 and NETU-11-23) in 153 healthy subjects was performed to evaluate a possible gender effect with netupitant and palonosetron (NEPA-13-11).

A gender effect for palonosetron had previously been established, and data from the current analysis confirm that exposure (geometric mean) is higher (40% for AUC_{0-t}, 31% for C_{max}) in females. Palonosetron $t_{1/2}$ is also longer in females by approximately 16%. The clinical implications of the gender findings for palonosetron are of limited significance, as the safety margin is large (doses have been administered and well tolerated up through 12-fold the proposed oral dose) and the dose-response relationship has not been demonstrated to be closely linked to plasma concentrations, and as such, a difference in the range observed would not impact efficacy.

For netupitant, females also had a higher exposure (geometric mean); there was a 35% increase for C_{max}, a 2% increase for AUC0-t and a 36% increase in t1/2 in females compared to males. For netupitant, these increases in exposure are not considered to be clinically relevant. The T_{max} did not differ between the genders for netupitant and palonosetron. Furthermore, in the population PK study, gender as a covariate did not influence the PK of netupitant, it`s metabolites, or palonosetron.

A gender effect for palonosetron had previously been established during the development program, showing a 1.20-1.30 fold increase in exposure for females compared to males. In the pooled data from NEPA-13-11, mean palonosetron C_{max} was approximately 1.30 fold higher and AUC was approximately 1.40 fold higher in females. T1/2 also was slightly longer (44 versus 37 hours), while T_{max} was not different between males and females (NEPA-13-11). The population PK evaluation did not reveal gender as a significant covariate affecting the disposition of palonosetron in patients participating in NETU-08-18, however the number of males participating was small (NETU-10-02).

- **Race**

In the population PK study population which comprised patients receiving MEC in Study NETU-08-18, there was no relationship between race and netupitant or palonosetron exposure, although the number of non-caucasian patients was small (16 Asians)

- **Weight**

The effect of weight on exposure was investigated in a population PK study (Study NETU-10-02)). Neither body weight or BMI had a significant impact on the PK of netupitant.

Body weight was found to contribute to inter-individual variability in V2 for palonosetron. Palonosetron has a large Vd with an estimated median V2 of 367 L for patients of median weight (71 kg), comparable to that observed in previous studies, indicative of extensive tissue distribution. Over the weight range observed for patients in this study (34 kg to 125 kg), V2 is calculated to vary from 257 L to 527 L. These results are consistent with a previously conducted population PK analysis for palonosetron.

- **Elderly**

In total 35 persons aged over 65 were included in PK studies all but four were aged under 75 years. There were two studies which specifically investigated PK in the over 65 population (NP 16600 and NETU 10-12)in addition some older people were also included in hepatic insufficiency study (NETU 10-10), and the

interaction studies in cancer patiens NETU-10-09. No older people were included in the interaction studies with palonosetron, midazolam, erythromycin, digoxin, dexamethasone, ketaconazole, and rifampicin.

Only two elderly participants were dosed in NP16600 therefore the results from this study are ignored. Twelve healthy older volunteers were evaluated in NETU-10-12 and compared to young healthy volunteers.

C_{max} and AUC0-∞ of netupitant showed a higher maximum plasma concentration in the elderly (mean C_{max} 880.8 µg/L) compared to young healthy volunteers (mean C_{max} 596 µg/L)

Exposure was also higher with mean AUC 0-∞ for the elderly population at 24739 h·µg/L compared to 20039 h·µg/L in young healthy volunteers (see table).

Table 20: Mean ± SD Netupitant Pharmacokinetic Parameters after Oral Dose Administration of Netupitant/Palonosetron FDC (300 mg/0.5 mg) in Fasted Conditions in Elderly Subjects (R+) and in Adult Subjects (R) and Results of Analysis of Variance

Parameter	R	R+	PE%*	90%CI
C_{max} [µg/L]	596.4±233.0	880.8±479.2	136.36	95.87 - 193.96
$AUC_{0-\infty}$ [h·µg/L]	20039±8396	24739±9390	124.91	95.29 - 163.75
AUC_{0-tz} [h·µg/L]	17150±6122	19604±6747	113.42	87.66 - 146.75

Values are arithmetic means ±SD; *Point estimate (PE): ratio of geometric means (R+/R)
CI: confidence interval, SD: standard deviation
R+: one capsule of 300 mg netupitant and 0.5 mg palonosetron in fasted state to elderly subjects
R: one capsule of 300 mg netupitant and 0.5 mg palonosetron in fasted state to younger adults (Reference)

Table 21: Number of elderly patients in netupitant PK trials, by age groups

	Age 65-74	Age 75-84	Age 85+
PK Trials	**31**	**3**	**1**

- **Children**

No PK studies in the paediatric population were submitted. A full waiver for the conduct of paediatric studies was granted by PDCO 2012 on the grounds of lack of significant therapeutic benefits over existing treatments.

Pharmacokinetic interaction studies

- In vitro

The metabolism of netupitant has been studied *in vitro* in human, rat and dog hepatocyte incubations, microsomal incubations of human, rat, dog, minipig and marmoset liver, as well as with specific recombinant human cytochrome P450 (CYP450) isoenzymes.

Human, rat, dog, minipig and marmoset liver microsomal incubations showed qualitatively similar metabolite patterns. The similarity in overall metabolism was confirmed by metabolite patterns from human, rat and dog hepatocyte incubations.

Netupitant is metabolized by CYP3A4 to several metabolites. Three major oxidative metabolites of netupitant have been identified after hepatocytes and liver microsomal incubations: M1 (RO0681133, a desmethyl derivative), M2 (RO0713001, a N-oxide derivative) and M3 (RO0731519, a OH-methyl derivative).

CYP3A4, the major human liver CYP450 isoenzyme, catalyzed the oxidative metabolism of netupitant (but not CYP2C9, CYP2D6 or CYP2C19). This isoenzyme is known to exhibit considerable variability (approximately 10 fold) in the human population. It is also inducible, and can be inhibited by other drugs, indicating the potential for variability in the clearance of netupitant and for drug-drug interactions.

In human liver microsomes, netupitant competitively inhibited the CYP3A4 mediated hydroxylation of testosterone and midazolam (apparent Ki of 1.1 and 2.2 µM, respectively). Therefore, interactions of netupitant with drugs mainly metabolized by CYP3A4 cannot be excluded. Additionally, the drug-drug interaction potential of metabolite M1 and metabolite M2 was investigated in vitro. M1 metabolite showed an inhibition potential similar to that of the parent drug (IC50 ~1.2 µM).

For the hydroxylation of diclofenac, catalyzed by CYP2C9, the IC50 value of netupitant was approximately 20 µM. Based on the low plasma concentration of netupitant expected in man, significant metabolic interactions with CYP2C9 metabolized drugs are considered unlikely. Other CYP450 isoenzymes (CYP1A2, CYP2C19, CYP2D6) were not inhibited by netupitant (IC50 > 100 µM) (Report 1003907).

From *in vitro* drug-drug-interaction studies focused on the inhibitory effect of netupitant on vincristine and cyclophosphamide metabolism in human liver microsomes, significant drug-drug interaction effects are not expected in humans in both cases ($C_{max}/K_i<0.1$ indicated a remote possibility of in vivo drug-drug interaction) (NETU-06-15, NETU-09-10). On the contrary drug-drug interaction effects are possible in humans when netupitant is co-administered with docetaxel: the IC50 value of netupitant in human liver microsomes was 3.7 µM when docetaxel was used as a substrate. An estimation of the C_{max}/Ki ratio is approximately 0.5 (NETU-09-09). As presented below, a clinical study evaluating docetaxel was performed.

Based on the results of in-vitro studies with P-glycoprotein (PgP), netupitant at 5 µM, modulates the Papp of 3H-digoxin in both directions in a similar fashion to verapamil. Considering the low plasma concentration of netupitant expected in human plasma, significant metabolic interactions with Pgp transported drugs are considered possible only for supra-therapeutic doses (NETU-06-13). A clinical study with digoxin was performed for in vivo confirmation.

Netupitant at concentrations of 0.2, 2 and 20 µM and M1, M2 and M3 at concentrations of 0.02, 0.2 and 2 µM did not induce CYP1A2, CYP2C9, CYP2C19 or CYP3A4 activity in human hepatocytes (NETU-10-27).

In vivo drug-drug interaction between netupitant and drugs that are substrates of BCRP is considered possible because C_{max}/IC50 ratio, calculated with C_{max} (bound+unboud) in the range 0.73-1.3 µM) and the IC_{50} determined in vesicular transfer inhibition assay, ranged between 0.12 and 0.21. However this result should be handled with caution, as the IC_{50} value could not be determined in MDCKII-BCRP inhibition assay due to the solubility limitation of 30 µM. Besides, at 10 µM there was no inhibition of the BCRP-mediated prazosin transport (NETU-12-81).

In vivo interaction of netupitant with human BSEP, MRP2 efflux transporters and with human OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2 uptake transporters, are predicted to be unlikely.

Based on the circulating C_{max} concentrations (bound + unbound) of netupitant metabolites (ranging from 0.07-0.11 µM, 0.17-0.35 µM and 0.07-0.16 µM for M1, M2 and M3, respectively) an in vivo interaction with all the transporters tested is predicted to be unlikely (NETU-12-81).

In summary, netupitant is metabolized mainly by CYP3A4, is a moderate inhibitor of CYP3A4 and a weak inhibitor of all other transport mechanisms evaluated.

In vitro metabolism studies for palonosetron have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

There have been no in vitro animal studies or any in vivo studies of enzyme induction. There were no findings suggesting enzyme induction in any of the investigations.

At high concentrations in vitro, palonosetron was a competitive inhibitor of some cytochrome isoforms but this is not considered likely to be clinically relevant.

The moderate extent of plasma protein binding suggests that small changes will have no influence on palonosetron availability. The absence of any evidence of enzyme induction and the fact that inhibition was only apparent at high concentrations in vitro suggests that interactions mediated by metabolic enzymes are unlikely. Potential pharmacokinetic interactions have not otherwise been investigated.

- **In vivo**

A number of interaction studies were conducted with netupitant including: the following cancer drugs (docetaxel, etoposide, and cyclophosphamide); palonosetron; CYP3A4 substrates (erythromycin, midazolam, dexamethasone); CVP3A4 inhibitors and inducers (ketoconazole, rifampicin); and P-gp substrates (digoxin)

CYP3A4 Substrates

Model CYP3A4 substrates erythromycin and midazolam were evaluated when administered concomitantly with netupitant alone (NP16599). In this study, the pharmacokinetics of netupitant were not altered in the presence of erythromycin or midazolam. However, exposure of both substrates was increased (C_{max} and AUC were approximately 30% higher for erythromycin while C_{max} and AUC were 40% and 144% higher for midazolam).

In addition, co-administration of the netupitant/palonosetron FDC with the CYP3A4 substrates ethinylestradiol and levonorgestrel, was evaluated in women as part of an oral contraceptive regimen (NETU-10-08). Although the analysis of the effect of the oral contraceptives on netupitant was not part of the study objectives, the data were reviewed with netupitant PK values from earlier studies (NETU-10-12; NETU-10-11; NETU-09-07; NETU-11-02), and indicated that there was no apparent effect of ethinylestradiol and levonorgestrel on netupitant.

The netupitant/palonosetron FDC had no effect on C_{max} and exposure ($AUC_{0-\infty}$) of ethinylestradiol. The 90% CI for AUC_{0-t} (126.8%) fell just outside the upper limit of bioequivalence criteria indicating a slightly higher systemic exposure after the combination compared to ethinylestradiol alone. For the levonorgesterel component, there was no effect of the FDC on levonorgestrel C_{max}, while exposure parameters ($AUC_{0-\infty}$ and AUC_{0-t}) were increased by approximately 40%, and the 90% CIs were outside bioequivalence range.

Dexamethasone

Dexamethasone is administered as a part of many chemotherapy regimens either to prevent nausea and vomiting or to prevent allergic reactions with medications such as Taxotere. In addition, dexamethasone is a known CYP3A4 substrate. A study was conducted to evaluate the effects of netupitant (at three different doses) on dexamethasone, using a dexamethasone regimen similar to that used in some antiemetic regimens for the prevention of CINV (NETU-06-07).

The mean plasma concentrations of dexamethasone were higher when dexamethasone was co-administered with netupitant. The increase appeared to be dependent on netupitant exposure. AUC0-24 was increased 1.5, 1.7 and 1.8 fold with co-administration of 100, 300 and 450 mg, respectively. Exposure increased further after multiple doses: AUC84-∞ was 1.7, 2.4 and 2.7-fold higher, respectively, after co-administration with netupitant.

CYP3A4 Inhibitors and Inducers

Administration of the CYP3A4 inhibitor ketoconazole with netupitant/palonosetron FDC increased the exposure of netupitant and resulted in a C_{max} of 1.3 fold, AUC0-∞ of 2.4 fold and AUC0-tz of 1.8 fold, when compared to the administration of netupitant/palonosetron FDC alone. The formation of M1 and M3 was also affected when netupitant was co-administered with ketoconazole compared to the intake of netupitant alone. C_{max} and AUC0-tz were lower for all three metabolites after co-administration of ketoconazole. Ketoconazole did not affect the pharmacokinetics of palonosetron (NETU-10-11).

Administration of the CYP3A4 inducer rifampicin with netupitant/palonosetron FDC alone decreased the exposure of netupitant. C_{max}, $AUC_{0-\infty}$ and AUC_{0-tz} 2.6, 5.9, and 5.5 fold, respectively. Co-administration of rifampicin resulted in a non significant decrease in palonosetron exposure (NETU-10-11).

Because *in vitro* studies showed that netupitant interacted with P-gp resulting in a concentration-dependent modulation of 3H-digoxin transport, a clinical study was conducted to test the clinical relevance of the *in vitro* observations. The PK of digoxin was similar in the presence and absence of netupitant in healthy volunteers (NETU-07-01).

Considering overall the *in vitro* interaction studies of netupitant and its three metabolites (M1, M2 and M3) with human BSEP, MRP2 and MDR1 efflux transporters and with human OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2 uptake transporters, in vivo drug-drug interactions are predicted to be unlikely.

Netupitant in vivo drug-drug interaction with BCRP might be considered possible because C_{max}/IC50 ratio, calculated with the IC50 determined in VT assay, ranges between 0.12 and 0.2. The IC50 value could not be determined in MDCKII-BCRP inhibition assay due to the solubility limitation of 30 µM and that at 10 µM there was not inhibition of the BCRP-mediated prazosin transport (NETU-12-81).

Agents Prescribed Together or Likely to be Coadministered

Palonosetron

Since netupitant and palonosetron are to be co-administered in the FDC, the possible PK interaction between the highest doses used in Phase 2 trials was evaluated in a PK study (netupitant 450 mg and palonosetron 0.75 mg) (NETU-06-27). The study showed that there was no effect of palonosetron on netupitant exposure and although palonosetron C_{max} was slightly higher in the presence of netupitant, no significant effect of netupitant on palonosetron exposure was demonstrated.

Chemotherapy Agents

Study NETU-10-09 evaluated the pharmacokinetics of 3 common chemotherapy agents (docetaxel, etoposide and cyclophosphamide) likely to be used in conjunction with the netupitant/palonosetron FDC; docetaxel and etoposide are also known CYP3A4 substrates while cyclophosphamide is metabolized by a number of CYP enzymes, including 3A4.

The study showed that concentrations of docetaxel and to a lesser extent, etoposide, were consistently elevated in patients who received the FDC compared to those who received palonosetron only. Mean exposure (AUC0-t) increases were 37% and 21% for docetaxel and etoposide, respectively, in the netupitant test period. Cyclophosphamide concentrations were not consistently affected and showed wide variability. Although concentrations of chemotherapy were elevated following netupitant administration, AE profiles were not different in the two study groups, indicating that there was no clinical impact of the higher chemotherapy concentrations in these patients.

There were no differences in the disposition of netupitant or its metabolites with any of the chemotherapeutic agents. PK parameters were consistent with previous values observed in healthy volunteer trials. Palonosetron mean exposure ($AUC_{0-\infty}$) was higher (65%) and the mean half-life was 20 h longer in the docetaxel group compared to the etoposide and cyclophosphamide groups. No dose adjustment is necessary, given the large safety margin for palonosetron.

In addition, the population PK analysis evaluated doxorubicin, epirubicin, fluorouracil and rescue medication as potential covariates that could influence the disposition of netupitant and/or palonosetron. In this population, none were found to have a significant effect on the disposition of netupitant or palonosetron (NETU-10-02). Other moderately emetogenic chemotherapy agents that are metabolised by CYP3A4 were not investigated for their potential to interact with netupitant e.g. vinorelbine, irinotecan, and imatinib.

2.4.3. Pharmacodynamics

Three specific pharmacodynamic studies were part of this product development program. Two studies evaluated netupitant alone, and the third (Thorough QT/QTc study) evaluated the netupitant-palonosetron FDC. In addition, a Phase 2 study, NETU-07-07 lead to the choice of the 300 mg netupitant dose for Phase 3 and a population PK/PD analysis was performed in conjunction with Study NETU-08-18 (NETU-10-02).

Mechanism of action

Netupitant is a selective antagonist of human substance P/neurokinin 1 (NK1) receptors.

Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. Chemotherapeutic substances produce nausea and vomiting by stimulating the release of serotonin from the enterochromaffin cells of the small intestine. Serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex. The development of acute emesis is known to depend on serotonin and its 5-HT_3 receptors have been demonstrated to selectively stimulate the emetic response.

Delayed emesis has been largely associated with the activation of tachykinin family neurokinin 1 (NK1) receptors (broadly distributed in the central and peripheral nervous systems) by substance P. As shown in in vitro and in vivo studies, netupitant inhibits substance P mediated responses.

Primary and Secondary pharmacology

Primary pharmacology

Two studies were submitted to demonstrate the primary pharmacology. In addition supportive data was provided by the Population Study NETU-08-18 (NETU-10-02)

NP16602: Apomorphine challenge in healthy volunteers was undertaken as a pharmacodynamic efficacy study. This was a randomised double-blind, placebo controlled trial of the anti-emetic effect of netupitant following an apomorphine challenge in healthy volunteers in which 32 subjects were randomly to 4 dosing groups (within each group 6 subjects received netupitant and 2 placebo). Another study in healthy volunteers (NETU-06-08) was undertaken to assess the degree of Neurokinin-1 receptor occupancy in the human brain after a single dose of netupitant in healthy male subjects.

Table 22: Dose Groups and Timing of Apomorphine Challenge

Netupitant Dose Group	Interval Between Netupitant Dose and Apomorphine Injection
100 mg (I)	24 h
100 mg (II)	8 h
300 mg	12 h
450 mg	12 h

Emesis occurring during the 90-minute period following apomorphine injection was evaluated by the degree of nausea, measured at 10 minute intervals using a visual analogue scale, the occurrence of vomiting and the total number of vomits and retches.

Blood samples for pharmacokinetic analysis were collected pre-dose and at 15 and 45 min and 1, 1.5, 2, 3, 5, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144 and 168 h post-dose. Blood and urine samples for laboratory safety tests were taken at screening, pre-dose, at 24, 72 and 168 h post-dose, and at follow-up (day 9-15). Vital signs were recorded at screening, pre-dose and 1, 2, 4, 8, 12, 24, 48, 72, 96, 129, 144 and 168 h post-dose, and at follow-up. 12-lead ECG recordings were performed at screening, pre-dose, 1, 2, 4, 8, 12, 24, 48 and 168 h post-dose and at follow-up.

Analysis of the results by plasma netupitant concentration at the time of apomorphine challenge showed a decrease in the incidence of vomiting with increasing netupitant levels. No subject in the highest concentration group (> 300 ng/mL, corresponding to 1 subject taking 300 mg and 5 subjects taking 450 mg) experienced vomiting, a statistically significant result compared to placebo ($p = 0.010$).

Subjects with lower netupitant concentrations also experienced less vomiting than the placebo group. In the three groups with lower netupitant concentrations, 50% of subjects experienced no vomiting (N=18), compared with 25% of subjects vomiting-free in the placebo group (N=8). In total, 15 out of the 24 subjects who received netupitant experienced no vomiting, with six subjects having fewer than 6 vomiting episodes. Only 2 of the 8 subjects receiving placebo experienced less than 6 vomiting episodes.

Retching was reduced in subjects treated with active drug, but no trend was observed between concentration groups. The results were skewed by one subject in the highest concentration group, who experienced a very

high number of retches. Nausea tended to increase with netupitant concentration, with the exception of the lowest concentration group (≤50 ng/mL), which recorded the lowest levels.

Table 23: Summary of Vomiting Episodes and Area under the Nausea VAS

Netupitant Concentration	**0 ng/mL (N=8)**	**≤ 50 ng/mL (N=6)**	**51-100 ng/mL (N=6)**	**101-300 ng/mL (N=6)**	**>300 ng/mL (N=6)**
Vomiting Episodes Mean	10.3	2.7	4.2	3.5	0.0
Range	0.0-27.0	0.0-10.0	0.0-18.0	0.0-13.0	0.0-0.0
AUC of Nausea VAS					
Mean	2207.9	1469.8	3089.8	3480.2	4117.8
Range	170-5435	10-3399	1184-5164	1552-5840	2030-6527

NETU-06-08 was undertaken to assess the degree of Neurokinin-1 receptor occupancy in the human brain after a single dose of netupitant in healthy male subjects

This was a single dose, randomised, open-label, PET study investigating the degree of occupancy of NK1 receptors in the human brain after single oral doses of netupitant in healthy male subjects. Subjects were randomised to a single dose of 100, 300 or 450 mg.

The study consisted of a screening visit, a baseline PET visit, a treatment period with up to 5 post dose PET scans and a follow-up visit. The screening assessments were performed within 28 days before dose administration, the baseline PET visit was performed within 7 days before dose administration and the follow-up visit was performed 14 ±2 days after dose administration.

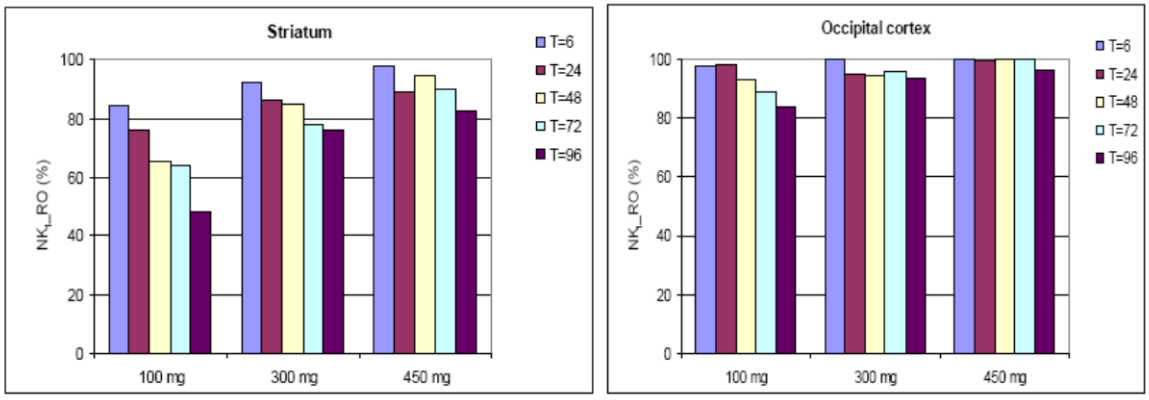
PET scans were performed 6, 24, 48, 72 and 96 hours after dose administration.

8 healthy white males aged between 20 to 25 years were randomised, 6 completed the study. Two subjects were withdrawn because the baseline PET scans were lost. These 2 subjects were replaced by two further subjects. Two of the eight were not treated (no reason given).

The results of this investigation demonstrated that netupitant is a potent selective NK1 receptor antagonist in the human brain with an ability to block NK1 receptors in the human brain for a relatively long time. The anticipated high NK1-RO (90% or higher) close to expected C_{max} (6 hours post dose) was achieved for occipital cortex and frontal cortex for all investigated doses as well as for striatum (for 300 and 450 mg netupitant) and anterior cingulate (for 100 and 450 mg netupitant).

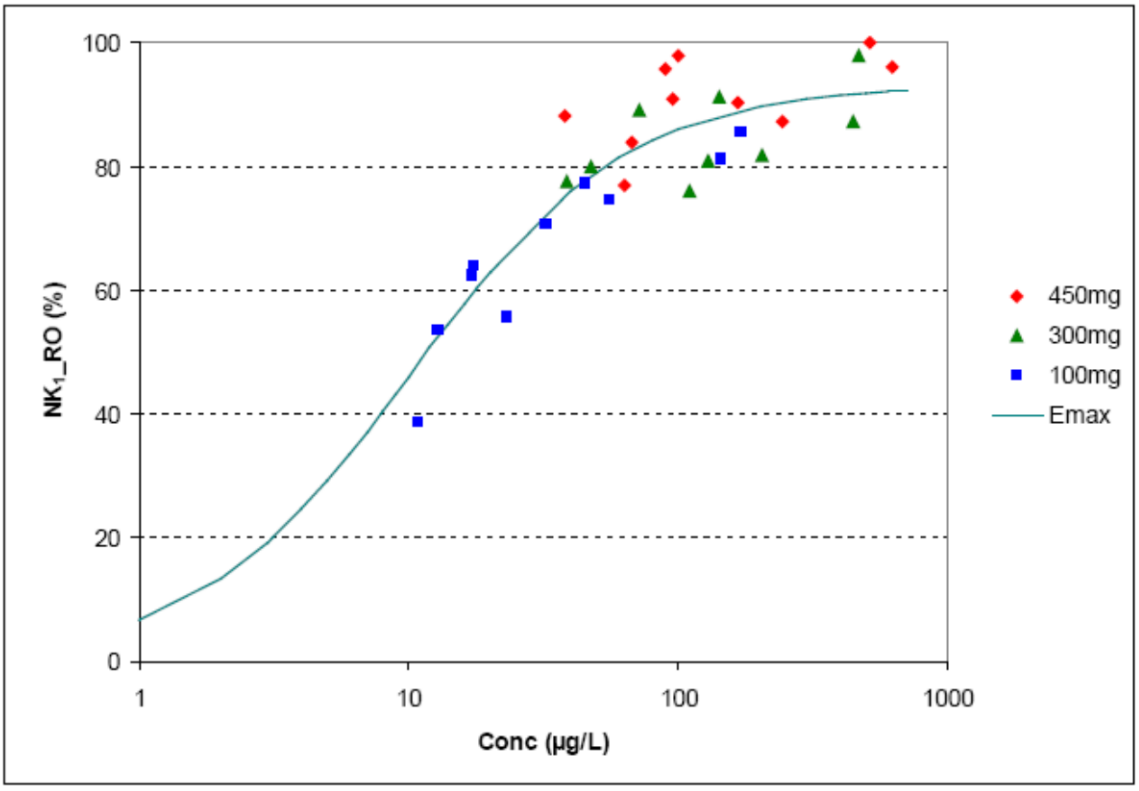
All doses showed a relatively long duration of blockade of the NK1 receptors and for most regions the NK1-RO declined slowly until 96 hours post dose in a dose-dependent fashion. In the 100 mg dose group, 4 of 6 regions still had a mean NK1-RO over 70% at 96 hours post dose. In the highest dose group (450 mg), 5 of 6 regions had a mean NK1-RO near to 80% or higher at 96 hours post dose. A comparison of the results for the dose groups (100 mg, 300 mg and 450 mg) showed a general but low increase in NK1-ROs with increasing dose. (Figure 3).

Figure 3: Average Neurokinin 1 Receptor Occupancy (NK1-RO), Obtained for Three Dose Groups at 6, 24, 48, 72 and 96 Hours After Administration of a Single Dose of 100, 300 and 450 mg Netupitant (N=2 for each dose) in Striatum and Occipital Cortex.



A clear relationship was observed between degree of NK1-RO in striatum and plasma concentrations of netupitant (Figure 4). Based on the PK/PD parameter estimates, a netupitant plasma concentration of 225 µg/L corresponds to NK1 receptor occupancy of 90% in striatum. A good fit of the predicted PK-PD relationship was obtained and the EC50 determined for striatum was 10.2 µg/L (CV: 14.5%). In contrast the other considered brain regions showed a more narrow range of NK1-RO and therefore the EC50 values for the cortex areas could only be estimated with low precision.

Figure 4: Relationship Between Plasma Concentrations of Netupitant (Log-transformed Values) and Striatal NK1-ROs at 6, 24, 48, 72 and 96 h After Oral Administration of 100, 300 and 450 mg of Netupitant



The PK parameters (C_{max} and T_{max}) were comparable to those obtained in previous single dose studies.

Population PD Analysis in Phase 3

During the population PK analysis carried out using data from the Phase 3 trial NETU-08-18 (NETU-10-02) in cancer patients treated with the FDC 300 mg/0.5mg, the relationship between concentrations of netupitant and its metabolites as well as palonosetron, and efficacy measures was investigated graphically. Measures of exposure (predicted CL, AUC_{inf}, and C_{max}) for netupitant, M1, M2, and M3, and palonosetron were correlated with measures of efficacy variables (complete response) at cycle 1.

Complete Response in the delayed, acute and overall phases were assessed via a graphical exploratory approach to visually determine if any correlations between drug exposures and these parameters were evident.

A clear relationship between exposure and response was not observed, demonstrating that effective concentrations of netupitant were achieved (NETU-10-02).

Secondary pharmacology

One safety study was conducted NETU-07-20: thorough QT study in health volunteers.

A Double-Blind Randomised Parallel-Group Trial to Investigate Possible ECG Effects of Netupitant/Palonosetron Using a Clinical and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (A Positive Control) in Healthy Men and Women: A Thorough ECG Trial.

The primary objective of this study was to demonstrate that the administration of netupitant in combination with palonosetron does not prolong the QT interval more than placebo in male and female healthy subjects. Secondary objectives were to evaluate the general safety and tolerability of netupitant in combination with palonosetron as well as the relative safety in comparison with moxifloxacin with focus on ECG parameters in healthy subjects and to evaluate the pharmacokinetics of netupitant (and its metabolites M1, M2, and M3) and palonosetron (and its metabolites M4 and M9) in plasma.

The study was a randomised, double-blind (except for the moxifloxacin active control), double-dummy, parallel-group, placebo and open-label positive-controlled study design involving four study groups: placebo; netupitant with palonosetron (200 mg + 0.50 mg); netupitant with palonosetron (600 mg + 1.50 mg); and moxifloxacin (400 mg). The study was carried out in one treatment period of three days with administration of study drug on Day 1.

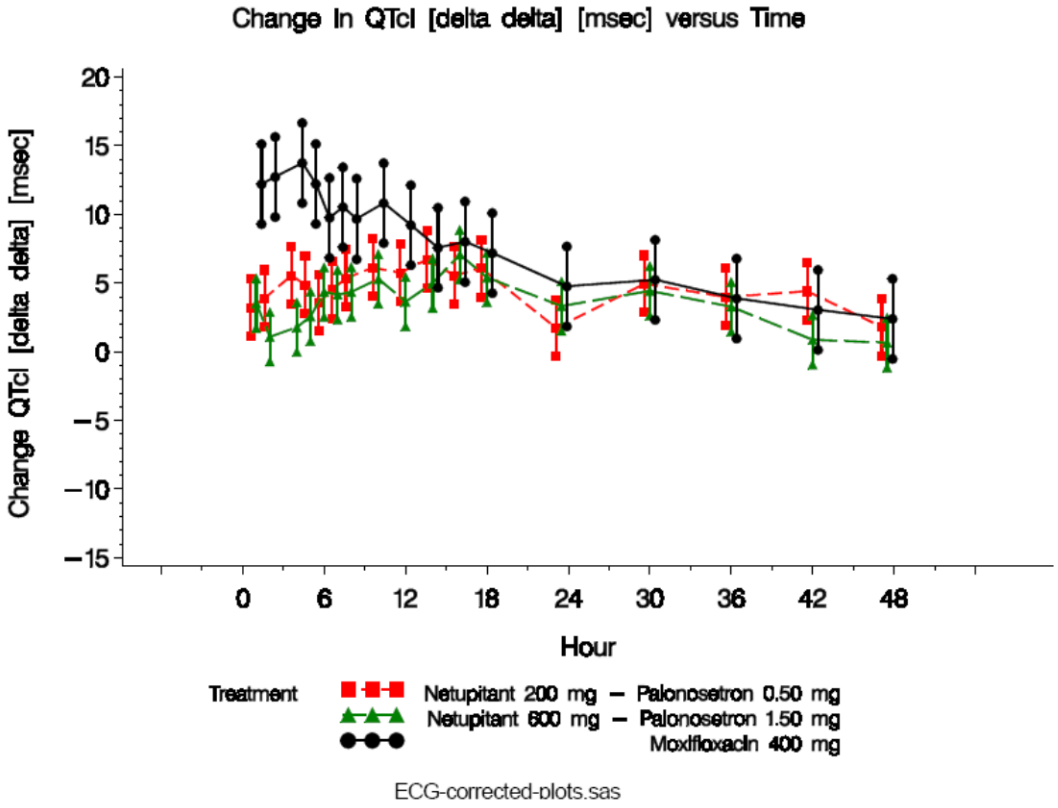
Two-hundred (200) healthy subjects (106 men and 94 women) participated in the treatment phase of the study. Men and women were included to reflect the target population for the therapy with netupitant. A centralized ECG reading lab was used to read the ECGs with interpretation by a high-resolution semi-automatic on-screen caliper method with annotations to minimize inter-reader variability. The central ECG laboratory was blinded to subjects and their treatment.

All treatments included a 24 h baseline and then all the subjects received a single dose of treatment, followed by ECG and pharmacokinetic measurements for 2 days.

The results of this ECG trial showed no signal of any effect on AV conduction or cardiac depolarization as measured by the PR and QRS interval durations. There was a non-dose related reduction in heart rate of 3 bpm in the palonosetron/netupitant groups of questionable clinical importance. There were no new clinically relevant morphological changes.

The effect of netupitant/palonosetron on cardiac repolarization using all of the QTc interval formulas shows no signal of relevant change. Figure 5 below shows the Change in QtcI (delta-delta) versus time for palonosetron/netupitant combinations and the positive control, moxifloxacin.

Figure 5: Change in QTcI Versus Time



- **PK Results**

The extent of absorption (AUC) for netupitant was proportional to the dose administered with a dose proportional increase of the geometric mean AUC of 4079 h*µg/L at 200 mg to 12213 h*µg/L at 600 mg oral dose. For C_{max} the same dose proportionality was observed with 219 µg/L at 200 mg and 648 µg/L at 600 mg dose. The inter subject variability of netupitant pharmacokinetics is high with a variability of 42% and 48% for AUC and C_{max} at 200 mg and 47% and 56% for AUC and C_{max} at 600 mg dose.

For palonosetron a dose proportional increase was observed for AUC (22641 h*ng/L at 0.5 mg to 67918 h*ng/L at 1.5 mg) and for C_{max} (822 ng/L to 2588 ng/L). The inter subject variability of palonosetron is lower as compared to netupitant with a variability of 25% and 29% for AUC and C_{max} at 0.5 mg and 20% and 23% for AUC and C_{max} at 1.5 mg dose.

The pharmacokinetics of netupitant and metabolites and palonosetron and metabolites confirmed that the time points of Holter 12-lead ECG at 1, 2, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 23.5, 30, 36, 42, and 47.5 hours post dose were adequately chosen since the C_{max} of all analytes lie within the ECG measurement time points.

- **PK/PD Modeling**

The PK/PD modeling indicated there was no relationship between changes in QTcI and plasma concentration of either palonosetron or netupitant.

During the population PK analysis (NETU-10-02) in MEC patients participating in trial NETU-08-18, the relationship between concentrations of netupitant, its metabolites as well as palonosetron, and efficacy and safety measures was investigated graphically. Measures of exposure (predicted CL, AUC_{inf}, and C_{max}) for

netupitant, M1, M2, and M3, and palonosetron were correlated with measures of cardiac safety (changes from baseline in troponin levels on Days 2 and 6).

The plots demonstrate that there was no overt relationship or trend between exposure parameters for netupitant, its metabolites, and palonosetron and safety, as measured by troponin levels (NETU-10-02).

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Overall measurable plasma netupitant concentrations were detected between 15 minutes and 3 hours after dosing in single dose oral studies. After this lag time, plasma concentrations followed a first order absorption process and reached C_{max} in approximately 4-5 hours. Netupitant is eliminated from the body in a multi-exponential fashion, with an apparent mean elimination half-life ranging from 30 to approximately 100 hours (across all studies for doses of 30 mg to 450 mg) with a few longer outliers. Netupitant is not dose proportional in doses from 10 to 300mg but Dose proportionality has been demonstrated for the 300mg to 450 mg doses.

No absolute studies on bioavailability with netupitant were carried out but it is estimated based on two IV studies with netupitant that the oral preparation has a greater than 60% bioavailability. Netupitant is highly protein bound. The mean volume of distribution in humans ranged from approximately 850L to over 2000L indicating substantial distribution of netupitant into the tissues.

Netupitant is metabolised in the liver and is primarily excreted excreted via the hepatic/biliary routes, with renal clearance (CLr) accounting for less than 5% of CL. In early studies, 3 active metabolites were identified (M1, M2 and M3). In plasma from humans who were administered oral netupitant, netupitant and its 3 major metabolites were extensively bound (> 97%) to plasma protein at concentrations ranging from 10 to 1500 ng/mL. Based on a gerbil foot tapping NK1 assay these metabolites appear to be pharmacologically active.

After one week daily dosing in healthy volunteers a greater than three times exposure to netupitant was shown. Given that this FDC is intended for single administration with each chemotherapy cycle subsequent administration can be assumed to be often separated by a 3 week interval to assure a complete washout from the previous administration. With a half-life of netupitant, active metabolites M1, M2, M3 and palonosetron averaging between approximately 40 and 80 h, at the start of a new chemotherapy cycle at least 6.3 half-lives would have elapsed and approximately 99% of the dose would have been eliminated before the next dose. Even in patients who underwent chemotherapy every 2 weeks (e.g., study NETU-10-29), at the start of a new chemotherapy cycle approximately 95% of the dose would have been eliminated prior to the next dose in 4.2 half-lives, allowing for clinically insignificant accumulation.

In an earlier study (n =11) investigating the effect of food netupitant alone showed a marked increase on exposure and C_{max} in the fed state whereas in a more recent study (n=22) exposing subjects to the FDC only a slight increase in exposure and C_{max} of netupitant in the fed states was shown. Given that the latter study was conducted with a larger population and with the FDC the results from this study are given greater emphasis. As the differences in PK with the FDC combination were marginal the FDC can be given with or without food.

The PK in the target population is similar to that in healthy volunteers though greater inter-subject variability was demonstrated in the cancer chemotherapy population. Inter-subject variability in the fed state for the

proposed netupitant dose is moderate, and high in the fasted state, in those with hepatic impairment, the elderly and those taking netupitant with etoposide.

There is a gender effect for both palonosetron and netupitant with higher exposure and C_{max} for palonosetron in females and higher C_{max} for netupitant not deflected in a greater incidence of adverse events in females compared to males. Exposure and C_{max} are also higher in older people in whom exposure to netupitant and palansetron increased by 25% and 37% respectively and C_{max} by 10% and 36% respectively. These differences are unlikely to be clinically relevant and so no dose adjustments are indicated in elderly subjects.

Nevertheless all but four of the older people exposed to the FDC were aged under 75 therefore there is limited exposure of the older old (> 75 years) to the FDC in PK studies.

As netupitant and palonosetron in the FDC showed increased exposure in older people in general it is possible that exposure with the same dose is greater in patients > 75 years. Therefore a precautionary statement to this age population was included in section 4.2 of the SmPC and the RMP reflects experience in patients aged 75 years and more as missing information.

No studies were carried out with the FDC on subjects with renal impairment. This was justified by the applicant on the basis that renal clearance accounts for only 5% of CL and a population PK/PD study NETU-10-02 (which included 118 subjects from the phase 111 study NETU-08-18) did not demonstrate any influence of renal impairment on PK therefore the FDC can be administered without dose adjustion. However no patients with severe renal impairment were included in this study. As no conclusions can be drawn regarding dosing in patients with severe renal impairment the SmPC states that the use in these patients should be avoided.

Overall, increases in exposure of netupitant and palonosetron in the FDC were observed in subjects with hepatic impairment presumably due to reduced hepatic metabolism. Exposure and C_{max} increased by 70% to 143% patients with moderate hepatic impairment. Although the increases were statistically significant, they are of questionable clinical significance and variability in the healthy control groups was large and renders the comparisons difficult to interpret. Safety data in the hepatic impairment study showed no differences between subjects with hepatic impairment and healthy subjects with respect to safety profile and no dose reduction are indicated. Considering that each dose is given as a once off before chemotherapy this is acceptable. Furthermore modelling of accumulation has demonstrated minimal accumulation of netupitant with 300mg administered at 3 or 2 weekly intervals. Given the lack of evidence for significant accumulation of netupitant with 2 or 3 weekly dosing, and the tolerance of higher exposure levels, no dose adjustment for moderate hepatic impairment is required.

Limited conclusions can be drawn however for patients with severe hepatic impairment due to the low number of subjects included in this group. Therefore a cautionary statement on increased exposure and on the limited data available in severe hepatic impairment was included in section 4.4. of the SmPC.

Netupitant is primarily metabolized via hepatic cytochrome P450 3A4. In general, genetic polymorphism of CYP3A4 results in a decrease in enzyme activity, but occurs in a small proportion of the population across all of the affected alleles. Specific studies to evaluate effect of genetic polymorphism of CYP3A4 on netupitant disposition were not conducted but considering that even a remarkable reduction of the CYP3A4 enzymatic activity such as that occurred when a strong CY3A4 inhibitor is co-administered with netupitant, is not expected to increase netupitant exposure more than approximately 2-fold and the large safety margin established for netupitant in the clinical program this is acceptable.

CYP3A4 inhibitor (ketoconazole) increased the AUC of netupitant 1.8 fold, whereas CYP3A4 inducer rifampicin as expected decreased the AUC to netupitant considerably (5.2 fold). This information is appropriately reflected in the SmPC.

Netupitant increased exposure to other CYP3A4 substrates e.g erythromycin, midazolam, levonorgestrel and dexamethasone therefore it should be used with caution in patients receiving concomitant orally anministered active substances that are metabolized through this enzyme as labelled in the SmPC. Co-administration of a single dose of 300mg netupitant with dexamethasone led to a significant increase in dexamethasone exposure in a time and dose related manner. The AUC_{0-24} (Day 1), the AUC_{24-36} (Day 2) and the AUC_{84-108} and $AUC_{84-\infty}$ (Day 4) of dexamethasone increased 2.4-fold, with co-administration of 300 mg netupitant. Therefore recommended oral dexamethasone dose should be reduced by approximately 50 % when co-administered with Akynzeo as stated in the SmPC. Dexamethasone, midazolam and erythromycin had no effect on netupitant levels.

Based on development program, the potential for netupitant interaction with chemotherapy agents metabolized by CYP3A4 was considered, and three *in vitro* studies were conducted with vincristine, cyclophosphamide and docetaxel as representative chemotherapeutic agents known to be metabolized by CYP3A4. These in vitro results were investigated in cancer patients (NETU-10-09) and an increase of AUC0-t values was reported for each chemotherapeutic agent when Akynzeo was concomitantly administered, as compared to other antiemetic treatments (palonosetron). On average, the exposure increased 1.35-fold for docetaxel, 1.28-fold for etoposide and 1.20-fold for cyclophosphamide. Therefore precautionary statements on chemotherapeutic agents that are substrates for CYP3A4 were included in the SmPC.

The potential of netupitant and its three main metabolites M1, M2 and M3 to inhibit UGT enzymes in both pooled human liver microsomes and a panel of cDNA expressed recombinant human UGT enzymes showed that *in vivo* interaction upon netupitant administration is possible at intestinal level during the absorption phase of orally administered drugs with poor/moderate oral bioavailability (F% < 50%) which are mainly metabolized by UGT2B7. Whereas the magnitude of such an effect in the clinical setting is not established a cautionary statement on this possible interaction was added to the SmPC and it was added to the RMP as a potential risk.

BCRP and P-gp are both inhibited *in vitro* by netupitant with similar IC50 values, i.e., 6 and 3 µM, respectively. Since in vitro data show that netupitant inhibits BCRP, and, even though clinical adverse events related to BCRP inhibition are rare, information on inhibition of the efflux transporter BCRP was included in the SmPC.

Pharmacodynamics

Two pharmacodynamic studies were performed one in which volunteers were exposed to doses ranging from 100mg to 450mg of netupitant between 8 to 12 hours prior to an apomorphine injection. A decrease in the incidence of vomiting was noted with increasing netupitant levels. No subject in the highest concentration group (> 300 ng/mL, corresponding to 1 subject taking 300 mg and 5 subjects taking 450 mg) experienced vomiting, a statistically significant result compared to placebo (p = 0.010). However nausea appeared to increase with increasing exposure. A PET study demonstrated that netupitant is a potent selective NK1 receptor antagonist in the human brain with an ability to block NK1 receptors for a relatively long time. In the population PD analysis a clear relationship was not demonstrated between exposure and response. However there was a correlation between Clearance/F and response.

Overall there is evidence from pharmacodynamic studies for the efficacy of the FDC and netupitant.

2.4.5. Conclusions on clinical pharmacology

Overall the PK and PD of netupitant and the FDC has been sufficiently characterised. Posology and relevant interactions are appropriately reflected in the product information.

2.5. Clinical efficacy

The applicant has presented reports for 3 efficacy clinical studies. 2 of these (NETU-07-07 & NETU -08-18) were designed to demonstrate the efficacy and safety of the combination in the setting of single cycle HEC and single and multiple cycle MEC respectively. PALO-10-01 was designed to evaluate the non-inferiority of oral vs. I.V. palonosetron in the setting of HEC.

Study NETU-10-29 was primarily designed to evaluate the safety of the FDC in both HEC and MEC settings, and will be dealt with in the clinical safety section of this report. Efficacy endpoints were secondary objectives in this study.

Table 24: Overview of Clinical Trials Providing Efficacy Data for the Netupitant/Palonosetron FDC Program

Trial No.	Design	No. of Patients randomized/ treated/FAS	Duration	Indication	Primary Endpoint	Role of Study for efficacy demonstration
NETU-07-07	Double-blind, randomized (1:1:1:1:1) parallel group	PALO oral 136/136/136* PALO + NETU 100 135/135/135* PALO +NETU 200 142/138/137* PALO +NETU 300 143/136/135* Aprepitant +Onda 138/134/-- Total 694/679/543*	Single-cycle	HEC	CR Overall phase (0-120 hr)	Netupitant dose selection/Pivotal evidence of NETU+PALO efficacy in HEC
NETU-08-18	Double-blind, randomized (1:1) parallel group	PALO oral 726/725/725 FDC 729/725/724 Total 1455/1450/1449	Single and Multiple cycles	MEC	CR Delayed phase (25-120 hr)#	Pivotal evidence of FDC efficacy in MEC
NETU-10-29	Double-blind, randomized (3:1) parallel group	FDC 309/308/309 Aprepitant + PALO oral 104/104/103 Total 413/412/412	Multiple cycles	MEC and HEC	Safety	Supportive evidence of FDC efficacy in MEC and HEC
PALO-10-01	Double-blind, randomized (1;1) parallel group	PALO oral 371/370/369 PALO IV 372/369/369 Total 743/739/738	Single-cycle	HEC	CR Acute phase (0-24 hr)	Evidence of efficacy of PO palonosetron alone in HEC

*For NETU-07-07 the numbers of patients are randomized/number treated/MFAS
# Key secondary endpoints: CR acute phase (0-24 hr), overall phase (0-120 hr)
FDC= Netupitant/Palonosetron Combination Fixed-Dose Capsule (palonosetron 0.50 mg/netupitant 300 mg)
Dexamethasone was included in all dose regimens.
PALO= Palonosteron; NETU= Netupitant; Onda= Ondansetron

2.5.1. Dose response studies

Early studies evaluated the clinical pharmacology of netupitant using an apomorphine challenge model (NP16602) followed by an NK1 receptor binding assay (PET study; NETU-06-08). These two studies led to an understanding that the therapeutic dose in humans was likely to be in the 100-300 mg dose range. Subsequently, Phase 2 study NETU-07-07 was designed to test 100 mg, 200 mg and 300 mg netupitant with palonosetron 0.50 mg against palonosetron 0.50 mg alone. Results led to selection of the netupitant/palonosetron 300 mg/0.50 mg combination dose used in Phase 3 trials.

2.5.2. Main studies

NETU-07-07:

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

Methods

Study Participants

The study population consisted of adult (≥ 18 years of age) chemotherapy naïve male or female patients with histologically or cytologically confirmed solid tumours who were scheduled to receive highly emetogenic cisplatin-based chemotherapy. Patients were required to have a Karnofsky index ≥ 70% and to be able to understand and follow study procedures and complete the patient diary. Female patients of childbearing potential were required to have a negative pregnancy test at screening and to practice concurrently two reliable methods 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 moderately or highly emetogenic chemotherapy from Day 2 to 5 following cisplatin administration, received (within 1 week prior to Day 1) or were scheduled to receive (Days 1 to 5 after cisplatin administration) moderately or highly emetogenic radiotherapy, took any drug with potential antiemetic efficacy within 24 hours prior to Day 1, took systemic corticosteroids within 72 hours prior to Day 1, or took NK1 receptor antagonists or any investigational drug within 4 weeks prior to Day 1, or had other medical conditions or personal circumstances that would interfere with interpretation of study results or expose the patient to an unacceptable risk.

Treatments

Eligible patients were randomised (stratified by gender) to one of the following treatment groups:

Group 1 - 0.5 mg oral palonosetron on Day 1 (with dexamethasone standard regimen: 20mg 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)

Group 5, consisting of a combination of a licensed NK-1 RA, a 5HT-3 RA and dexamethasone was added as an exploratory arm reflecting current practice regarding these agents.

Preliminary results of a drug-drug interaction study indicated that a clinically relevant increase in dexamethasone exposure occurred when it is administered with netupitant. Therefore, the standard dexamethasone regimen was reduced proportionally to balance dexamethasone exposure across all study arms. The adjusted regimen was the same as for aprepitant.

Objectives

The objective of the study 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.

Outcomes/endpoints

The primary outcome was complete response rate at 120h (overall) following initiation of Cycle 1 chemotherapy regimen. Complete response was defined as no emetic episodes and no rescue medication.

Secondary outcome measures included;

- CR at 0-24h (acute phase) and 25-120h (delayed phase),
- Complete protection, defined as no emesis, no rescue medication, and no significant nausea (defined as <25mm on VAS)
- Total control, as above with no nausea (defined as <5mm on VAS)
- No nausea
- No significant nausea
- No rescue medication
- No emesis,

These were evaluated during the acute (0-24h), delayed (25-120h) and overall (0-120h) phases. They were also evaluated for each 24h subset during the total evaluation period.

Other secondary endpoints were;

- Time to 1st emetic episode
- Time to rescue medication
- Time to treatment failure (defined as time to emetic episode or rescue medication)

- Severity of nausea as measured by VAS in each 24h period
- Patient global satisfaction with anti-emetic medication as measured by VAS in each 24jh period

Safety assessments included physical examinations, 12-lead ECGs, vital signs, haematology, blood chemistry, urinalysis, and adverse events.

Sample size

The sample size was estimated to be 680 patients, distributed across five treatment groups (136 patients per group). The assumption was a responder rate of 70% in the netupitant and palonosetron group (plus dexamethasone regimen) and 50% in the palonosetron alone group (plus dexamethasone regimen). For a one-sided test of difference, using α =0.0166 (obtained as type I error divided by the number of comparisons = 0.050/ 3), a sample size of 129 evaluable patients per group was needed to ensure 85% power for each comparison. The number was rounded up to 136 patients per treatment group.

Randomisation

Patients were assigned to treatment groups using a randomisationlist that was stratified by gender. Within strata (gender), patients meeting the inclusion and exclusion criteria were assigned to one of five treatment groups in a balanced design (i.e., in the ratio 1:1:1:1:1).

A randomisationlist was prepared prior to the start of the study. According to this randomisationlist, sealed cartons containing the study drug and additional study drug were supplied to the investigational sites. Patients were randomised by the investigator using an interactive voice response system (IVRS) in accordance with study-specific procedures.

A dynamic adaptive stratification type of randomisation method that balanced the five treatment groups according to the patient gender was used. Treatments were balanced across the entire study, not within each individual site.

The general strategy of this randomisation was to give additional probability to receiving a specific treatment if it was underrepresented in the current randomisation status. Patients who were randomised but never received study treatment were not considered during the following patient randomisation/treatment assignment. This ensured that a balance among treatment groups in the treated population was being maintained. The investigator was trained to immediately notify the IVRS if a randomised patient did not receive study treatment. The relevant algorithm to this method tailored for this study was described in the appropriate IVRS document.

Blinding (masking)

To maintain study blinding, matching placebos were manufactured for each of the study drugs and additional study drug.

Statistical methods

The primary study objective was to find out whether or not at least one of three doses of netupitant combined with palonosetron was more effective than palonosetron alone based on the complete response rate at 0-120 hours (CR 0-120).

Therefore, the primary statistical analysis of efficacy was designed to reject the composite null hypothesis that none of the three combinations of the active netupitant dose combined with palonosetron was more effective than palonosetron alone. The Holm-Bonferroni method was used to control for the type I error.

The primary efficacy endpoint was the complete response during 0-120 hours.

The complete response rate during 0-120 hours was summarized by treatment arm. The number and the proportion of the patients with CR 0-120 were presented in a frequency table.

For the response rate and for the difference in response rate between each palonosetron plus netupitant dose group and palonosetron alone group, the 95% CI were provided. Pairwise comparisons between palonosetron plus netupitant dose group and palonosetron alone group were performed using Chi-square test.

The main question of the study was whether or not the null-hypothesis (H0) that none of the regimens of netupitant combined with palonosetron was superior to the oral palonosetron alone (0.5 mg) can be rejected in favour of the alternative hypothesis that at least one dose of oral netupitant and palonosetron was superior to oral palonosetron alone (0.5 mg), considering the complete response rate at 0-120 hours. The primary test was performed using a logistic regression adjusted for the covariate (gender), where each dose of netupitant combined with a fixed dose of palonosetron and dexamethasone was compared to palonosetron alone and dexamethasone. In order to test the null hypothesis, three one-sided tests were conducted with three separate null hypotheses: Hi (i=1, 2, 3) with the corresponding p-values pi that stated the linear coefficient that corresponds to the i-th active treatment in the logistic regression model was not positive. The general null-hypothesis, therefore, becomes the intersection of these three, and the Holm-Bonferroni procedure for testing the general hypothesis was used as follows. The three p-values were ordered in the increasing order as p(1)<p(2)<p(3) If the smallest of the three p-values p(1) did not exceed 0.05/3 then the corresponding Hi was rejected and the p(2) was compared to 0.05/2, and if p(2)<= 0.05/2, then the hypothesis corresponding to p(2) was also rejected, and the remaining p(3) was compared to 0.05. In case p(3) ≤ 0.05, then the corresponding Hi was also rejected. At this point, all the null hypotheses that were not been rejected remain not rejected, and the procedure terminated with the global H0 rejected only if at least one of the Hi was rejected. For the primary analysis, patients with missing data were classified as not having a complete response.

The same logistic regression model was used to compare each dose of palonosetron plus netupitant to each other. This was done on a descriptive level, i.e. without adjustment for multiplicity.

A sensitivity analysis of the primary endpoint was added which excluded patients who did not complete diaries or did not provide information about emetic episode and/or use of rescue medication who were considered, in the primary analysis, as non responders following the worst case principle. The sensitivity analysis was only performed for the MFAS population.

Additional analyses were suggested by the FDA during the interactions for planning the phase III development. The details of the changes are as follows:

i. Analysis considering the CR in the delayed phase (defined as 25-120 hours after chemotherapy) as the primary efficacy endpoint.

Since the delayed phase is the time frame where NK1 receptor antagonists are expected to be more effective, in the FDA opinion, the most sensitive endpoint for establishing the contribution of netupitant to the efficacy of the combination product is the CR 25-120 rather than the original primary efficacy endpoint CR 0-120. For

this reason CR 25-120 was suggested to be the primary efficacy endpoint for the phase III development. Also, NETU- 07-07, in the light of his potential new role of pivotal study, should have been analysed accordingly.

ii. Analysis using the Cochran-Mantel-Haenszel (CMH) test stratified by gender. The original analysis of the primary endpoint CR 0-120 was performed using a logistic regression model adjusted for gender. The FDA requested to replace this statistical test with the Cochran-Mantel-Haenszel (CMH) test stratified by gender.

iii. Analysis using a hierarchical procedure to control the type I error.

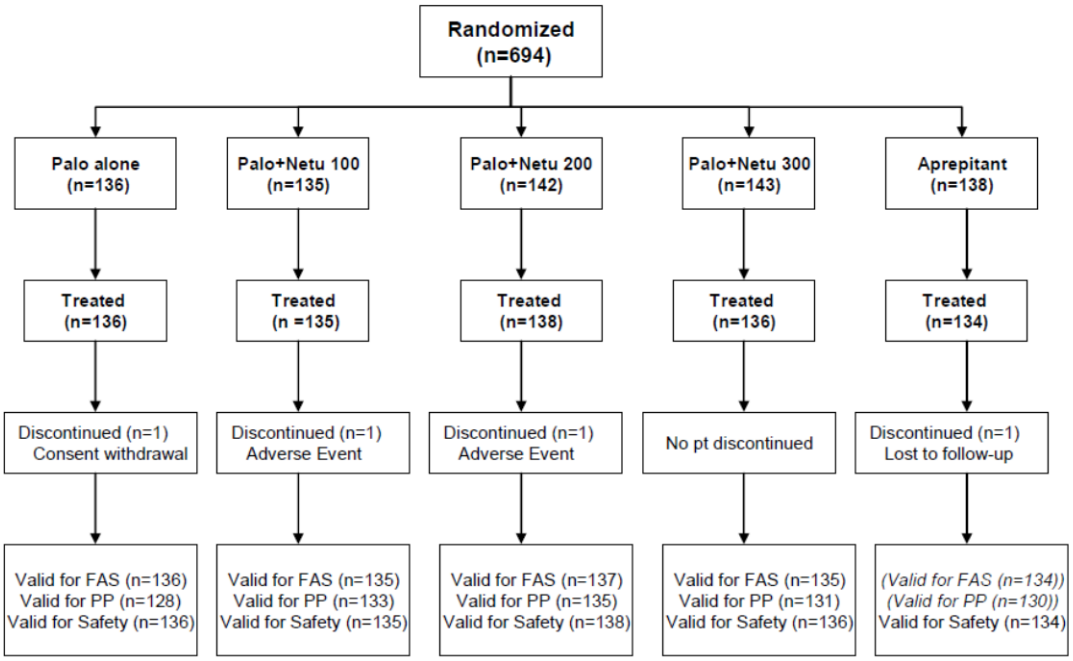
The procedure is to be applied to three endpoints CR in the delayed (CR 25-120), acute (CR 0-24) and overall (CR 0-120) phases. In the original plan, CR 0-24 and CR 25-120 were secondary efficacy endpoints and, as such, no specific procedure was in place for dealing with multiplicity.

iv. Sensitivity analysis on the Intention-To-Treat (ITT) population defined as all randomised patients.

As mentioned, the efficacy analysis was originally performed considering the MFAS as the primary population of analysis. In addition, analysis on the PP population and a sensitivity analysis on complete cases were performed.

Results

Participant flow



Recruitment

The first patient was enrolled to the trial on February 4th 2008, with last patient last visit on November 22nd 2008.

Conduct of the study

The sponsor conducted a trial site audit to support the use of this study as the pivotal efficacy trial for HEC indication.

One site in Russia (site No. 120) presented multiple major audit findings, ranging from failure to meet eligibility criteria and administration of prohibited medications to inconsistencies between source data and Case Report Forms (CRFs). Regardless of these findings, according to intent to treat principles, the site remains part of all planned analyses. However, to explore whether this site has had any impact on the treatment effect, the sponsor provided the CR rates obtained after exclusion of all 39 patients enrolled at this site.

The following table summarizes the CR rates in the overall (0-120 hours), acute (0-24 hours) and delayed (25-120 hours) phases after the start of chemotherapy administration, which were obtained for the full analysis set (FAS) and the CR rates without/withdrawing the 39 patients from site No. 120.

Table 25: Complete Response Rates for the Overall, Acute and Delayed Phases

	PALO alone	PALO + NETU 100 mg	PALO + NETU 200 mg	PALO + NETU 300 mg	APREP + ONDA
FAS					
N	136	135	137	135	134
Number (%) of patients with CR					
Overall phase	104 (76.5)	118 (87.4)	120 (87.6)	121 (89.6)	116 (86.6)
Acute phase	122 (89.7)	126 (93.3)	127 (92.7)	133 (98.5)	127 (94.8)
Delayed phase	109 (80.1)	122 (90.4)	125 (91.2)	122 (90.4)	119 (88.8)
Without site 120					
N	129	128	129	126	126
Number (%) of patients with CR					
Overall phase	99 (76.7)	111 (86.7)	114 (88.4)	112 (88.9)	108 (85.7)
Acute phase	115 (89.2)	119 (93.0)	119 (92.3)	124 (98.4)	119 (94.4)
Delayed phase	104 (80.6)	115 (89.8)	119 (92.3)	113 (89.7)	111 (88.1)

CR rates across all treatment groups and in all three periods achieved after excluding all 39 patients from site 120 are consistent with the CR rates from FAS. The differences in CR rates, with and without site 120, for the netupitant 300 mg plus palonosetron 0.5 mg group are 0.7% in both, the overall and delayed phases, and 0.1% in the acute phase. When considering all treatment groups, the largest difference is 1.1%. Furthermore, the differences in CR rates did not seem to be systematically in one direction. This evidence supports the lack of impact of this site and the overall robustness of the study conclusions.

Baseline data

The demographics of the safety population are presented below, along with a description of the disease types represented in this population.

Table 26: Demography – Safety Population

Parameter	PALO Alone (N=136)	PALO+ 100 NETU (N=135)	PALO+ 200 NETU (N=138)	PALO+ 300 NETU (N=136)	Aprepitant
Gender					
Male	78 (57.4%)	77 (57.0%)	80 (58.0%)	77 (56.6%)	75 (56.0%)
Female	58 (42.6%)	58 (43.0%)	58 (42.0%)	59 (43.4%)	59 (44.0%)
Age (years)					
Mean (SD)	54.2 (9.7)	55.0 (9.5)	54.4 (9.8)	54.1 (9.7)	54.4(10.3)
Median	55.0	55.0	55.0	53.0	55.5
Min / Max	27.0 / 77.0	19.0 / 77.0	24.0 / 82.0	19.0 / 77.0	25.0 / 75.0
Race					
White	136 (100.0%)	135 (100.0%)	137 (99.3%)	136 (100.0%)	134 (100.0%)
Asian	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
Country					
Russia	86 (63.2%)	86 (63.7%)	88 (63.8%)	88 (64.7%)	87 (64.9%)
Ukraine	50 (36.8%)	49 (36.3%)	50 (36.2%)	48 (35.3%)	47 (35.1%)

☐ HYPERLINK \l "T3" ☐Section 14, Table 3☐, ☐ HYPERLINK \l "T4_3" ☐Table 4.3☐

Table 27: Summary of Cancer History – Safety Population

Parameter	PALO Alone (N=136)	PALO+ 100 NETU (N=135)	PALO+ 200 NETU (N=138)	PALO +300 NETU (N=136)	Aprepitant (N=134)
Primary cancer diagnosis*					
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%)
Time since histological diagnosis (days)					
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
Extent at study entry					
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%)
Site of metastasis					
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.%)	1 (0.7%)	0 (0.%)
Other	17 (12.5%)	19 (14.1%)	16 (11.6%)	18 (13.2%)	23 (17.2%)

*Diagnosis categories were defined by the Sponsor based on site of primary cancer.☐ HYPERLINK \l "T6_3" ☐Section 14, Table 6.3☐

Chemotherapy administered to study participants is summarized in Table 28. Approximately 15% of patients were treated with cisplatin alone while cisplatin with concomitant chemotherapy with low (Hesketh level <3) or moderate to high (Hesketh level ⩾3) emetogenic potential was administered to 51% and 34% of patients, respectively. Overall, the chemotherapy administered was comparable across treatment groups.

Table 28: Chemotherapy – Safety Population

	PALO alone (N=136)		PALO + 100 NETU (N=135)		PALO + 200 NETU (N=138)		PALO + 300 NETU (N=136)		APREPITANT (N=134)	
Type of chemotherapy, n (%)										
Cisplatin alone	21	(15.4)	21	(15.6)	20	(14.5)	19	(14.0)	20	(14.9)
Concomitant										
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)
Chemotherapy post 120 hours,n (%)										
Yes	8	(5.9)	4	(3.0)	10	(7.2)	7	(5.1)	8	(6.0)
Time of concomitant chemotherapy, n (%)										
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)
Mean cisplatin dose (mg/m^2)										
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	

□□□

Numbers analysed

Table 29: 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)
Reason for discontinuation										
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)

□□□

The populations were defined as follows:

The full analysis set population (FAS) was defined as all patients who were randomised to treatment and received a highly emetogenic chemotherapy regimen and at least one dose of study treatment. Following the intent-to-treat principle, patients were assigned to the study treatment group according to the treatment to which they have been randomised. The FAS was used for summarizing demography and baseline characteristics.

The modified FAS (MFAS) population consisted of the FAS population excluding patients randomised to aprepitant treatment arm. This was the primary population for efficacy evaluation. MFAS was used for demography, baseline characteristics and efficacy parameters analysis.

The per-protocol (PP) population consisted of all patients included in the MFAS who completed the 0-120 study period and were compliant with the study protocol. The PP population was analyzed for the primary efficacy parameter, demographic data, and selected baseline characteristics.

The safety population consisted of all patients who received at least one study treatment and had at least one safety assessment after the treatment administration. Patients were assigned to the study treatment group according to the actual treatment received. The safety population was analyzed for demography, baseline characteristics and safety analysis.

Outcomes and estimation

- **Primary and key secondary endpoints – Original and post hoc analyses**

The CR rates from the overall and acute phases are presented below, with both the original and post hoc reanalysis presented.

Table 30:: Complete Response Rate for the Delayed Phase: MFAS Population

	Palo alone (N=136)	Palo + Netu 100 mg (N=135)	Palo + Netu 200 mg (N=137)	Palo + Netu 300 mg (N=135)
Delayed phase (25-120 hours)				
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 test*		0.017	0.008	0.016

*including gender as covariate/stratum

Table 31: Complete Response Rate for the Acute and Overall Phases: MFAS Population

	Palo alone (N=136)	Palo + Netu 100 mg (N=135)	Palo + Netu 200 mg (N=137)	Palo + Netu 300 mg (N=135)
Acute phase (0-24 hours)				
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 test*		0.278	0.383	0.002
Overall phase (0-120 hours)				
Number (%) of Patients	98 (76.6)	117 (88.0)	119 (88.1)	117 (89.3)
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 test*		0.018	0.016	0.003

*including gender as covariate/stratum

The results from the MFAS population were supported by those from the PP population and the sensitivity analysis.

On individual study days, i.e., 0-24 hours, 25-48 hours, 49-72 hours, 73-96 hours, and 97-120 hours, the netupitant 300 mg group showed the highest percentage of responder at each day. The difference between netupitant 300 mg and palonosetron alone ranged from 7% to 9% and was statistically significant on each day (chi-square p-value< 0.050), with the exception of day 4.

- **Secondary endpoints**
  - No Emesis

Only the 300mg netupitant dose showed consistent benefit through all the treatment phases.

Table 32: Number and Percent of Patients with No Emesis – MFAS Population

	PALO alone (N=136)	PALO + NETU100 mg (N=135)	PALO + NETU200 mg (N=137)	PALO + NETU 300 mg (N=135)
Overall (0-120 hours)				
Number (%) of Patients	104 (76.5)	118 (87.4)	120 (87.6)	123 (91.1)
Difference from palonosetron alone (%) with 95% CI		10.9 (1.9, 20.0)	11.1 (2.1, 20.1)	14.6 (6.0, 23.2)
p-value[1]		0.018	0.017	0.001
Acute Phase (0-24 hours)				
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[1]		0.278	0.383	0.007
Delayed Phase (25-120 hours)				
Number (%) of Patients	109 (80.1)	122 (90.4)	125 (91.2)	124 (91.9)
Difference from palonosetron alone (%) with 95% CI		10.2 (1.9, 18.6)	11.1 (2.9, 19.3)	11.7 (3.6, 19.8)
p-value[1]		0.018	0.010	0.006

[1]p-value from logistic regression analysis with gender as covariate

☐ HYPERLINK \l "T19_1" ☐Section 14, Table 19.1☐, ☐ HYPERLINK \l "T20_3" ☐Table 20.3☐

- No Nausea and No Significant Nausea

Table 33: Patients with No Nausea – MFAS Population

	PALO alone (N=136)	PALO + NETU100 mg (N=135)	PALO + NETU200 mg (N=137)	PALO + NETU 300 mg (N=135)
Overall (0-120 hours)				
Number (%) of Patients	69 (50.7)	74 (54.8)	85 (62.0)	83 (61.5)
Difference from palonosetron alone (%) with 95% CI		4.1 (-7.8, 16.0)	11.3 (-0.4, 23.0)	10.7 (-1.0, 22.5)
p-value[1]		0.490	0.058	0.070
Acute Phase (0-24 hours)				
Number (%) of Patients	102 (75.0)	98 (72.6)	106 (77.4)	108 (80.0)
Difference from palonosetron alone (%) with 95% CI		-2.4 (-13, 8.1)	2.4 (-7.7, 12.5)	5.0 (-4.9, 14.9)
p-value[1]		0.654	0.648	0.317
Delayed Phase (25-120 hours)				
Number (%) of Patients	73 (53.7)	80 (59.3)	89 (65.0)	92 (68.1)
Difference from palonosetron alone (%) with 95% CI		5.6 (-6.2, 17.4)	11.3 (-0.3, 22.9)	14.5 (3.0, 26.0)
p-value[1]		0.348	0.057	0.014

[1]p-value from logistic regression analysis☐ HYPERLINK \l "T19_3" ☐Section 14, Table 19.3☐, ☐ HYPERLINK \l "T20_1" ☐Table 20.1☐

Table 34: Patients with no Significant Nausea

	PALO alone (N=136)	PALO + NETU100 mg (N=135)	PALO + NETU200 mg (N=137)	PALO + NETU 300 mg (N=135)
Overall (0-120 hours)				
Number (%) of Patients	108 (79.4)	108 (80.0)	118 (86.1)	121 (89.6)
Difference from palonosetron alone (%) with 95% CI		0.6 (-9.0, 10.2)	6.7 (-2.2, 15.6)	10.2 (1.7, 18.7)
p-value[1]		0.897	0.142	0.021
Acute Phase (0-24 hours)				
Number (%) of Patients	127 (93.4)	127 (94.1)	129 (94.2)	133 (98.5)
Difference from palonosetron alone (%) with 95% CI		0.7 (-5.1, 6.5)	0.8 (-5.0, 6.5)	5.1 (0.5, 9.8)
p-value[1]		0.811	0.793	0.050
Delayed Phase (25-120 hours)				
Number (%) of Patients	110 (80.9)	110 (81.5)	123 (89.8)	122 (90.4)
Difference from palonosetron alone (%) with 95% CI		0.6 (-8.7, 9.9)	8.9 (0.6, 17.2)	9.5 (1.2, 17.8)
p-value[1]		0.893	0.039	0.004

[1]p-value from logistic regression analysis☐ HYPERLINK \l "T19_4" ☐Section 14, Table 19.4☐, ☐ HYPERLINK \l "T20_2" ☐Table 20.2☐

While there was no statistically significant benefit of the FDC in the acute phase, there was a significant benefit in the delayed and overall phases for the 300mg dose with respect to no nausea (<5mm on VAS)

The 300mg dose demonstrated statistically significant benefit over palonosetron alone in all phases with regard to no significant nausea (25mm on VAS)

- Total control rate (no emesis, no rescue medication, no nausea)

Table 35: Total Control Rate – MFAS Population

	PALO alone (N=136)	PALO + NETU100 mg (N=135)	PALO + NETU200 mg (N=137)	PALO + NETU 300 mg (N=135)
Overall (0-120 hours)				
Number (%) of Patients	71 (52.2)	78 (57.8)	87 (63.5)	82 (60.7)
Difference from palonosetron alone (%) with 95% CI		4.8 (-7.1, 16.7)	11.3 (-0.4, 23.0)	9.3 (-2.5, 21.1)
p-value[1]		0.415	0.058	0.118
Acute Phase (0-24 hours)				
Number (%) of Patients	97 (71.3)	97 (71.9)	105 (76.6)	108 (80.0)
Difference from palonosetron alone (%) with 95% CI		0.5 (-1.5, 20.3)	5.3 (-5.1, 15.7)	8.7 (73.3, 86.7)
p-value[1]		0.916	0.316	0.093
Delayed Phase (25-120 hours)				
Number (%) of Patients	71 (52.2)	80 (59.3)	89 (65.0)	89 (65.9)
Difference from palonosetron alone (%) with 95% CI		7.1 (-4.7, 18.9)	12.8 (1.2, 24.3)	13.7 (2.1, 25.3)
p-value[1]		0.236	0.032	0.021

[1]p-value from logistic regression analysis with gender as covariate

☐ HYPERLINK \l "T16_3" ☐Section 14, Table 16.3☐, ☐ HYPERLINK \l "T17_3" ☐Table 17.3☐

Only the 300mg dose showed any significant benefit, and then only in the delayed phase.

- Complete protection (no emesis, no rescue medication, no significant nausea)

Table 36: Complete Protection Rate – MFAS Population

	PALO alone (N=136)	PALO + NETU100 mg (N=135)	PALO + NETU200 mg (N=137)	PALO + NETU 300 mg (N=135)
Overall (0-120 hours)				
Number (%) of Patients	95 (69.9)	103 (76.3)	110 (80.3)	112 (83.0)
Difference from palonosetron alone (%) with 95% CI		6.4 (-4.1, 17.0)	10.4 (0.2, 20.6)	13.1 (3.1, 23.1)
p-value[1]		0.221	0.045	0.010
Acute Phase (0-24 hours)				
Number (%) of Patients	119 (87.5)	121 (89.6)	121 (88.3)	131 (97.0)
Difference from palonosetron alone (%) with 95% CI		2.1 (-5.4, 9.7)	0.8 (-6.9, 8.6)	9.5 (3.3, 15.8)
p-value[1]		0.573	0.839	0.006
Delayed Phase (25-120 hours)				
Number (%) of Patients	100 (73.5)	108 (80.0)	120 (87.6)	114 (84.4)
Difference from palonosetron alone (%) with 95% CI		6.5 (-3.6, 16.5)	14.1 (4.8, 23.3)	10.9 (1.3, 20.5)
p-value[1]		0.201	0.004	0.027

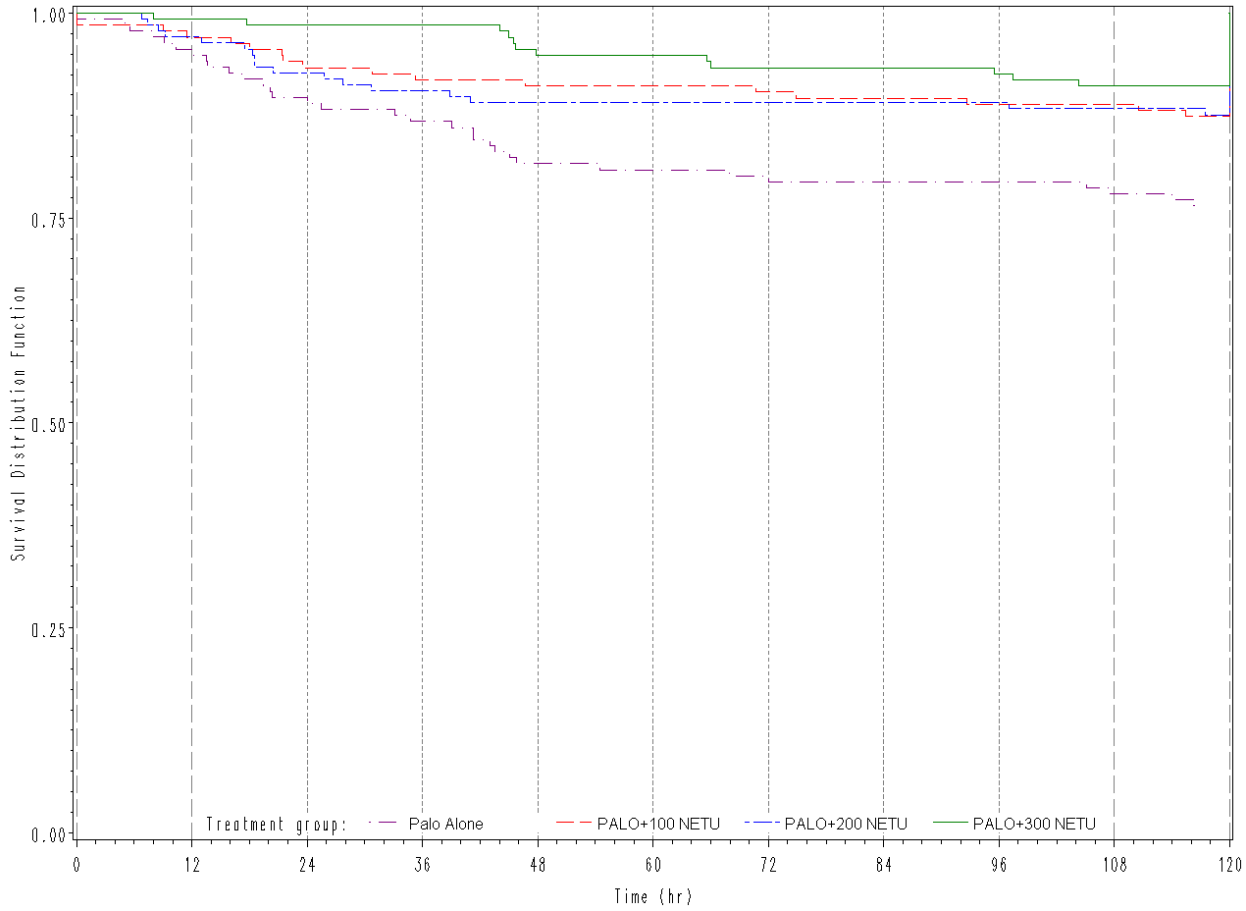
[1]p-value from logistic regression analysis with gender as covariate
☐ HYPERLINK \l "T16_2" ☐Section 14, Table 16.2☐, ☐ HYPERLINK \l "T17_2" ☐Table 17.2☐
Significant benefit was seen for the 300mg dose in all phases.

- Time to first emetic event

Kaplan Meier curves of netupitant 300 mg and palonosetron alone started to diverge a few hours after chemotherapy. Curves of netupitant 100 mg and 200 mg were very similar, but diverged from the curve for palonosetron alone later than the netupitant 300 mg curve did. The curves clearly show the higher efficacy of netupitant 300 mg in the first 24 hours and up to 44 hours compared to lower doses of netupitant.

Since more than 75% of patients were considered censored at the end of the 120 hour observation period in all treatment groups (i.e. more than 75% of patients had no emetic episode throughout 120 hours), neither the 25% quantile nor the median time to first emetic episode could be calculated. A log-rank test stratified by gender showed that time to first emetic episode was significant longer for netupitant (p=0.003) and in each netupitant group ($p \leq 0.020$) than in the palonosetron alone group.

Figure 6: Time to First Emetic Episode (hour) – MFAS Population



- Patient global satisfaction

For the MFAS population, the daily mean patient global satisfaction ranged from 89.1 to 91.2 for the palonosetron alone group and from 92.3 to 93.8, 92.0 to 94.6, and 94.0 to 95.3 for the netupitant 100 mg, 200 mg, and 300 mg doses, respectively. During each 24-hour interval, the median score was 97.0 or 98.0 in all treatment groups describing a very high patient satisfaction with the therapy for controlling the nausea and vomiting. Although the mean global satisfaction was smaller for palonosetron alone than for each dose of netupitant, the differences between palonosetron alone and the netupitant doses were small (0.85 to 5.51) and generally were not statistically significant.

- No Rescue medication

In the MFAS population, antiemetic rescue medication to treat emesis or nausea was taken by 6 (4.4%), 3 (2.2%), and 2 (1.5%) patients in the palonosetron, netupitant 100 mg, and netupitant 300 mg groups, respectively. Rescue medication included metoclopramide and ondansetron. Three patients (2 in the palonosetron group, 1 in the netupitant 300 mg group) received antiemetics as prevention of nausea and vomiting for a subsequent cycle of chemotherapy. Since the antiemetic drugs were administered as prevention and cannot be considered as rescue medication, those three patients were not counted.

- Exploratory analysis – Aprepitant and Ondasetron arm

Table 37: Efficacy Comparisons for the Aprepitant Regimen Versus Palonosetron Alone or Netupitant 300 mg in the Overall Phase – FAS Population

Parameter		PALO alone (N=136)	PALO + NETU 300 mg (N=135)	Aprepitant + Ondansetron (N=134)
Complete Response	Number (%) of Patients	104 (76.5)	121 (89.6)	116 (86.6)
	Diff. vs PALO (95% CI)		13.2 (4.4, 21.9)	10.1 (0.9, 19.3)
	p-value[1]		0.004	0.027
	Diff. vs NETU 300 mg (95% CI)			3.1 (-4.7, 10.8)
	p-value[1]			0.451
Complete Protection	Number (%) of Patients	95 (69.9)	112 (83.0)	105 (78.4)
	Diff. vs PALO (95% CI)		13.1 (3.1, 23.1)	8.5 (-1.9, 18.9)
	p-value[1]		0.010	0.091
	Diff. vs NETU 300 mg (95% CI)			4.6 (-4.8, 14.0)
	p-value[1]			0.348
Total Control	Number (%) of Patients	68 (50.0)	80 (59.3)	75 (56.0)
	Diff. vs PALO (95% CI)		9.3 (-2.5, 21.1)	6.0 (-5.9, 17.9)
	p-value[1]		0.117	0.295
	Diff. vs NETU 300 mg (95% CI)			3.3 (-8.5, 15.1)
	p-value[1]			0.602
No Emesis	Number (%) of Patients	104 (76.5)	123 (91.1)	117 (87.3)
	Diff. vs PALO (95% CI)		14.6 (6.0, 23.2)	10.8 (1.8, 19.9)
	p-value[1]		0.001	0.021
	Diff. vs NETU 300 mg (95% CI)			3.8 (-3.6, 11.2)
	p-value[1]			0.325
No Nausea	Number (%) of Patients	69 (50.7)	83 (61.5)	78 (58.2)
	Diff. vs PALO (95% CI)		10.7 (-1.0, 22.5)	7.5 (-4.4, 19.3)
	p-value[1]		0.069	0.196
	Diff. vs NETU 300 mg (95% CI)			3.3 (-8.4, 15.0)
	p-value[1]			0.600
No Significant Nausea	Number (%) of Patients	108 (79.4)	121 (89.6)	115 (85.8)
	Diff. vs PALO (95% CI)		10.2 (1.7, 18.7)	6.4 (-2.6, 15.4)
	p-value[1]		0.019	0.145
	Diff. vs NETU 300 mg (95% CI)			3.8 (-4.0, 11.6)

Parameter		PALO alone (N=136)	PALO + NETU 300 mg (N=135)	Aprepitant + Ondansetron (N=134)
	p-value[1]			0.351
No Rescue Medication	Number (%) of Patients	130 (95.6)	133 (98.5)	131 (97.8)
	Diff. vs PALO (95% CI)		2.9 (-1.1, 6.9)	2.2 (-2.1, 6.4)
	p-value[1]		0.168	0.308
	Diff. vs NETU 300 mg (95% CI)			0.8 (-2.5, 4.0)
	p-value[1]			0.660

[1]p-value from logistic regression analysis□□□Section 14, Tables 66.1□-□□□73.2□

- **Ancillary analyses**

The applicant conducted a post-hoc analysis to assess the difference in complete response between the treatment arms in the delayed phase as the primary objective. In addition, the applicant conducted this analysis using CMH rather than logistic regression as the statistical method. These measures have been described in the preceding section.

Summary of efficacy for trial NETU-07-07

Title: A Randomised, 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

Study identifier	**NETU-07-07**	
Design	Multicenter, multinational, randomised, double-blind, double-dummy, parallel group, stratified study	
	Duration of main phase:	
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	**Superiority** Exploratory for Group 5 (aprepitant + ondansetron)	
Treatments groups	PALO alone	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) N=136
	PALO+NETU	**100 or 200 or 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) N=135 (100 mg); 142 (200 mg); 143 (300 mg)

	APREPITANT/ONDANSETRON		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) N=138
Endpoints and definitions	Primary endpoint	CRR 0-120	Complete response rate (defined as no emetic episodes, no rescue medication) within 120 hours after the start of the highly emetogenic chemotherapy administration
	Secondary endpoint	CR 0-24 CR 25-120	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)
	Secondary endpoint	CP	Complete protection (defined as no emesis, no rescue therapy, no significant nausea (nausea <25 mm on VAS)) Total control rate=TCR (defined as 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
	Secondary endpoint	TTF	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)
	Secondary endpoint	SN	Severity of nausea measured by means of VAS for each 24-hour interval
Database lock	Database closed on 26 January 2009, data unblinded on 27 January 2009		

Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population	**MFAS**				
Descriptive statistics and estimate variability	Treatment group	PALO alone	Palo/Netu 100	Palo/Netu 200	Palo/Netu 300
	Number of subject	136	135	137	135
	CRR 0-120 (% of patients)	76.5%	87.4%	87.6%	89.6%
	p-value (logistic regression)	–	**0.019**	**0.017**	**0.004**
Post-hoc analysis/ addendum n°1	**p-value obtained with CMH analysis***	–	**0.018**	**0.016**	**0.003**

Analysis population	**PP**				
Descriptive statistics and estimate variability	Treatment group	PALO alone	Palo/Netu 100	Palo/Netu 200	Palo/Netu 300
	Number of subject	136	133	135	131
	CRR 0-120 (% of patients)	76.6%	88.0%	88.1%	89.3%
	p-value (logistic regression)	_	**0.015**	**0.013**	**0.006**

Analysis description	**Secondary analysis**				
Analysis population and time point description	MFAS				
Descriptive statistics and estimate variability	Treatment group	PALO alone	Palo/Netu 100	Palo/Netu 200	Palo/Netu 300
	Number of subject	136	135	137	135
	CRR 0-24 (% of patients)	89.7%	93.3%	92.7%	98.5%
	p-value (logistic regression)	_	0.278	0.383	**0.007**
	p-value obtained with CMH analysis*	_	0.278	0.383	**0.002**
	CRR 25-120	80.1%	90.4%	91.2%	90.4%
	p-value (logistic regression)	_	**0.018**	**0.010**	**0.018**
	p-value obtained with CMH analysis*	_	**0.017**	**0.008**	**0.016**
	TCR 0-120	52.2%	57.8%	63.5%	60.7%
	p-value (logistic regression)	_	0.415	0.058	0.118
	TCR 0-24	71.3%	71.9%	76.6%	80.0%
	p-value (logistic regression)	_	0.916	0.316	0.093
	TCR 25-120	52.2%	59.3%	65.0%	65.9%
	p-value (logistic regression)	_	0.236	0.032	0.021

Notes	*p-value obtained with CMH analysis : following post-hoc analysis as requested by the FDA p-value include gender as covariate

Analysis description	**Sensitivity analysis**				
Analysis population and time point description	**ITT**				
Descriptive statistics and estimate variability	Treatment group	PALO alone	Palo/Netu 100	Palo/Netu 200	Palo/Netu 300
	Number of subject	136	135	**142[1]**	**143[2]**
	CRR 0-24 (% of patients)	89.7%	93.3%	89.4%	93.0%
	p-value **obtained with CMH analysis**	–	0.278	0.934	0.317
	CRR 25-120	80.1%	90.4%	88.0%	85.3%
	p-value **obtained with CMH analysis**	–	**0.017**	0.072	0.241
	CRR 0-120	76.5%	87.4%	84.5%	84.6%
	p-value **obtained with CMH analysis**	–	**0.018**	0.089	0.078
Notes	As requested by the FDA an analysis on the ITT population has been performed as a sensitivity analysis. Out of 694 randomised patients, 17 were not included in the FAS population, because they were not treated (15 patients) or did not receive HEC (2 patients). Among these 17 patients - 5 patients were randomised to palo+ netu 200 mg[1] - 8 to palo+netu 300 mg[2] - 4 to aprepitant + ondansetron group (all not treated). All these patients were discontinued from the study apart the one having not received the HEC in palo+netu 300 mg group.				

NETU-08-18:

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.

Methods

Study Participants

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 tumour. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, fulfil 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.

Treatments

Patients were randomised 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 fulfil 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 of 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.

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.

Outcomes/endpoints

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.

Safety: Safety assessments included physical examination, vital signs, 12-lead electrocardiogram (ECG), Left Ventricular Ejection Fraction (LVEF), cardiac Troponin I (cTnI) levels, laboratory tests (haematology, 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).

Sample size

The sample size was estimated to be 1460 patients, equally distributed in 2 treatment groups (730 patients per group).

The assumption was a CR rate in the time interval 25-120 hours of cycle 1 of 60% in the netupitant/palonosetron fixed combination group and 51% in the palonosetron group. For a 2-sided test of difference using α =0.050, a sample size of 661 evaluable patients per group was needed to ensure 90% power to detect the above mentioned 9% difference. This number was increased to 730 patients per treatment group for a total of 1460 patients, to ensure an adequate number of evaluable patients.

Regarding the key secondary efficacy endpoints, this same sample size gave the study a power of about 60% (61%) to detect a difference of 6% in the CR rate in the acute phase (assuming rates of 70% and 64% in the fixed combination and palonosetron groups, respectively). The power to detect a difference of 9% in terms of CR in the overall phase was close to 90%.

Randomisation

Patients were assigned to treatment groups through a static central blocked randomisation scheme, stratified by region (US, Latin America including Mexico, Europe, Commonwealth of Independent States [i.e., former Soviet Republics], Asia) and age class (age <55 years and age $\geq$ 55 years).

Patients meeting the inclusion and exclusion criteria were assigned to one of the two treatment groups in a balanced design (1:1), according to specific procedures using the Randomisation and Trial Supply Management (RTSM) system, accessed by Electronic Data Capture (EDC) or Interactive Voice Response System (IVRS). Two randomisation lists were prepared, one for each age class. For each region a different block of the relevant list was allocated, i.e., each time a new region started to randomize patients or each time a block for the relevant region was completed, the next unused block was attributed to that region.

Blinding (masking)

To maintain study blinding, matching placebos were manufactured for each of the study drugs and additional study drug.

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 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 favour 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.

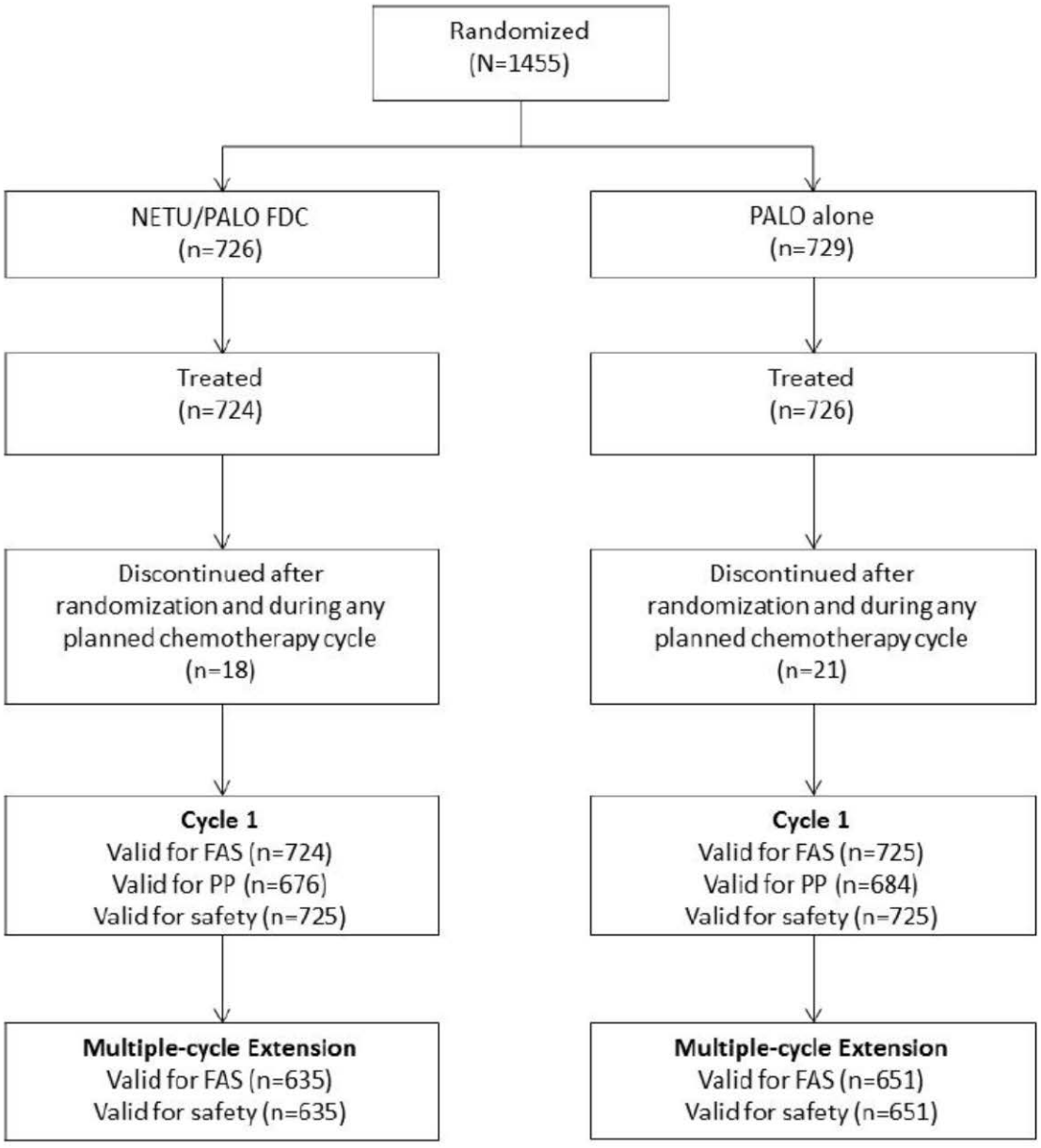
Laboratory data were summarized as follows: descriptive statistics for observed values and change from baseline (and the same cycle ‘screening’ for cycle 2 onwards), shift tables from baseline (and the same cycle ‘screening’ for cycle 2 onwards) with respect to normal ranges, and tabulation of the number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

Results

Participant flow



Source: Section 14, Table 14.1.1.1 and Table 14.1.1.2, Listing 16.2.1 and Listing 16.2.3
Abbreviations: FAS=Full Analysis Set; FDC=Fixed-Dose Combination; N or n=Number of patients; NETU=netupitant; PALO=palonosetron; PP=Per-Protocol.

Recruitment

The first patient was recruited to the trial on April 21st 2011, with LPLV on November 6th 2012. The CSR is dated June 12th 2013.

Conduct of the study

No significant trial conduct issues occurred in this clinical trial which might affect the results of the trial.

Baseline data

The demographic profile of the Cycle 1 Safety population is presented below.

Table 38: Demographics – Safety Population (Cycle 1)

Parameter	NETU/PALO FDC (N=725)		PALO alone (N=725)		Overall (N=1450)	
Gender, n (%)						
Male	14	(1.9)	14	(1.9)	28	(1.9)
Female	711	(98.1)	711	(98.1)	1422	(98.1)
Childbearing potential	*222*	*(31.2)*	*223*	*(31.4)*	*445*	*(31.3)*
Race, n (%)						
White	574	(79.2)	579	(79.9)	1153	(79.5)
Black	1	(0.1)	3	(0.4)	4	(0.3)
Asian	101	(13.9)	103	(14.2)	204	(14.1)
Hispanic	46	(6.3)	36	(5.0)	82	(5.7)
Other	3	(0.4)	4	(0.6)	7	(0.5)
Age (years)						
N	725		725		1450	
Mean (SD)	53.7	(10.66)	54.1	(10.65)	53.9	(10.65)
Median	54.0		54.0		54.0	
Min, max	22, 79		28, 78		22, 79	
Weight (kg)						
N	725		725		1450	
Mean (SD)	71.31	(15.639)	71.84	(15.881)	71.58	(15.757)
Median	70.00		70.00		70.00	
Min, max	34.0, 130.0		30.2, 169.0		30.2, 169.0	
Height (cm)						
N	725		725		1450	
Mean (SD)	160.5	(7.77)	160.7	(7.19)	160.6	(7.48)
Median	160.0		161.0		160.0	
Min, max	121, 187		139, 186		121, 187	
BMI (kg/m^2)						
N	725		725		1450	
Mean (SD)	27.69	(5.804)	27.77	(5.693)	27.73	(5.747)
Median	27.10		27.30		27.13	
Min, max	14.2, 54.7		12.6, 57.5		12.6, 57.5	

Abbreviations: BMI=Body Mass Index; FDC=Fixed-Dose Combination; max=maximum; min=minimum; N=Number of patients in group; n=number of patients with data; NETU=Netupitant; PALO=Palonosetron; SD=Standard Deviation.

The cycle 1 population was very homogenous in terms of disease types that the other efficacy studies, with the vast majority of patients having a primary breast cancer diagnosis;

Table 39: Summary of Cancer History – Safety Population (Cycle 1)

Parameter	NETU/PALO FDC (N=725)		PALO alone (N=725)		Overall (N=1450)	
Primary cancer diagnosis, n (%)						
Breast	708	(97.7)	705	(97.2)	1413	(97.4)
Other	17	(2.3)	20	(2.8)	37	(2.6)
Time since histological diagnosis (days)						
N	725		725		1450	
Mean (SD)	84.7	(361.11)	95.5	(568.52)	90.1	(476.11)
Median	29.0		30.0		29.0	
Min, max	0, 5715		-6, 10720		-6, 10720	
Extent at study entry, n (%)						
Primary	593	(81.8)	601	(82.9)	1194	(82.3)
Metastatic	118	(16.3)	113	(15.6)	231	(15.9)
Local recurrence	14	(1.9)	11	(1.5)	25	(1.7)
Site of metastasis, n (%)						
Liver	21	(2.9)	15	(2.1)	36	(2.5)
Lung	28	(3.9)	17	(2.3)	45	(3.1)
Lymph nodes	78	(10.8)	85	(11.7)	163	(11.2)
Bone	27	(3.7)	26	(3.6)	53	(3.7)
Brain	2	(0.3)	0		2	(0.1)
Other	12	(1.7)	6	(0.8)	18	(1.2)

Abbreviations: FDC=Fixed-Dose Combination; max=maximum; min=minimum; N=Number of patients; n=number of patients with data; NETU=Netupitant; PALO=Palonosetron; SD=Standard Deviation.

Chemotherapy regimens were similar across the treatment groups

Table 40: Chemotherapy in Cycle 1– Safety Population (Cycle 1)

Parameter	NETU/PALO FDC (N=725)	PALO alone (N=725)	Overall (N=1450)
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

Abbreviations: FDC=Fixed-Dose Combination; max=maximum; min=minimum; N=Number of patients in group; n=number of patients with data; NETU=Netupitant; PALO=Palonosetron; SD=Standard Deviation.

Table 41: Concomitant Chemotherapy in Cycle 1– Safety Population (Cycle 1)

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)
Time of concomitant chemotherapy, n (%)						
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)
Type of chemotherapy, n (%)						
Anthracyclines and related substances	**1**	**(0.1)**	**0**		**1**	**(0.1)**
Epirubicin	1	(0.1)	0		1	(0.1)
Nitrogen mustard analogues	**1**	**(0.1)**	**0**		**1**	**(0.1)**
Cyclophosphamide	1	(0.1)	0		1	(0.1)
Podophyllotoxin derivatives	**5**	**(0.7)**	**3**	**(0.4)**	**8**	**(0.6)**
Etoposide	5	(0.7)	3	(0.4)	8	(0.6)
Pyrimidine analogues	**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)
Taxanes	**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)
Vinca alkaloids and analogues	**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)

Abbreviations: FDC=Fixed-Dose Combination; N=Number of patients in group; n=number of patients with data; NETU=Netupitant; PALO=Palonosetron.

Multiple-cycle extension phase

The demographics for the Safety population in the MCE phase are also presented below. Other patient characteristics data are presented in the CSR

Table 42: Demographics – Safety Population (Extension)

Parameter	NETU/PALO FDC (N=635)		PALO alone (N=651)		Overall (N=1286)	
Gender, n (%)						
Male	11	(1.7)	13	(2.0)	24	(1.9)
Female	624	(98.3)	638	(98.0)	1262	(98.1)
Childbearing potential	*189*	*(30.3)*	*207*	*(32.4)*	*396*	*(31.4)*
Race, n (%)						
White	491	(77.3)	514	(79.0)	1005	(78.1)
Black	1	(0.2)	1	(0.2)	2	(0.2)
Asian	99	(15.6)	99	(15.2)	198	(15.4)
Hispanic	42	(6.6)	35	(5.4)	77	(6.0)
Other	2	(0.3)	2	(0.3)	4	(0.3)
Age (years)						
N	635		651		1286	
Mean (SD)	53.7	(10.69)	54.0	(10.59)	53.9	(10.64)
Median	54.0		54.0		54.0	
Min, max	22, 79		28, 78		22, 79	
Weight (kg)						
N	635		651		1286	
Mean (SD)	71.39	(15.682)	71.60	(15.530)	71.50	(15.600)
Median	70.00		70.00		70.00	
Min, max	34.0, 130.0		30.2, 126.0		30.2, 130.0	
Height (cm)						
N	635		651		1286	
Mean (SD)	160.3	(7.68)	160.5	(7.15)	160.4	(7.42)
Median	160.0		160.0		160.0	
Min, max	121, 187		139, 186		121, 187	
BMI (kg/m^2)						
N	635		651		1286	
Mean (SD)	27.79	(5.845)	27.75	(5.629)	27.77	(5.734)
Median	27.10		27.30		27.16	
Min, max	14.2, 54.7		12.6, 48.4		12.6, 54.7	

Abbreviations: BMI=Body Mass Index; FDC=Fixed-Dose Combination; max=maximum; min=minimum; N=Number of patients in group; n=number of patients with data; NETU=Netupitant; PALO=Palonosetron; SD=Standard Deviation.

Numbers analysed

Table 43: Summary of Patient Disposition

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)

The following definitions of analysis populations were used for cycle 1.

The Full Analysis Set (FAS) was defined as all patients who were randomised to treatment and received a MEC regimen and the study drug. Following the Intent-To-Treat (ITT) principle, patients were assigned to the study drug group according to the treatment to which they had been randomised. The FAS was used for summarizing demography and baseline characteristics, primary and all efficacy analyses. The FAS was the main population for the efficacy analyses.

The Per-Protocol (PP) population consisted of all patients included in the FAS who completed the 0-120 study period with no major protocol violations. The PP population was used for demography, other baseline characteristics and for supportive primary and key secondary efficacy analyses.

The ITT population consisted of all patients who were randomised to treatment. Following the ITT principle, patients were assigned to the study drug group according to the treatment to which they had been randomised. The ITT population was used for demography and for the primary efficacy endpoint sensitivity analysis.

The Safety population consisted of all patients who received at least one study drug and had at least one safety assessment after the treatment administration. Patients were assigned to the study drug group according to the actual treatment received. A safety assessment after treatment administration was defined as any ECG or vital signs or laboratory result or evaluation of the presence or absence of AE. The safety population was used for demography, baseline characteristics and all safety analyses.

The PK population consisted of all patients who participated in the PK portion of the study. Patients that had at least one measurable concentration of netupitant and palonosetron and corresponding information regarding the time and date of drug administration and the PK sample were included.

The following definitions of analysis populations were used for the multiple-cycle extension.

The FAS was defined as all patients who entered the multiple-cycle extension and received a MEC regimen and the study drugs in the first cycle of the multiple-cycle extension. Following the ITT principle, patients were assigned to the study drug group according to the treatment to which they had been randomised at cycle 1. The FAS was used for summarizing demography and baseline characteristics and for efficacy analyses.

The Safety population consisted of all patients who entered the multiple-cycle extension and received at least one study drug and had at least one safety assessment after the treatment administration. A safety assessment after treatment administration was any ECG or vital signs or laboratory result or evaluation of the presence or absence of AE. Patients were assigned to the study drug group according to the actual treatment they received. In cases where a patient received different treatments in different study cycles in error, he/she was to be included in the safety population for the treatment actually received at cycle 1. For by-cycle summaries, the patient was analyzed in each cycle according to the actual treatment received. The safety population was used for demography, baseline characteristics and all safety analyses.

Outcomes and estimation

- **Primary and key secondary endpoints**

Table 44: Complete Response Rate for the Delayed, Acute and Overall Phases of Cycle 1 – FAS (NETU-08-18)

	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.

- **Ancillary analyses**

None

Summary of efficacy for trial NETU-08-18

Title: A phase III multicenter, randomised, 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.			
Study identifier	**NETU-08-18**		
Design	Phase III multicenter, randomised, double-blind, double-dummy, parallel group study		
	Duration of main phase:		Date of first enrollment: 21 April 2011 Date of last completed: 06 November 2012
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	**Superiority**		
Treatments groups	PALO alone		Oral palonosetron 0.50 mg + oral dexamethasone 20 mg N=726
	PALO+NETU		Oral netupitant/palonosetron (300 mg/0.50 mg) FDC + dexamethasone 12 mg N=729
Endpoints and definitions	**Primary endpoint**	CR 25-120	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 endpoint	CR 0.24	Proportion of patients with CR during the acute phase (0-24 hours) at cycle 1
	Key secondary endpoint	CR 0.120	Proportion of patients with CR during the overall phase (0-120 hours) at cycle 1
	Other secondary endpoints		Proportion of patients at cycle 1 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
Database lock	Database locked on 08 February 2013, data unblinded on 20 February 2013		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population	**FAS**		
Descriptive statistics and estimate variability	Treatment group	**PALO alone**	**Palo/Netu 300**
	Number of subject	725	724
	CRR 25-120 (% of patients)	69.5%	76.9%
	95%CI[a]	[66.1;72.8]	[73.7;79.9]
	Difference from palo alone, % (95% CI[b])	7.4 (2.9;11.9)	
	OR[c] (95% CI)	1.48 (1.16;1.87)	
	p-value[d]	**0.001**	
Analysis population	**PP**		
Descriptive statistics and estimate variability	Number of subject	684	676
	CRR 25-120 (% of patients)	70.2%	76.9%
	95%CI[a]	[66.6;73.5]	[73.6;79.9]
	Difference from palo alone, % (95% CI[b])	6.7 (2.1;11.4)	
	OR[c] (95% CI)	1.42 (1.11;1.82)	
	p-value[d]	**0.005**	
Notes	[a] 95% CI using Wilson score method. [b] 95% CI using Newcombe-Wilson's method. [c] netupitant/palonosetron vs. palonosetron alone [d] Odds ratio and p-value from Cochran-Mantel-Haenszel test, stratified by age class and region		
Results and Analysis			
Analysis description	**Secondary Analysis**		
Analysis population	**FAS**		
Descriptive statistics and estimate	Treatment group	**PALO alone**	**Palo/Netu 300**
	Number of subject	725	724

variability	**CRR 0-24** (% of patients)	85.0%	88.4%
	95%CI[a]	[82.2;87.4]	[85.9;90.5]
	Difference from palo alone, % (95% CI[b])	3.4 (-0.1;6.9)	
	OR[c] (95% CI)	1.37 (1.00;1.87)	
	p-value[d]	0.047	
	CRR 0-120 (% of patients)	66.6%	74.3%
	95%CI[a]	[63.1;70.0]	[71.0;77.4]
	Difference from palo alone, % (95% CI[b])	7.7 (3.0;12.3)	
	OR[c] (95% CI)	1.47 (1.17;1.85)	
	p-value[d]	**0.001**	
Analysis population	**PP**		
Descriptive statistics and estimate variability	Treatment group	**PALO alone**	**Palo/Netu 300**
	Number of subject	684	676
	CRR 0-24 (% of patients)	585 (85.5)	597 (88.3)
	95%CI[a]	(82.7;88.0)	(85.7;90.5)
	Difference from palo alone, % (95% CI[b])	2.8 (-0.8;6.4)	
	OR[c] (95% CI)	1.29 (0.93;1.78)	
	p-value[d]	0.122	
	CRR 0-120 (% of patients)	67.1%	74.1%
	95%CI[a]	(63.5;70.5)	(70.7;77.3)

	Difference from palo alone, % (95% CI[b])	7.0 (2.2;11.8)	
	OR[c] (95% CI)	1.41 (1.11;1.79)	
	p-value[d]	**0.004**	
Notes	[a] 95% CI using Wilson score method. [b] 95% CI using Newcombe-Wilson's method. [c] netupitant/palonosetron vs. palonosetron alone [d] Odds ratio and p-value from Cochran-Mantel-Haenszel test, stratified by age class and region		
Analysis population	**FAS-Cycle 1 – Subgroup exploratory analysis on complete response by region**		
Descriptive statistics and estimate variability	Treatment group	**PALO alone**	**Palo/Netu 300**
	Number of subject	725	724
	US	32	32
	CRR 25-120 (% of patients)	50%	46.9%
	CMH test p-value	0.805	
	Latin America	58	59
	CRR 25-120 (% of patients)	50%	72.9%
	CMH test p-value	0.011	
	Europe	301	300
	CRR 25-120 (% of patients)	75.1%	76.7%
	CMH test p-value	0.652	
	Commonwealth of Independent States	234	233
	CRR 25-120 (% of patients)	70.5%	82%
	CMH test p-value	0.004	
	Asia	100	100

	CRR 25-120 (% of patients)	68%	78%
	CMH test p-value	0.113	

Analysis performed across trials (pooled analyses and meta-analysis)

No formal statistical analyses were performed to compare the efficacy results generated in the efficacy clinical trials due significant differences in the methodologies used in those trials.

Clinical studies in special populations

No specific studies were carried out to investigate the efficacy of the FDC in special populations. Subjects who had severe renal or hepatic impairment were excluded from the pivotal efficacy and safety studies. For data on elderly patients see pharmacology part of this report.

Supportive studies

Study PALO-10-01 was a phase III, multicenter, multinational, randomised, double-blind, double-dummy, parallel group, stratified study in patients receiving HEC. Patients were randomised on Day 1 of their first chemotherapy cycle before administration of HEC to one of the following treatment groups:

- Oral palonosetron 0.50 mg (Aloxi) and oral dexamethasone 20 mg both given on Day 1, followed by dexamethasone (8 mg) twice daily (bid) from Days 2 through 4.
- I.V. palonosetron 0.25 mg (Aloxi) and oral dexamethasone 20 mg both given on Day 1, followed by dexamethasone (8 mg bid) from Days 2 through 4.

Patients participated in the study for a maximum of 37 days (including a screening period of up to 14 days, 6+2 days on study of which 4 days on active treatment, and a follow-up visit or a telephone call 21±2 days after Day 1).

Study PALO-10-01 was intended to provide evidence of efficacy of oral palonosetron 0.50 mg in the HEC setting in comparison to I.V. palonosetron 0.25 mg, focusing on the 0-24 hour period.

The primary efficacy objective was the demonstration of non-inferiority of oral palonosetron 0.50 mg versus I.V. palonosetron 0.25 mg in terms of proportion of patients with CR in the acute phase (defined as no emesis and no rescue medication within 24 hours after the start of the HEC administration).

The percentage of patients with CR in the acute phase in the FAS was 89.4% in the oral palonosetron group and 86.2% in the I.V. palonosetron group. The difference in proportion between the oral and I.V. palonosetron groups was 3.21% (99%CI: -2.74% to 9.17%).

Non-inferiority of oral palonosetron versus I.V. palonosetron was demonstrated since the lower limit of the two-sided 99% CI for the difference in proportions was greater (i.e. closer to zero) than the pre-defined non-inferiority margin set at -15%. Similar results were obtained in the PP population with a difference in proportions between the oral and I.V. palonosetron group of 3.77% (99% CI: -3.22% to 10.76% from stratum-adjusted CMH method for difference in proportions). Planned sensitivity analyses supported the results obtained on the primary efficacy endpoint.

Study NETU-10-29 was a safety trial providing also supportive efficacy information in MEC and HEC. It was a multinational, randomised active-controlled, double-blind, double-dummy, unbalanced (3:1), parallel group, stratified multi-cycle trial evaluating the safety and describing the efficacy of the FDC vs aprepitant + palonosetron. The study was stratified by chemotherapy emetogenicity and gender.

The primary study objective was to assess the safety and tolerability of a single oral dose of FDC in initial and repeated cycles of chemotherapy. The secondary objective was to describe the efficacy of the FDC during the acute (0-24 hours), delayed (25-120 hours) and overall (0-120 hours) phases of initial and repeated cycles of chemotherapy. Efficacy data were supportive of the conclusions drawn from the pivotal trials.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

CHMP scientific advice given to the design and conduct of the clinical studies was broadly followed. The patient population recruited to clinical trials was appropriate and generally representative of those normally receiving such chemotherapy regimens. It was noted by the CHMP that in the MEC study NETU-08-18 an anthracycline plus cyclophosphamide (AC) regime was chosen to support the MEC indication. Recently, in the MEC setting, MASCC/ESMO clinical antiemetic guidelines have given special consideration to patient-related risk factors contributing to the emetogenic potential for patients receiving AC-based chemotherapy. While historically guidance has been based solely on the emetogenicity of the chemotherapy the young age and female gender of the population that typically receive AC-based chemotherapy may put this group at an increased risk for CINV over what AC chemotherapy alone would suggest.

It is taken into consideration by the CHMP that AC chemotherapy has previously served as gold standard of the MEC regimen in antiemetic efficacy pivotal trials being a “worst-case” emetogenicity representative for MEC chemotherapy. Notwithstanding the recent change of the clinical antiemetic guidelines this model is currently considered to be familiar to clinicians for use to prevent CINV induced by MEC. Therefore, to adequately inform prescribers, the fact that an AC regimen was used in the MEC pivotal trial was included into the SmPC.

Dose levels and groups as described are considered appropriate with regards to the objectives of the pivotal trials submitted and dexamethasone doses were appropriately adjusted to balance exposure across groups. Objectives were appropriate in the context of the clinical evaluation of agents for the treatment or prevention of chemotherapy-induced nausea and vomiting. The primary and secondary outcomes and endpoints of the studies were appropriate and in accordance with advice previously received from CHMP. Sample size calculations and statistical methods were appropriate, the randomisation schemes appear to be robust and blinding methods are considered satisfactory.

For study PALO-10-01 the determination of the non-inferiority margin and subsequent sample size calculation was appropriate and in accordance with non-inferiority margins from other CINV trials in the public domain.

For study NETU-07-07 a sponsor audit of a site in Russia presented multiple major audit findings. Complete response rates with and without all 39 patients enrolled at this site were consistent with the CR rates from the FAS and differences in CR rates did not seem to be systematically in one direction supporting the lack of impact of this site and the overall robustness of the study conclusions.

The CHMP guidance document for the evaluation of medicinal products for the prevention and treatment of CINV states that patients entering a multiple cycle extension phase of a trial should be re-randomised prior to allocation of treatment to ensure that both treatment arms are balanced. For study NETU-08-18, re-randomisation did not occur following enrolment into the Multiple-Cycle Extension (MCE) . Therefore the applicant was asked to reanalyse this phase. Presented results supported the persistence of the antiemetic effect in multiple cycles and are considered satisfactory.

Efficacy data and additional analyses

NETU 07-07 (HEC study)

Study NETU-07-07 evaluated palonosetron alone versus palonosetron plus netupitant 100 mg, 200 mg and 300 mg in patients receiving highly emetogenic chemotherapy (cisplatin-based regimen). All patients also received concomitant dexamethasone. The primary efficacy endpoint was the proportion of patients with complete response (no emetic episodes and no rescue medication) in the overall phase.

Results for the primary endpoint showed statistical significance in favour of netupitant 300 mg plus palonosetron (p=0.004) with a difference of netupitant 300 mg plus palonosetron versus palonosetron alone on the order of 13.2%, which can be considered clinically meaningful. Secondary efficacy parameters consistently showed an advantage of the 300 mg netupitant dose compared to lower netupitant doses, particularly in the delayed and overall phases.

The percentage of patients in the 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%. The logistic regression analysis, including gender as a covariate, showed that all netupitant plus palonosetron doses were statistically superior to palonosetron alone. The contribution of netupitant in the delayed phase (25-120 hour time period) can therefore be considered demonstrated. In addition, a sensitivity analysis done by excluding patients with missing data about emetic episodes/use of rescue medication who were considered as failures in the primary analysis were statistically significant and supported the results of primary analysis (p=0.008), as well as an additional sensitivity analysis with subjects allocated to the actual treatment received (p=0.008).

The study was not powered to demonstrate differences in efficacy between the respective Netupitant doses. results showed that the 300 mg netupitant dose was statistically superior to palonosetron alone in the acute, delayed and overall period. The 200 and 100 mg netupitant doses were statistically superior to palonosetron alone in the overall and delayed periods only. Secondary efficacy parameters consistently showed an advantage of the 300 mg netupitant dose compared to lower netupitant doses, particularly in the delayed and overall phases. Additionally the analysis of safety data including treatment-emergent adverse events (TEAEs), laboratory values, vital signs and 12-lead ECGs in Study NETU-07-07 did not raise any safety concerns for the administration of palonosetron in combination with netupitant at any of the three dose levels tested. Furthermore, there were no increases in severity of AEs over the dosing range of 100 mg to 300 mg in NETU-07-07 and it is reasonable that the 300 mg dose was carried forward into later clinical trials NETU-08-18 and NETU-10-29 for confirmation of that finding.

In a post-hoc analysis the efficacy of the aprepitant/ondansetron regimen versus the netupitant 300 mg /palonosetron regimen was compared. Primary and secondary parameters were analyzed for the overall, acute and delayed phase as an exploratory analysis. The percentage of responders in the netupitant 300 mg arm was numerically higher than the aprepitant/ondansetron for all efficacy endpoints during each phase.

NETU-08-18 (MEC study)

Study NETU-08-18 evaluated the efficacy of netupitant plus palonosetron (with dexamethasone) versus palonosetron alone (with dexamethasone) in breast cancer patients receiving moderately emetogenic chemotherapy (cyclophosphamide and either doxorubicin or epirubicin). The primary efficacy endpoint was the percentage of patients with CR in the delayed phase at cycle 1.

During the first chemotherapy cycle the percentage of patients in the delayed phase with CR was higher in the combination group (76.9%) than the palonosetron alone group (69.5%), with a difference from the palonosetron alone group of 7.4% which can be considered a clinically relevant difference. The superiority of netupitant/palonosetron to palonosetron alone was demonstrated (CMH OR: 1.47 with 95% CI from 1.17 to 1.85; 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).

Overall, 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 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.

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.

The impact of nausea and vomiting on patients' daily lives was assessed using the Functional Living Index–Emesis (FLIE), a validated specific patient-reported outcome measure of the impact of nausea and vomiting on daily life. The proportion of patients with Overall no impact on daily life was 6.3% higher (p value =0.005) in the Akynzeo group (78.5%) than in the palonosetron group (72.1%).

The proportion of patients with no impact on daily life of the Vomiting Domain was 5.6% higher (p value =0.001) in the Akynzeo group (90.1%) than in the palonosetron group (84.4%). The proportion of patients with no impact on daily life of the Nausea Domain was 5.8% higher (p value =0.015) in the Akynzeo group (71.5%) than in the palonosetron group (65.8%).

PALO-10-01

This study demonstrated the non-inferiority of oral palonosetron 0.50 mg compared with I.V. palonosetron 0.25 mg in terms of the primary efficacy endpoint i.e. CR in the acute phase. The two treatment groups showed a similar efficacy profile when considering CR in the delayed and overall phases after administration of HEC, and other secondary endpoints in all phases, including, among others, the proportion of patients with no emesis, with no rescue medication, with no nausea or with no significant nausea and the complete protection rate. The data generated were considered supportive for the HEC setting.

2.5.4. Conclusions on the clinical efficacy

Oral administration of Akynzeo in combination with dexamethasone has been shown to prevent acute and delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in two separate pivotal studies.

Results of the pivotal studies show a statistical superiority in terms of acute, overall and, notably, of delayed emesis (endpoint of major clinical interest) of netupitant plus palonosetron over palonosetron alone in cancer patients receiving cisplatin regimen and a combination of anthracyclines plus cyclophosphamide regimen.

The advantages of this fixed-dose combination [netupitant+palonosetron] include an improvement of the benefit/risk due to an addition of therapeutic activity of the substances, particularly in the delayed phase of emesis.

2.6. Clinical safety

Patient exposure

The overall safety population included a total of 4331 subjects. The ISS database contains safety data from 3280 patients with cancer who received at least one dose of the investigational medicinal product or the active comparators during the Phase 2/3 CINV studies; of these patients, 1862 were treated in the Phase 3 multi-cycle studies. Supporting data are presented from 1051 subjects who received at least one dose of the investigational product in healthy volunteer studies (N = 702) and studies in special populations (N = 349).

During the development programme, a total of 1939 subjects received any dose of netupitant and palonosetron in combination (either as the FDC or extemporaneous formulation), including 1442 cancer patients participating in Phase 2/3 studies, The 1939 subjects who were exposed to netupitant-palonosetron combination (any dose) had a total of 5843 exposures.

A total of 1538 subjects and patients were exposed to the netupitant-palonosetron combination at the proposed market dose (300/0.50 mg) during the clinical program with a total number of 5441 exposures: 1169 patients with cancer received at least one dose while participating in one of the Phase 2/3 studies.

There were **550 patients who received 6 or more consecutive cycles of chemotherapy**; 317 of these received the FDC (300/0.50 mg). A total of 1033 MEC and 286 HEC patients received the proposed market dose of 300 mg netupitant and 0.50 mg palonosetron.

Table 45: Number of Subjects Exposed to Netupitant-Palonosetron, Its Components, and Comparators by ISS Groupings (Safety Population)

	Netupitant / Palonosetron Combination (mg) [a]					**Comparators**			
	100/0.50	**> 100 - < 300**	**300/0.50**	**> 300**	**TOTAL**	Placebo	Other [b]	*Aprepitant in combination with*:	
								Palonosetron	Ondansetron
	(N=135)	(N=199)	(N=1538)	(N=67)	(N=1939)	(N=165)	(N=115)	(N=104)	(N=134)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Healthy Volunteer Studies		61 (30.7)	265 (17.2)	67 (100.0)	393 (20.3)	77 (46.7)	115 (100.0)		
Phase 2/3 Cancer Patients	135 (100.0)	138 (69.3)	1169 (76.0)		1442 (74.4)			104 (100.0)	134 (100.0)
Phase 3 Multicycle			1033 (67.2)		1033 (53.3)			104 (100.0)	
Special Populations									
NETU-08-03						60 (36.4)			
NETU-09-11			28 (1.8)		28 (1.4)	28 (17.0)			
NETU-10-09			40 (2.6)		40 (2.1)				
NETU-10-10			36 (2.3)		36 (1.9)				

a: In netupitant-palonosetron combination, doses of palonosetron were 0.50, 0.75, and 1.50 mg
b: Other contains: apomorphine, dexamethasone, erythromycin, midazolam, and moxifloxacin

[Module 5.3.5.3, ISS Table 1.1.2.3Table 1.1.2.4 Module 5.3.5.3, ISS Table 1.1.1.3Table 1.1.1.4

Table 46: Number of Patients Exposed to Study Treatment in Phase 2/3 CINV Trials, Categorized by Emetogenicity

	Palonosetron		Netupitant / Palonosetron Combination			Comparators		TOTAL
	IV	Oral				*Aprepitant in combination with*:		
Dose (mg)	0.25	0.50	100/0.50	200/0.50	300/0.50	Palonosetron	Ondansetron	
	N=369	N=1231	N=135	N=138	N=1169	N=104	N=134	(N = 3280)
Phase 2/3 – cancer patients[1]								n (%)
HEC	369	506	135	138	211	25	134	1518 (46.3)
MEC	–	725	–	–	958	79	–	1762 (53.7)
Phase 3 multicycle[2]								
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

Table 47: Demographic and Baseline Characteristics – Phase 2/3 Patients with Cancer (Safety Population)

	Netupitant/Palonosetron Combination			TOTAL
	100/0.50 mg (N=135)	200/0.50 mg (N=138)	300/0.50 mg (N=1169)	(N=1442)
Age (years)				
Mean (SD)	55.0 (9.478)	54.4 (9.792)	54.5 (10.560)	54.5 (10.386)
Median	55.0	55.0	55.0	55.0
Minimum, maximum	19.0, 77.0	24.0, 82.0	19.0, 79.0	19.0, 82.0
Age stratification – n (%)				
< 65 Years	112 (83.0)	118 (85.5)	955 (81.7)	1185 (82.2)
≥ 65 Years	23 (17.0)	20 (14.5)	214 (18.3)	257 (17.8)
< 75 Years	133 (98.5)	136 (98.6)	1149 (98.3)	1418 (98.3)
≥ 75 Years	2 (1.5)	2 (1.4)	20 (1.7)	24 (1.7)
Gender – n (%)				
Male	77 (57.0)	80 (58.0)	244 (20.9)	401 (27.8)
Female	58 (43.0)	58 (42.0)	925 (79.1)	1041 (72.2)
Race – n (%)				
White	135 (100.0)	137 (99.3)	968 (82.8)	1240 (86.0)
Black	–	–	4 (0.3)	4 (0.3)
Hispanic or Latino	–	–	47 (4.0)	47 (3.3)
Asian	–	1 (0.7)	148 (12.7)	149 (10.3)
Am. Indian / AK Nat	–	–	1 (0.1)	1 (0.1)
Other	–	–	1 (0.1)	1 (0.1)
Weight (kg)				
Mean (SD)	73.4 (15.353)	70.7 (14.242)	71.1 (16.294)	71.3 (16.028)
Median	71.0	69.3	70.0	70.0
Minimum, maximum	39.0, 121.0	44.0, 120.0	34.0, 145.0	34.0, 145.0
Height [a] (cm)				
n	0	0	1033	1033
Mean (SD)	–	–	162.3 (8. 799)	162.3 (8.799)
Median	–	–	162.0	162.0
Minimum, maximum	–	–	120.7, 192.0	120.7, 192.0
BMI [a] (calculated as kg/m^2)				
n	0	0	1033	1033
Mean (SD)	–	–	26.9 (5.827)	26.9 (5.827)
Median	–	–	26.4	26.4
Minimum, maximum	–	–	14.1, 54.7	14.1, 54.7

SD = standard deviation; Am. Indian/AK Nat = American Indian or Alaska Native; BMI = body mass index

a: Not collected in Study NETU-07-07

The study population of 1442 patients with cancer treated with combinations of netupitant (100, 200, and 300 mg) and palonosetron (0.50 mg) in the Phase 2/3 studies comprised 401 men (27.8%) and 1041 females (72.2%), was predominantly white (86.0%), and had a mean (SD) age of 54.5 (10.4) years; by age stratification, the majority (82.2%) of treated patients were < 65 years of age. As with the overall safety population, gender differences were largely attributable to those observed in Study NETU-08-18 (711 females vs 14 males who received the netupitant/palonosetron FDC [300/0.50 mg]). There were no other notable demographic differences between patients who received palonosetron 0.50 mg in combination with netupitant doses of 100, 200, or 300 mg. Overall, the demographic and baseline characteristics of patients with cancer in the Phase 2/3 studies were well balanced, regardless of palonosetron dose (0.25 mg IV or 0.50 mg PO) or 5-HT_3 receptor antagonist.

Adverse events

Phase 2/3 Cancer Patients

Cycle 1

During cycle 1 in the Phase 2/3 studies, overall 61.7% (2024/3280 patients) reported at least 1 TEAE. The percent of patients was similar in the netupitant-palonosetron groups (65.5%, 944/1442 patients) and the palonosetron groups (59.1%, 945/1600 patients). In the comparator groups, the overall incidence of patients with at least 1 TEAE was 56.7% (135/238).

Throughout the programme TEAEs were most commonly reported in body systems (SOC) that are most often involved with the cytotoxic effects of chemotherapy administration. In cycle 1, across the treatment groups, TEAEs were most commonly reported (> 10%) in the following SOCs

- blood and lymphatic system disorders (21.8%, 716/3280);
- skin and subcutaneous tissue disorders (19.0%, 624/3280);
- gastrointestinal (GI) disorders (15.1%, 496/3280);
- general disorders and administration site conditions (14.6%, 478/3280); and
- investigations (10.1%, 332/3280)

The frequencies of patients reporting TEAEs in each of these SOCs were similar across the total (all doses) netupitant-palonosetron, palonosetron, and comparator groups, except for skin and subcutaneous tissue disorders, which were reported less frequently in the total comparator group (7.1%, 17/238 patients) than in the total netupitant-palonosetron (22.3%, 321/1442 patients) and total palonosetron groups (17.9%, 286/1600 patients); and blood and lymphatic system disorders, which were also reported less frequently in the total comparator group (13.9%, 33/238 patients) than in the total netupitant-palonosetron (24.5%, 353/1442 patients) and total palonosetron groups (20.6%, 330/1600 patients).

Among the patients treated with netupitant-palonosetron, the frequency of patients experiencing at least 1 TEAE ranged from 40.7% (55/135 patients) in the 100/0.50 mg group to 70.0% (818/1169 patients) in the 300/0.50 mg group. In the palonosetron groups, the frequency of TEAEs was 51.8% in the 0.25 mg IV group (191/369 patients) and 61.3% in the 0.50 oral group (754/1231 patients).

Similarly, the percent of patients with at least 1 TEAE assessed as being related to study drugs by the investigator was similar in the netupitant-palonosetron groups (9.6%, 138/1442 patients) and the palonosetron groups (6.6%, 105/1600 patients) during cycle 1 in the Phase 2/3 studies. In the comparator groups, the percentage of patients with a related TEAE was 12.2% (29/238). No clear pattern was seen across the netupitant-palonosetron dose groups or between the 2 palonosetron dose groups.

The most frequently reported TEAEs (i.e., those reported by > 5% of patients in any treatment group overall) were alopecia, neutropenia, leukopenia, asthenia, headache, fatigue, diarrhoea, and decreased appetite but these events generally occurred in similar percentages of patients across the 3 treatment groups.

In the Phase 2/3 cancer patients overall, most TEAEs were of mild (27.4%, 900/3280) or moderate (24.5%, 803/3280) intensity. Less than 10% of patients had severe TEAEs (9.8%, 320/3280) which were mostly caused by chemotherapy toxicity (haematologic disorders and alopecia). The frequency distribution of severity was similar across the treatment groups.

As far as drug-related TEAEs, the only PTs that were reported in ≥ 2% of patients overall or in any total treatment group were headache and constipation. Headache occurred in 2.2% of patients in the netupitant-palonosetron groups, 2.0% in the palonosetron groups and 1.7% in the aprepitant+palonosetron comparator groups. Constipation occurred at a frequency of 1.6% after oral palonosetron and 2.0% after the FDC 300/0.50 mg but was not greater than 2.0% in the overall dose groups.

There was no increased incidence of TEAE or suggestion of accumulated toxicity with repeated dosing.

Table 48: Overview of Treatment-emergent Adverse Events – Cycle 1 (Phase 2/3 Cancer Patients)

	Netupitant–Palonosetron (mg)				Palonosetron (mg)			Comparators			All Patients
				Total	IV	Oral	Total	*Aprepitant plus:*		Total	
	100/0.50 (N=135)	200/0.50 (N=138)	300/0.50 (N=1169)	(N=1442)	0.25 (N=369)	0.50 (N=1231)	(N=1600)	Palonosetron (N=104)	Ondansetron (N=134)	(N=238)	(N=3280)
Number (%) of patients with ≥ 1:											
TEAE	55 (40.7)	71 (51.4)	818 (70.0)	944 (65.5)	191 (51.8)	754 (61.3)	945 (59.1)	64 (61.5)	71 (53.0)	135 (56.7)	2024 (61.7)
Drug-related TEAE	18 (13.3)	24 (17.4)	96 (8.2)	138 (9.6)	24 (6.5)	81 (6.6)	105 (6.6)	3 (2.9)	26 (19.4)	29 (12.2)	272 (8.3)
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)
Drug-related serious TEAE	–	1 (0.7)	1 (0.1)	2 (0.1)	–	2 (0.2)	2 (0.1)	–	–	–	4 (0.1)
TEAE leading to death	1 (0.7)	–	7 (0.6)	8 (0.6)	12 (3.3)	8 (0.6)	20 (1.3)	–	–	–	28 (0.9)
TEAE leading to discontinuation	–	1 (0.7)	13 (1.1)	14 (1.0)	1 (0.3)	5 (0.4)	6 (0.4)	4 (3.8)	–	4 (1.7)	24 (0.7)
Drug-related TEAE leading to discontinuation	–	1 (0.7)	1 (0.1)	2 (0.1)	–	2 (0.2)	2 (0.1)	–	–	–	4 (0.1)

TEAE = treatment-emergent adverse event

Table 49: Patients with Treatment-emergent Adverse Events with an Incidence ≥5% – Cycle 1 Phase 2/3 Cancer Studies, Patients Treated with Netupitant-Palonosetron

	Netupitant-Palonosetron Combination			All Doses
	100/0.50 mg (N=135) n (%)	200/0.50 mg (N=138) n (%)	300/0.50 mg (N=1169) n (%)	(N=1442) n (%)
Number of patients with any TEAE	55 (40.7)	71 (51.4)	818 (70.0)	944 (65.5)
Blood and lymphatic system disorders	14 (10.4)	10 (7.2)	329 (28.1)	353 (24.5)
Leukocytosis	10 (7.4)	7 (5.1)	17 (1.5)	34 (2.4)
Leukopenia	1 (0.7)	2 (1.4)	134 (11.5)	137 (9.5)
Neutropenia	–	–	221 (18.9)	221 (15.3)
Neutrophilia	5 (3.7)	4 (2.9)	7 (0.6)	16 (1.1)
Cardiac disorders	7 (5.2)	11 (8.0)	38 (3.3)	56 (3.9)
Gastrointestinal disorders	16 (11.9)	22 (15.9)	175 (15.0)	213 (14.8)
Constipation	3 (2.2)	4 (2.9)	51 (4.4)	58 (4.0)
Diarrhoea	3 (2.2)	3 (2.2)	27 (2.3)	33 (2.3)
Dyspepsia	3 (2.2)	9 (6.5)	24 (2.1)	36 (2.5)
General disorders and administration site conditions	12 (8.9)	17 (12.3)	181 (15.5)	210 (14.6)
Asthenia	4 (3.0)	12 (8.7)	81 (6.9)	97 (6.7)
Fatigue	6 (4.4)	4 (2.9)	69 (5.9)	79 (5.5)
Infections and infestations	1 (0.7)	–	55 (4.7)	56 (3.9)
Investigations	12 (8.9)	24 (17.4)	108 (9.2)	144 (10.0)
Alanine aminotransferase increased	6 (4.4)	7 (5.1)	25 (2.1)	38 (2.6)
Neutrophil count increased	4 (3.0)	10 (7.2)	6 (0.5)	20 (1.4)
Metabolism and nutrition disorders	10 (7.4)	10 (7.2)	95 (8.1)	115 (8.0)
Decreased appetite	4 (3.0)	5 (3.6)	42 (3.6)	51 (3.5)
Musculoskeletal and connective tissue disorders	1 (0.7)	–	32 (2.7)	33 (2.3)
Nervous system disorders	10 (7.4)	15 (10.9)	115 (9.8)	140 (9.7)
Headache	5 (3.7)	11 (8.0)	80 (6.8)	96 (6.7)
Respiratory, thoracic and mediastinal disorders	8 (5.9)	6 (4.3)	48 (4.1)	62 (4.3)
Skin and subcutaneous tissue disorders	1 (0.7)	3 (2.2)	317 (27.1)	321 (22.3)
Alopecia	–	–	294 (25.1)	294 (20.4)
Vascular disorders	6 (4.4)	5 (3.6)	39 (3.3)	50 (3.5)

Abbreviations: n = number of patients; TEAE = treatment emergent adverse event

Note: patients with multiple events counted only once per line.

All Cycles

Considering all cycles in the Phase 2/3 studies, the incidence of AEs was higher compared to cycle 1 only, as multi-cycle events were added for this analysis. Overall, there were 72.3% (2373/3280) of patients with at least 1 TEAE in all cycles compared to 67.1% (2024/3280 patients) in cycle 1.

The percent of patients with TEAEs was higher in the netupitant-palonosetron groups (78.2%, 1127/1442 patients) than in the palonosetron groups (67.5%, 1080/1600 patients) and in the comparator groups (69.7%, 166/238 patients).

The percent of patients with TEAEs assessed as being related to study drugs by the investigator was similar in the netupitant-palonosetron groups (13.5%, 194/1442 patients) and in the comparator groups (13.4%, 32/238) and lower in the palonosetron groups (8.4%, 134/1600 patients). No clear pattern was seen across the netupitant-palonosetron dose groups or between the 2 palonosetron dose groups.

Phase 3 Multi-cycle Studies

All Cycles

Of the 1862 patients in the multi-cycle study safety population, 89.7% (1670/1862) experienced at least 1 TEAE in the two multi-cycle studies, with a similar frequency across the 3 treatment groups: 90.3% (933/1033 patients) in the netupitant-palonosetron group, 88.6% (642/725 patients) in the palonosetron group, and 91.3% (95/104 patients) in the comparator aprepitant+palonosetron group.

Overall, 11.7% of patients experienced at least 1 TEAE assessed as being related to study drugs by the investigator, with higher percentages of patients in the netupitant-palonosetron group (12.7%, 131/1033 patients) and in the palonosetron group (11.2%, 81/725 patients) than in the comparator aprepitant+palonosetron group (5.8%, 6/104 patients). However, the number of patients in the comparator group is small and may therefore not allow a fair comparison.

Serious adverse event/deaths/other significant events
Serious Adverse Events

Phase 2/3 Cancer Patients

Cycle 1

The overall incidence of serious TEAEs during cycle 1 of the Phase 2/3 studies was 3.8%; 2.3% in the netupitant-palonosetron groups, 5.4% in the palonosetron group, and 1.7% in the aprepitant+5-HT_3 group.

The most commonly reported events were coded to the system organ classes of blood and lymphatic system disorders (1.2%, overall), GI disorders (0.8%), general disorders and administration site conditions (0.5%), and respiratory, thoracic, and mediastinal disorders (0.5%).

By preferred term, neutropenia and febrile neutropenia were the most commonly reported serious TEAEs; these are known to be frequent events associated with the administration of chemotherapy. Both of these serious TEAEs were reported in the palonosetron (0.9% and 0.6% for neutropenia and febrile neutropenia) and netupitant-palonosetron groups (0.2% and 0.3%, respectively), but not in the aprepitant+5-HT_3 group.

Table 50: Serious TEAEs Occurring in > 1 Patient Overall, Sorted by Frequency of Occurrence – Cycle 1 (Phase 2/3 Cancer Patients)

	Netupitant–Palonosetron (mg)				Palonosetron Alone (mg)			Comparators			All Patients
				Total	IV	Oral	Total	*Aprepitant plus:*		Total	
	100/0.50	200/0.50	300/0.50		0.25	0.50		PALO	OND		
Preferred Term	(N=135) n (%)	(N=138) n (%)	(N=1169) n (%)	(N=1442) n (%)	(N=369) n (%)	(N=1231) n (%)	(N=1600) n (%)	(N=104) n (%)	(N=134) n (%)	(N=238) n (%)	(N=3280) 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)

	Netupitant–Palonosetron (mg)				Palonosetron Alone (mg)			Comparators			All Patients
				Total	IV	Oral	Total	*Aprepitant plus:*		Total	
	100/0.50	200/0.50	300/0.50		0.25	0.50		PALO	OND		
Preferred Term	(N=135) n (%)	(N=138) n (%)	(N=1169) n (%)	(N=1442) n (%)	(N=369) n (%)	(N=1231) n (%)	(N=1600) n (%)	(N=104) n (%)	(N=134) n (%)	(N=238) n (%)	(N=3280) 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)

PALO = palonosetron; OND = ondansetron; TEAE = treatment-emergent adverse event

Four patients (< 0.1%) in cycle 1 of the Phase 2/3 studies had serious TEAEs that were considered by the investigator to be related to investigational product: 2 patients in the netupitant-palonosetron groups (events of *loss of consciousness* and *acute psychosis*) and 2 patients in the palonosetron group (0.50 mg PO; events of *abdominal pain* and *constipation* in 1 patient, and *diarrhoea* and *asthenia* in 1 patient).

All Cycles

Across all cycles of the Phase 2/3 studies (including cycle 1, the overall subject incidence of serious TEAEs was 6.3%, with similar incidences being noted among patients treated with netupitant-palonosetron (6.0%; 87/1442), palonosetron (6.2%; 99/1600), and aprepitant+5-HT_3 (8.0%; 19/238). Overall, a similar pattern is seen for all cycles compared to cycle 1; serious TEAEs were most commonly (≥ 1% overall incidence) reported within the system organ classes of blood and lymphatic system disorders (2.1%) and GI disorders (1.3%). By preferred term, the most frequently (≥ 0.5%) reported serious TEAEs were febrile neutropenia (0.9%), neutropenia (0.8%), and anaemia (0.5%), also consistent with cycle 1 data.

In addition to the 4 patients in cycle 1 having serious treatment-related TEAEs, 1 patient in the netupitant-palonosetron group experienced a treatment-related serious TEAE before her 6th cycle during the Phase 2/3 studies (for a total of 5 patients with related serious TEAEs during all cycles of the Phase 2/3 studies. This patient experienced ventricular extrasystoles judged by the investigator to have a probable causal relationship with investigational product.

Phase 3 Multi-cycle Studies

All Cycles

The overall subject incidence of SAEs was 6.9% across all cycles of the Phase 3 multi-cycle program, with SAEs being reported more frequently for patients in the aprepitant+palonosetron group (18.3%) than in the netupitant-palonosetron (8.2%) or palonosetron groups (3.3%). In general, the most common SAEs were categorised within the system organ classes of blood and lymphatic system disorders (3.1% netupitant-palonosetron; 1.1% palonosetron; 4.8% aprepitant+palonosetron), GI disorders (1.8% netupitant-palonosetron; 0.3% palonosetron; 3.8% aprepitant+palonosetron), and infections and infestations (1.5% netupitant-palonosetron; 0.7% palonosetron; 3.8% aprepitant+palonosetron), consistent with those expected for a population of patients with cancer receiving multicycle chemotherapy.

By preferred term, the most common SAEs (≥ 0.3% overall) observed in patients were febrile neutropenia (1.2%), neutropenia (0.7%), vomiting (0.4%), anaemia (0.4%), and leucopenia (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 anaemia was the most frequently reported SAE among patients in the aprepitant+palonosetron group (2.9%; 3/104). For other individual preferred terms, there did not appear to be a pattern observed with respect to the types of SAEs that were reported with greater subject incidence, and the low incidence of each of these SAEs across treatment groups precludes meaningful comparison.

Table 51: Phase 3 Multicycle Studies: Serious Adverse Events Occurring in > 1 Patient Overall, Sorted by Frequency of Occurrence (All Cycles)

	NETU/PALO	PALO	Comparator	TOTAL
Preferred Term	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 any serious TEAE	85 (8.2)	24 (3.3)	19 (18.3)	128 (6.9)
Febrile neutropenia	16 (1.5)	6 (0.8)	1 (1.0)	23 (1.2)
Neutropenia	10 (1.0)	2 (0.3)	1 (1.0)	13 (0.7)
Vomiting	6 (0.6)	1 (0.1)	1 (1.0)	8 (0.4)
Anaemia	5 (0.5)		3 (2.9)	8 (0.4)
Leukopenia	3 (0.3)	2 (0.3)		5 (0.3)
Pneumonia	4 (0.4)			4 (0.2)
Urinary tract infection	3 (0.3)		1 (1.0)	4 (0.2)
Pulmonary embolism	2 (0.2)	1 (0.1)	1 (1.0)	4 (0.2)
Cardiopulmonary failure	3 (0.3)			3 (0.2)
Stomatitis	3 (0.3)			3 (0.2)
Asthenia	2 (0.2)	1 (0.1)		3 (0.2)
Neoplasm malignant	2 (0.2)		1 (1.0)	3 (0.2)
Nausea	1 (0.1)	1 (0.1)	1 (1.0)	3 (0.2)
Peritonitis	1 (0.1)		2 (1.9)	3 (0.2)
Renal failure	1 (0.1)		2 (1.9)	3 (0.2)
Abdominal pain	2 (0.2)			2 (0.1)
Diarrhoea	2 (0.2)			2 (0.1)
Multi-organ failure	2 (0.2)			2 (0.1)
Pyrexia	2 (0.2)			2 (0.1)
Femur fracture	2 (0.2)			2 (0.1)
Neoplasm progression	2 (0.2)			2 (0.1)
Metrorrhagia	2 (0.2)			2 (0.1)
Haemoptysis	2 (0.2)			2 (0.1)
Thrombocytopenia	1 (0.1)		1 (1.0)	2 (0.1)
Electrolyte imbalance	1 (0.1)	1 (0.1)		2 (0.1)
Convulsion	1 (0.1)		1 (1.0)	2 (0.1)
Deep vein thrombosis	1 (0.1)		1 (1.0)	2 (0.1)
Atrial fibrillation		2 (0.3)		2 (0.1)
Ileus			2 (1.9)	2 (0.1)
Thrombosis		2 (0.3)		2 (0.1)

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

Protocols included: NETU-08-18 and NETU-10-29

Deaths

Of the 3280 patients in the 4 key Phase 2/3 studies in patients with cancer, 39 patients (1.2%) died on-study. None of the deaths was considered by the investigator to be related to investigational product, with most of the deaths being attributable to disease-related progression or to complications due the toxic effects of chemotherapy.

In the Phase 2/3 studies, 28 patients (0.9%) died during cycle 1, and 11 patients died during the remaining chemotherapy cycles, as follows:

- In cycle 1, of the 28 patients who died, 20 patients out of 1600 (1.3%) had received either IV or oral palonosetron (19 were treated in single-cycle Study PALO-10-01 and 1 in Study NETU-08-18); 8 patients (of 1442 [0.6%]) had received netupitant-palonosetron and no subjects in the aprepitant+5-HT_3 group had a fatal TEAE during cycle 1.
- During the remaining cycles (i.e., patients in the Phase 3 multi-cycle studies), 19 patients died (of 1862 patients treated during the multi-cycle studies [1.0%]). There did not appear to be an influence of repeated dosing on the incidence of fatal adverse events, as the overall incidence of adverse events resulting in death was similar across chemotherapy cycles (range of incidences: 0.1% [cycle 2 and cycle 4] to 0.4% [cycle 1 and cycle 6]). Overall, for patients in the Phase 3 multi-cycle studies, the incidence of fatal TEAEs (across all cycles, 1 through 6) was generally comparable across treatment groups: TEAEs resulting in death were experienced by 1.5% of patients in the netupitant-palonosetron group, 0.3% of patients in the palonosetron group, and 1.0% of patients in aprepitant+palonosetron group.

In addition to the deaths reported above, there were 5 patients in Study NETU-10-29 who experienced TEAEs with a final fatal outcome, but who were not included in the data as on-study deaths: 3 of these patients (2 in the netupitant-palonosetron group and 1 in the aprepitant+5-HT_3 group) died after completion of all chemotherapy cycles to which they were scheduled (i.e., these patients, per protocol, were considered to have completed study); 1 patient withdrew from the study due to an AE (which ultimately had a fatal outcome); and 1 patient withdrew from the study due to other reasons (investigator assessment: worsening of global health condition) and died a few days after discontinuation.

Of the remaining patients in the netupitant-palonosetron clinical development programme (i.e., healthy volunteers and patients in special population studies), 2 died on-study. Both were cancer patients treated with the netupitant/palonosetron FDC (300/0.50 mg) prior to docetaxel chemotherapy in drug-interaction Study NETU-10-09. Neither death was assessed by the investigator as being related to netupitant/palonosetron FDC. In the first case, the patient (81-year-old male with prostate cancer) was hospitalised because of dehydration, neutropenia, and pneumonia, and died following circulatory and respiratory insufficiency associated with pneumonia. The events were considered to be related (possibly and definitely) to docetaxel. In the second case, the patient (a 63-year-old female with lung adenocarcinoma) was hospitalised after experiencing respiratory failure with dyspnoea, and later died after developing severe neutropenia (nonserious) and pulmonary oedema. The death was attributed to progression of lung cancer, and was not considered to be related to docetaxel or to investigational product.

The most frequent preferred terms in the Phase 2/3 patients who died during the Phase 2/3 studies (n=39) were multi-organ failure (5 patients), death (4 patients), acute cardiac failure, cardiopulmonary failure, pneumonia and renal failure (3 patients each). There were 17 deaths in the netupitant-palonosetron groups (17/1442), 21 deaths in palonosetron-treated groups (21/1600; of which 9/1231 in the palonosetron oral group) and 1 death in the active comparator groups (1/238).

Table 52: Patients with Treatment-emergent Adverse Events Leading to Death, by Preferred Term – All Cycles (Phase 2/3 Cancer Patients)

	Netupitant–Palonosetron (mg)				Palonosetron Alone (mg)			Comparators			All Patients
				Total	IV	Oral	Total	*Aprepitant plus:*		Total	
Preferred Term	100/0.50 (N=135)	200/0.50 (N=138)	300/0.50 (N=1169)	(N=1442)	0.25 (N=369)	0.50 (N=1231)	(N=1600)	PALO (N=104)	OND (N=134)	(N=238)	(N=3280)
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)
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)

	Netupitant–Palonosetron (mg)				Palonosetron Alone (mg)			Comparators			All Patients
				Total	IV	Oral	Total	*Aprepitant plus:*		Total	
Preferred Term	100/0.50 (N=135)	200/0.50 (N=138)	300/0.50 (N=1169)	(N=1442)	0.25 (N=369)	0.50 (N=1231)	(N=1600)	PALO (N=104)	OND (N=134)	(N=238)	(N=3280)
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)

PALO = palonosetron; OND = ondansetron; TEAE = treatment-emergent adverse event; CNS = central nervous system

Laboratory findings

Routine laboratory tests included haematology and chemistry at screening, day 2 and day 6 of each cycle during the Phase 3 multi-cycle studies. Troponin concentrations (cTnI) were measured at the same time points in the two multi-cycle Phase 3 studies.

As expected, in patients receiving chemotherapy over multiple cycles, leucopenia (including neutropenia, monocytopenia and granulocytopenia), anaemia and thrombocytopenia were observed with generally similar reductions in patients receiving netupitant-palonosetron, palonosetron or aprepitant+palonosetron. There was no apparent influence of repeat exposure to investigational product on haematology parameters. No clinically meaningful differences in haematology were observed between the treatment groups after both single cycle and multiple cycle exposure.

During all cycles, the most frequently reported (> 5.0% overall) marked laboratory abnormalities among subjects in the netupitant-palonosetron, palonosetron, and aprepitant+palonosetron groups were hyperglycaemia (8.4%, 7.6%, and 6.7%, respectively) and hyponatraemia (5.5%, 6.3%, and 6.7%). Hyperglycaemia was reported as a TEAE for 119 (of 1862 [6.4%]) patients in the Phase 3 multi-cycle studies (6.1% of patients in the netupitant-palonosetron group; 7.3% of patients in the palonosetron group; and 2.9% of patients in the aprepitant+palonosetron group).

Table 53: Patients with New Laboratory Abnormalities: Blood Chemistry – All Cycles Phase 3 Multicycle Studies (Safety Population)

	Netupitant/ Palonosetron 300/0.50 mg	Palonosetron 0.50 mg	Aprepitant plus Palonosetron	TOTAL
	(N=1033) n (%)	(N=725) n (%)	(N=104) n (%)	(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)

Note: New abnormalities were defined as abnormal values that reached CTCAE grade 3 or 4 but were not present at baseline.ISS Table

There were no obvious trends indicative of treatment-related effects on chemistry parameters across all treatment groups.

A total of 58 patients (3.1%) had post dose cTnI elevations ≥ 0.12 ng/mL during these Phase 3 multi-cycle studies which included 33 patients (3.2%) in the netupitant-palonosetron FDC group, 22 patients (3.0%) in the palonosetron group, and 3 patients (2.9%) in the aprepitant+palonosetron group . The majority of cTnI elevations were seen in cycle 5 or 6.

Pregnancy

As of the cut-off date of 30 June 2013, two cases of exposed pregnancy occurred during the FDC development program. One female healthy volunteer treated with 600 mg netupitant and 1.50 mg palonosetron (Study NETU-07-20) had a positive serum pregnancy test at the final visit. The entire gestation was uneventful and the woman gave birth to a normal newborn. The second subject was treated with the FDC (300/0.50 mg) in a bioequivalence study (NETU-11-02). The pregnancy was uneventful, delivery was without complications, and the newborn was healthy.

Vital Signs

Vital signs included the monitoring of blood pressure (systolic and diastolic) and pulse rate and were measured at screening for each cycle plus pre-dose, 5, 24, and 120 hours post-dose at each cycle.

After the start of chemotherapy, mean systolic and diastolic blood pressures were slightly lower in all treatment groups during cycle 1 compared to baseline; however, these changes were not clinically meaningful. There were no patterns or trends over time in vital signs during the Phase 3 multi-cycle studies, and none of the results appeared to be indicative of a clinical concern. There was little variability in mean blood pressure values over time.

Safety in special populations

For the multi-cycle Phase 3 studies, patients with varying degrees of renal impairment were evaluated for safety including TEAEs, serious TEAEs, and ECGs. In addition TEAEs and serious TEAEs are further analysed by the intrinsic factors of gender, age class, race, and region. The extrinsic factor of emetogenicity (i.e., HEC and MEC) is analysed using both the Phase 2/3 cancer patient population and the multi-cycle Phase 3 patients.

Renal impairment

Per protocol patients were qualified for enrolment provided that serum creatinine was equal to or less than 1.5 mg/dL or creatinine clearance was ≥ 60 mL/min. The multi-cycle Phase 3 studies did not enrol patients with severe renal dysfunction (creatinine clearance < 30 mL/min) and included more patients with normal renal function ([creatinine clearance ≥ 90 mL/min] 1198/1862, 64.3%) than patients with either mild renal impairment ([creatinine clearance ≥ 60 to < 90 mL/min] 580/1862, 31.1%) or moderate renal impairment ([creatinine clearance ≥ 30 to < 60 mL/min] 80/1862, 4.3%). This difference is consistently seen in all the treatment groups: in the netupitant-palonosetron group there are 668 normal renal function patients, 317 mild renal impairment patients, and 45 moderate renal impairment patients; in the palonosetron group the patients are 476, 218, and 30, respectively; and in the aprepitant+palonosetron group they are 54, 45, and 5, respectively. No clear difference was observed in the incidence of TEAEs or ECG parameters for patients with normal renal function compared to those of patients with mild and moderate renal impairment in the Phase 3 multicycle studies.

The percentage of patients with at least 1 TEAE was similar in the 3 renal function subgroups for each treatment group, with the most commonly reported TEAEs in each subgroup reflecting those in the overall safety population. In addition, the percentage of cycles during which patients experienced any TEAE was similar across the renal function subgroups for each treatment group.

Changes in ECGs during the Phase 3 multicentre studies were small and generally larger in the mild and moderate renal impairment subgroups than in patients with normal renal function although the small number of patients in the moderate renal impairment subgroup makes comparison difficult. Few patients had outlier

values for QTcF > 480 ms or > 500 ms, and no clear pattern in the incidence of outliers could be seen across the renal subgroups in any treatment group.

Gender

The multi-cycle Phase 3 studies included more female patients (1628/1862, 87.4%) than male patients (234/1862, 12.6%). This imbalance is mainly driven by the safety population in Study NETU-08-18 (which compared netupitant-palonosetron and palonosetron) which was primarily comprised of females (1422/1450, 98.1%), with a minority (28/1450, 1.9%) of males, due to the protocol-specified chemotherapy regimen (MEC, AC/EC) mostly indicated for breast cancer. As a consequence, this difference is seen in both the netupitant-palonosetron group (866 females, 167 males) and the palonosetron group (711 females, 14 males), while the aprepitant+palonosetron group, which comprises patients from Study NETU-10-29 only, had a similar number of females (51) and males (53).

The percentage of patients with at least 1 TEAE considering all cycles was slightly lower in the male subgroup than the female subgroup overall (85.5% and 90.3%, respectively), with the most commonly reported TEAEs in males and in females reflecting those in the overall safety population.

Age

The multi-cycle Phase 3 studies included more patients with < 65 years (1519/1862, 81.6%) than patients with ≥ 65 year (343/1862, 18.4%). As detailed below, 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. Almost all the patients included in the multi-cycle Phase 3 studies were < 75 years (1821/1862, 97.8%) and only a minority (41/1862, 2.2%) was ≥ 75 years of age. Therefore, the number of patients in the subgroup ≥ 75 years of age was too small to allow a meaningful comparison with the other group.

Emetogenicity

The percentage of patients with at least 1 TEAE overall was higher in the MEC subgroup than in the HEC subgroup during cycle 1 and all cycles both overall and in each of the treatment groups. It should be noted that for the “all cycles” population, where the difference is observed as well, the HEC subgroup (1518 patients) is comprised of 1418 patients from NETU-07-07 and PALO-10-01 (cycle 1 only). In the analysis of cycles with TEAEs, the percentage of cycles during which patients experienced any TEAE was higher in MEC patients than HEC patients in each treatment group. Within each subgroup (MEC and HEC), no differences were seen between the treatment groups in the proportion of patients with TEAEs.

The differences in the types and incidence of TEAEs between the MEC and HEC subgroups are considered to reflect the differences between the chemotherapy regimens and potentially the mix of patients (primarily women in the MEC-AC group) in these subgroups. The difference in the incidence of events in cycle 1 may be partially explained by the difference in the toxicity pattern of the MEC and HEC regimens, with MEC mainly affecting the bone marrow with a nadir between 7-14 days post chemotherapy, while HEC toxicity primarily targets the kidney and has a cumulative effect on renal function. Also in cycle 1, the incidence of alopecia may have contributed to the difference between the MEC and HEC subgroups, being reported in cycle 1 by 31% of MEC patients and 1.5% of HEC patients, and may reflect the different proportion of female patients receiving an AC-based regimen for breast cancer, known to cause greater incidence of more severe chemotherapy-induced alopecia compared with cisplatin.

The percentage of patients with serious TEAEs, however, is higher in the HEC subgroup than in the MEC subgroup in cycle 1 (5.4% vs 2.4%) and similar in the 2 subgroups in all cycles (6.1% and 6.4%). This suggests that in cycle 1 HEC patients reported fewer TEAEs, but they experienced more serious events.

ECG

For cycle 1 in the Phase 2/3 cancer patients, an analysis of ECG data showed that at 5 hours after treatment (approximate T_{max} for netupitant/palonosetron FDC), a comparable increase from baseline in QTcF was seen in the netupitant-palonosetron group, the palonosetron group, and the comparator group. Similar changes from baseline in QTcF values were also observed at 24 hours post dose with mean QTcF values returning to baseline values or lower at 120 hours after treatment. At subsequent cycles, in the multi-cycle studies a similar pattern was observed, with comparable changes from the same-cycle pre-dose reference values for each treatment group.

An outlier analysis showed that the proportion of patients with QTcF increases from baseline to >500 ms was low in the netupitant-palonosetron, palonosetron and comparator groups in cycle 1 of the Phase 2/3 studies. In the multi-cycle studies, considering all cycles, the percentage of patients who had new QTcF interval values > 500 ms was low and comparable between treatment groups (1.1% in the netupitant-palonosetron group, 0.8% in the palonosetron group, and 1.0% in the comparator group). Moreover, the proportion of patients with QTcF increases of >60 ms from baseline or same cycle pre-dose was also low and comparable in the netupitant-palonosetron group and in the palonosetron at each cycle. The lower proportion of patients with QTcF increases of > 60 ms in the comparator arm is likely related to the reduced pro-arrhythmic potential of the chemotherapeutic agents used in study NETU-10-29. No increased risk of clinically relevant QT prolongation is expected after the administration of netupitant/palonosetron FDC.

Outlier responses in QTc interval are difficult to assess in view of normal intra-individual and circadian variability in this parameter. Recommended assessment criteria that could indicate a potential safety signal include a change in QTcF from baseline to > 500 msec in more than 5% of patients and from baseline of > 60 msec in more than 15% of patients (Morganroth et al. 2010).

In cycle 1, the percentage of patients with new treatment-emergent ECG abnormalities after baseline was comparable between the treatment groups (37.5%, 37.4%, and 39.1% in the netupitant-palonosetron, palonosetron, and aprepitant +palonosetron groups, respectively). The most frequently reported new treatment-emergent ECG abnormalities were flat T-wave (11.3% overall) followed by sinus tachycardia (9.2% overall), both of which occurred in similar percentages of patients across the treatment groups. In the subgroup of patients who received at least 6 consecutive cycles of the same treatment in the Phase 3 multicycle studies, the overall frequency of new treatment-emergent ECG abnormalities tended to increase by cycle in the netupitant-palonosetron group and the palonosetron group from cycle 1 (36.6% [116/317 patients] and 40.3% [77/191 patients], respectively) to cycle 5 (50.8% [161/317 patients] and 52.4% [100/191 patients], respectively). The frequency of new U-waves was low (0.50%) and comparable across the treatment groups.

Study NETU-07-20 was a double-blind randomised parallel-group trial to investigate possible ECG effects of single oral doses of netupitant/palonosetron using a clinical and a supratherapeutic dose compared to placebo and moxifloxacin (a positive control) in healthy men and women (a thorough QT study).

The objective of the study was to demonstrate that the administration of netupitant in combination with palonosetron does not prolong the QT interval more than placebo in male and female healthy subjects.

Subjects were males and females between 18 and 45 years of age (inclusive), in good physical health, and with a body mass index ≥19 and <29 kg/m2.

The study was conducted in compliance of ICH E14 guidance and the primary endpoint was to determine the effect of the combination on QTc interval as corrected by individually derived heart rate correction factor.

There were 4 treatment groups:

1. Placebo to netupitant and placebo to palonosetron
2. 200 mg netupitant and 0.50 mg palonosetron
3. 600 mg netupitant and 1.50 mg palonosetron
4. 400 mg moxifloxacin

The time matched analysis for the QTcI endpoint revealed that the moxifloxacin group met the assay sensitivity criteria with 12 time points > mean of 5 msec. The time matched results for QTcI, QTcF and QTcB showed that at no time point did palonosetron and netupitant dose groups exceed the upper confidence interval of 10 msec. As far as the effect on QTcI interval is concerned, the changes observed were considered to be random changes consistent with spontaneous variability in QTc interval and not to indicate a pharmacological effect due to the administration of netupitant/palonosetron combination. This conclusion was supported by a lack of dose-response or concentration-response relationship and overall, the results of this ECG trial showed no signal of any effect on AV conduction or cardiac depolarization as measured by the PR and QRS interval durations.

No statistical or experimental evidence was found to demonstrate any potential relationship for corrected QT interval or QT intervals with plasma palonosetron concentrations after single dose administration of intravenous palonosetron including supratherapeutic doses up to 2.25 mg, 9-fold greater than the current marketed 0.25 mg intravenous dose.

The expert cardiologist notes that following the first cycle, mean increases in QTc intervals at 5 hours and 24 hours were very small (< 12 msec) and within normal limits. These increases were comparable for the three treatments administered (namely, the FDC, palonosetron alone or a comparator combination). The number of outliers with significant categorical responses (QTc interval > 500 msec or an increase from baseline of > 60 msec) was very low (maximum 0.6%) and consistent with what would be observed normally in such populations.

Hepatic Change

The applicant performed an analysis for netupitant-palonosetron to cause severe liver toxicity (DILI) to assess the potential of hepatotoxic signals induced by patients' exposure to treatment. Such an analysis of the potential was undertaken in the Phase 3 multi-cycle clinical trials. Overall, the analysis of all cases described in an expert review indicated that exposure to netupitant and palonosetron was not associated with the development of severe liver injury. The diagnostic profile was mainly represented by mild hepatocellular liver injury. All patients recovered or improved and no patients discontinued the study because of hepatoxicity. The main confounding factor in the occurrence of liver events is chemotherapy, which represents a known cause of liver injury. Data from the FDC development program do not suggest a particular risk of hepatotoxicity associated with netupitant-palonosetron FDC exposure after single or repeated cycles of chemotherapy.

Safety related to drug-drug interactions and other interactions

Netupitant is a substrate and a moderate inhibitor of cytochrome P450 isoenzyme 3A4 (CYP3A4). Studies have shown that when a CYP3A4 inhibitor (ketoconazole) was administered with netupitant, approximately 2-fold increases in netupitant exposure were observed. Likewise, coadministration of a CYP3A4 inducer (rifampicin) resulted in a 5- to 6-fold reduction in netupitant exposure (NETU-10-11).

Based on pharmacokinetic interaction studies performed during the development program, administration of the FDC with CYP3A4 substrates may result in increased exposure to the substrate. Exposure to midazolam, erythromycin, dexamethasone, docetaxel, etoposide, and levonorgestrel were all increased during coadministration with netupitant. These additional studies indicate that netupitant is a mild to moderate inhibitor of CYP3A4 (NP16599, NETU-06-07, NETU-10-08, NETU-10-09).

The PK of netupitant was not affected by CYP3A4 substrates erythromycin, midazolam, dexamethasone, or oral contraceptives. Furthermore, 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 not essentially different.

Netupitant does not influence the exposure of digoxin, a P-glycoprotein substrate (NETU-07-01). Nevertheless a slight increase of digoxin C_{max} (9%) was observed. Netupitant also has no effect on the PK of palonosetron (NETU-06-27).

Table 54: Overview of Drug Interactions with Netupitant

Type of Drug Interaction	Compound	PK Effect of Test Compound on Netupitant	PK Effect Of Netupitant on Test Compound	Source
CYP3A4 inducer	Rifampicin	Decreased netu exposure area under the curve (AUC) up to 6-fold and Cmax 2.6-fold	Not measured	NETU-10-11
CYP3A4 inhibitor	Ketoconazole	Increased netu exposure AUC 1.8-2.4 fold, Cmax increased 1.3 fold	Not measured	
CYP3A4 substrate	Dexamethasone	No effect	Dex exposure (AUC and Cmax) was significantly increased, ranging from 1.7-2.7 fold. Reduction in dexamethasone dose recommended	NETU-06-07
CYP3A4 substrate	Midazolam	No effect	Increase exposure (AUC) of approximately 2-fold	NP16599
CYP3A4 substrate	Erythromycin	No effect	Increased exposure (AUC) approximately 30%	NP16599
CYP3A4 substrate	Levonorgestrel	Direct comparison not measured; no marked differences on rate and extent of absorption of netupitant or its metabolites compared to historical data	Increased exposure to levonorgestrel by about 40%	NETU-10-08
CYP3A4 substrate	Ethinyl-estradiol		No effect	
P-gp inhibitor probe	Digoxin	Direct comparison not measured; no marked differences on rate and extent of absorption of netupitant compared to historical data.	No effect	NETU-07-01
Others Co-administered	Palonosetron	No effect	No effect	NETU-06-27
Chemo-therapy CYP3A4 substrate	Docetaxel	Direct comparison not measured; no marked differences on rate and extent of absorption of netupitant compared to historical data	Increase in C_{max} by 50% and AUC_{0-t} by 37%	NETU-10-09
Chemo-therapy CYP3A4 substrate	Etoposide		Slight increases in exposure (approximately 21% for AUC_{0-t}). C_{max} not changed	
Common chemo-therapy agent	Cyclophospha-mide		No consistent differences between treatments were shown. Mean increase of systemic exposure was 8%-14%	

Discontinuation due to adverse events

Cycle 1

Of the 3280 patients with cancer treated in the Phase 2/3 studies, 24 (0.7%) reported AEs during cycle 1 that resulted in withdrawal from the study. Of these AEs, those that were reported for > 1 patient were neutropenia (3/1169 patients [0.3%]) in the netupitant-palonosetron 300/0.50 mg group, and nausea (2/1231 patients [0.2%]) in the palonosetron 0.50 mg group. Four subjects (0.1%) experienced AEs leading to withdrawal from the study that, in the opinion of the investigator, were related to investigational product. Of these patients, 2 (of 1442 [0.1%]) had received netupitant-palonosetron (AEs of loss of consciousness and acute psychosis [both serious]), and 2 (of 1600 [0.1%]) had received palonosetron 0.50 mg only (AEs of nausea and urticaria)

All Cycles

Seventy-seven (2.3%) patients reported TEAEs during any chemotherapy cycle of the Phase 2/3 studies that led to these patients being withdrawn from studies, with the greatest incidence of subject withdrawals being in the aprepitant+5-HT_3 group (5.5%; 13/238) compared with the netupitant-palonosetron groups (3.1%; 44/1442) or palonosetron group (1.3%; 20/1600).

By preferred term, the most frequently (≥ 0.2% overall) reported events leading to withdrawal from the study, regardless of seriousness and relationship, that occurred during any cycle (including cycle 1) were neutropenia (0.2%), malignant neoplasm (0.2%), and neoplasm progression (0.2%). Treatment-emergent AEs leading to withdrawal from the study that were reported for > 2 patients in any group were neutropenia (0.3% [5/1442]), neoplasm progression (0.3% [5/1442]), and malignant neoplasm (0.3% [4/1442]) in the netupitant-palonosetron groups; and nausea (3 patients [0.2%]) in the palonosetron group. In the aprepitant+5-HT_3 group, the most common TEAEs leading to withdrawal from the study were thrombocytopenia, ileus, peritonitis, blood creatinine increased, and malignant neoplasms, occurring at an incidence of 2 patients each (of 238 [0.8%]).

Of the 77 patients with cancer in the Phase 2/3 studies who experienced TEAEs leading to withdrawal from the study, 6 (0.2%) had TEAEs during any cycle that were considered by the investigator to be related to the investigational product (2 subjects (0.1%) treated with netupitant-palonosetron combinations who reported one AE each of loss of consciousness and acute psychosis; and 4 subjects (0.3%) treated with palonosetron 0.50 mg who reported one AE each of nausea, electrocardiogram repolarisation abnormality, pharyngeal oedema, and urticaria.

Post marketing experience

At the time of submission the netupitant-palonosetron FDC was not marketed in any country.

More than 5.8 million vials of intravenous palonosetron (CINV and PONV) have been sold worldwide in the period July 2013-July 2014, corresponding to approximately 886'500 patients exposed to the injectable formulation for the CINV indication and 555'400 for the PONV indication. A total of 58'000 capsules have been sold during the same period, corresponding to approximately 9'700 patients exposed.

Recently the European Medicines Agency (EMA) indicated that the potential for serotonin syndrome across the class of 5-HT_3 antagonists exists and this represents a possible safety concern; consequently, the EU SmPC of Aloxi was amended to reflect the potential risk. This was also taken into consideration for Akynzeo.

Other than the potential for serotonin syndrome, no new important identified and potential risks for palonosetron have been identified in addition to those already reported in the EU-RMP (severe hypersensitivity reactions, severe constipation, QT prolongation and convulsion), which are under a continuous monitoring and in-depth evaluation.

During the reporting period no marketing authorisation renewals or registration applications were rejected, and no marketing authorisations were withdrawn or suspended for safety reasons. No actions were taken due to product defects and quality issues.

2.6.1. Discussion on clinical safety

Clinical safety was assessed through the 4 pivotal studies that were performed in the target population: prevention of CINV in patient receiving HEC or MEC. The study population was predominantly white (86.0%), and had a mean (SD) age of 54.5 (10.4) years.

A total of 1538 subjects and patients were exposed to the netupitant-palonosetron combination at the proposed market dose (300/0.50 mg) during the clinical programme with a total number of 5441 exposures: 1169 patients with cancer received at least one dose while participating in one of the Phase 2/3 studies. There were 550 patients who received 6 or more consecutive cycles of chemotherapy and 317 of these received the FDC (300/0.50 mg).

Adverse reactions were compared across netupitant-palonosetron (1442 patients) and palonosetron (1600 patients) and comparator groups (238). Common adverse reactions reported with Akynzeo were headache (3.6%), constipation (3.0%) and fatigue (1.2%). None of these events was serious. The frequency of headache, constipation and fatigue was similar (2.9%, 2.5% and 0.7%, respectively) in patients receiving oral palonosetron 0.5 mg alone.

Cases of severe constipation and of complications due to constipation were observed in the clinical trials and, in accordance with the product information on Aloxi (palonosetron), information included in the SmPC and in the RMP as an important identified risk.

For cycle 1, the frequencies of patients reporting TEAEs were similar across the total (all doses) netupitant-palonosetron, palonosetron, and comparator groups, except for skin and subcutaneous tissue disorders, which were reported less frequently in the total comparator group (7.1%, 17/238 patients) than in the total netupitant-palonosetron (22.3%, 321/1442 patients) and total palonosetron groups (17.9%, 286/1600 patients); and blood and lymphatic system disorders, which were also reported less frequently in the total comparator group (13.9%, 33/238 patients) than in the total netupitant-palonosetron (24.5%, 353/1442 patients) and total palonosetron groups (20.6%, 330/1600 patients). Whereas the incidence of certain adverse reactions such as leucopenia or alopecia seemed to increased with dose of the FDC in the Phase 2/3 combined safety population for Cycle 1 this could not be shown in study NETU-07-07 where frequency and severity of TEAEs were comparable across treatment groups without indication of dose-dependence. It is acknowledged that, unlike in the combined safety population NETU-07-07 study included similar numbers and types of cancer patients at each netupitant dose level but, considering that netupitant is a known CYP3A4 inhibitor precautionary statements were included into the SmPC to monitor patients receiving chemotherapeutic agents that are substrates for CYP3A4 for possible increased toxicity.

SAE profiles shown in the clinical trial programme were consistent with the patient population and the fact that they were undergoing chemotherapy. The overall subject incidence of SAEs was 6.9% across all cycles of the Phase 3 multi-cycle programme, with SAEs being reported more frequently for patients in the aprepitant+palonosetron group (18.3%) than in the netupitant-palonosetron (8.2%) or palonosetron groups (3.3%). In general, the most common SAEs were categorised within the system organ classes of blood and

lymphatic system disorders (3.1% netupitant-palonosetron; 1.1% palonosetron; 4.8% aprepitant+palonosetron), GI disorders (1.8% netupitant-palonosetron; 0.3% palonosetron; 3.8% aprepitant+palonosetron), and infections and infestations (1.5% netupitant-palonosetron; 0.7% palonosetron; 3.8% aprepitant+palonosetron), all of which might be seen in a population of patients with cancer receiving multi-cycle chemotherapy. By preferred term, the most common SAEs (≥ 0.3% overall) observed in patients were febrile neutropenia (1.2%), neutropenia (0.7%), vomiting (0.4%), anaemia (0.4%), and leucopenia (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).

A total of 46 cancer patients who participated in the clinical development programme died; 41 deaths occurred during the treatment period (39 in the Phase 2/3 trials and 2 in the PK interaction study); 5 patients died after their participation in study NETU-10-29. None of the deaths was considered related to study medication. Both the frequency and the nature of deaths are considered consistent with what would be expected in the population enrolled and with disease related progression or complications of cytotoxic effects of chemotherapy.

Leucopenia (including neutropenia, monocytopenia and granulocytopenia), anaemia and thrombocytopenia were observed with generally similar reductions in patients receiving netupitant-palonosetron, palonosetron or aprepitant+palonosetron. There was no apparent influence of repeat exposure to investigational product on haematology parameters. No clinically meaningful differences in haematology were observed between the treatment groups after both single cycle and multiple cycle exposure. There were no obvious trends indicative of treatment-related effects on chemistry parameters across all treatment groups.

There was a low incidence of withdrawal due to adverse events. Overall, seventy-seven (2.3%) patients reported TEAEs during any chemotherapy cycle of the Phase 2/3 studies that led to withdrawal from the study, a total of 44 patients in the netupitant-palonosetron groups (3.1%), 20 in the palonosetron group (1.3%) and 13 (5.5%) in the aprepitant+5-HT_3 group. The adverse events causing withdrawal is considered to reflect the condition being treated and the adverse events of associated chemotherapy.

Subgroup analyses based on renal function, age, gender, race, region and emetogenicity (HEC or MEC) did not reveal any statistically significant differences that would require special consideration. Adverse event profiles across the subgroups evaluated reflected those in the overall safety population.

The percentage of patients with at least one TEAE overall was higher in the MEC subgroup compared to HEC during cycle 1 and all cycles both overall and in each of the treatment groups and it is agreed that this may reflect the different toxicities of chemotherapy regimens.

A thorough ECG trial demonstrated that netupitant and palonosetron had no clinically important effects on heart rate, PR and QRS interval duration or cardiac morphology. The effects on cardiac repolarization by any of the ECG data analyses including a careful pharmacodynamic-pharmacokinetic analysis also showed no netupitant/palonosetron effects on cardiac repolarization. No statistical or experimental evidence was found to demonstrate any potential relationship for corrected QT interval or QT intervals with plasma palonosetron concentrations after single dose administration of intravenous palonosetron including supratherapeutic doses up to 2.25 mg, 9-fold greater than the current marketed 0.25 mg intravenous dose.

Following the first cycle, mean increases in QTc intervals at 5 hours and 24 hours were very small (< 12 msec) and within normal limits. These increases were comparable for the three treatments administered (namely, the FDC, palonosetron alone or a comparator combination). The number of outliers with significant

categorical responses (QTc interval > 500 msec or an increase from baseline of > 60 msec) was very low (maximum 0.6%) and consistent with what would be observed normally in such populations.

Nevertheless the magnitude of the QT prolongation observed (5 to 7 ms in healthy volunteers) might translate into more profound effects in patients vomiting, with diarrhoea, treated with other drugs susceptible to increase QT interval, with cardiac conditions (heart failure…) or similar problems which decrease their repolarisation reserve. Therefore, as with other $5HT_3$ receptor antagonists a precautionary statement was in included into section 4.4 of the SmPC and identified as a potential risk in the Risk Management Plan.

In vitro data demonstrated that netupitant is a P-gp inhibitor. In a study performed in healthy volunteers, netupitant did not affect the exposure of digoxin, a P-gp substrate, whereas it significantly increases its C_{max} (by 9%).Clinically this effect may be relevant notably in female patients in whom the therapeutic margin for digoxin is narrower than in men. Furthermore, netupitant will be administered to patients the renal status of whom would be probably altered either due to the age and/or to chemotherapy (e.g.cisplatin). As it cannot be ruled out that digoxin exposure may increase in a significant manner in the clinical setting a precautionary statement to the use of P-gp substrates was implemented in the SmPC and this was added as an important potential risk due to netupitant into the RMP.

Based on the current SmPC, palonosetron is not expected to be an inhibitor and an inducer of CYPs. However, since the granting of the MA for palonosetron, a new EU Guideline on drug-drug Interactions was published (CPMP/EWP/560/95/Rev. 1; came into effect January 2013). The investigation of the involvement of efflux and uptake transporters in the interaction profile of a new drug entity is now strongly recommended. No data of such feature was submitted therefore the applicant is recommended to carry out an additional in vitro study evaluating the involvement of efflux and uptake transporters in palonosetron disposition and its effect as an inhibitor of these transporters by the end of March 2016.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, the FDC was well tolerated. Many adverse reactions are likely to be associated with either the underlying condition or associated cytotoxic therapies. Similarly SAEs and deaths reflect the patient population and concurrent treatment. The known PK interaction of netupitant with CYP3A4, which might be associated with an increase in the exposure to chemotherapy agents metabolised via this pathway is adequately addressed in SmPC and RMP.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes in the RMP as requested by PRAC andCHMP.

The CHMP endorsed the Risk Management Plan version 2.2 with the following content:

Safety concerns

Important identified risks	Severe hypersensitivity reactions, including anaphylaxis, anaphylactic/anaphylactoid reactions and shock Severe constipation (due to palonosetron)
Important potential risks	QT/QTc interval prolongation Convulsive events (due to palonosetron) Serotonin syndrome (due to palonosetron) Liver transaminases increase Teratogenic effects Interaction with CYP3A4 inhibitors and inducers (due to netupitant) Interaction with CYP3A4 substrates (e.g. corticosteroids and benzodiazepines) (due to netupitant) Phospholipidosis (due to netupitant) Possible interaction with BCRP substrates (due to netupitant) Possible interaction with UGT-2B7 substrates (due to netupitant) Possible interaction with P-gp substrates (due to netupitant)
Missing information	Effects on pregnancy and lactation Effects on fertility Effects in patients with end-stage renal disease undergoing haemodialysis Effects in patients with severe hepatic impairment Effects in children Effects in patients aged 75 years or more

Pharmacovigilance plan

In vivo drug interaction study to evaluate the duration of inhibitory effects of Akynzeo on CYP3A4 enzyme activity beyond 4 days after Akynzeo administration. Expected date of report: June 2016

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
QT/QTc prolongation	Warnings and precaution for use because of this safety concern are included in section 4.4. Listed in section 4.8. Section 5.1 summarises the results of the clinical studies with respect to this safety concern. Section 5.3 summarizes the relevant preclinical safety data. Prescription only medicine	Not applicable
Severe hypersensitivity reactions including anaphylaxis, anaphylactic/anaphylactoid reactions and shock	Appropriate contraindication is included in section 4.3. Section 4.4 includes a pertinent warning associated with allergic reactions to excipients. Prescription only medicine	Not applicable
Severe constipation (due to palonosetron)	Warnings and precaution for use in association with this safety concern are included in section 4.4. Constipation listed in section 4.8. Prescription only medicine	Not applicable
Convulsive events (due to palonosetron)	None proposed Prescription only medicine	Not applicable
Serotonin syndrome (due to palonosetron)	Warnings and precaution for use in association with this safety concern are included in section 4.4 and 4.5. Prescription only medicine	Not applicable
Liver transaminases increase	Listed in section 4.8. Prescription only medicine	Not applicable
Interaction with CYP3A4 inhibitors and inducers (due to netupitant)	Section 4.5 provides information about potential interactions. Prescription only medicine	Not applicable
Interaction with CYP3A4 substrates (due to netupitant)	Section 4.5 provides information about potential interactions. Section 4.2 provides recommendation about the dose reduction of oral dexamethasone. Appropriate posology tables for co-administered dexamethasone are provided in section 5.1. Prescription only medicine	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Phospholipidosis (due to netupitant)	Preclinical safety data are summarised in section 5.3. Prescription only medicine	Not applicable
Interaction with BCRP (due to netupitant)	Section 4.5 provides information about potential interactions. Prescription only medicine	Not applicable
Interaction with glucuronidation isozyme UGT2B7 (due to netupitant)	Section 4.5 provides information about potential interactions. Prescription only medicine	Not applicable
Interaction with P-gp substrates	Section 4.5 provides information about potential interactions. Prescription only medicine	Not applicable
Teratogenic effects	Preclinical safety data are summarised in section 5.3. Prescription only medicine	Not applicable
Effects on pregnancy and lactation	Relevant information is included in section 4.6. Preclinical safety data are summarised in section 5.3. Prescription only medicine	Not applicable
Effects on fertility	Relevant information is included in section 4.6 and section 5.3. Prescription only medicine	Not applicable
Effects in patients with end stage renal disease undergoing haemodialysis	Information about the lack of data is included in section 4.2. Prescription only medicine	Not applicable
Effects in patients with severe hepatic impairment	Information about the limited data available is included in sections 4.2, 4.4 and 5.2. Prescription only medicine	Not applicable
Effects in children	Information about the lack of data is included in section 4.2. Prescription only medicine	Not applicable
Effects in patients aged 75 years or more	Information about the limited data available is included in section 4.2. Prescription only medicine	Not applicable

No additional risk minimisation measures are necessary.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Within a pivotal study with cancer patients receiving cisplatin based regimen (NETU-07-07) the applicant could show for the primary endpoint "proportion of patients with complete response in the overall phase" statistical superiority in favour of netupitant 300 mg plus palonosetron (p=0.004). The difference versus oral palonosetron 0.5 mg alone, which is already marketed in the EU, ranked in the order of 13.2%, which can be considered clinically meaningful. The percentage of patients in the MFAS with delayed CR was 80.1% in the palonosetron alone group and 90.4% in the netupitant 300 mg plus palonosetron group. The contribution of netupitant in the 25-120 hour time period (delayed phase) can therefore be considered demonstrated.

In the second pivotal study (NETU-08-18) evaluating the efficacy of netupitant plus palonosetron versus palonosetron alone in breast cancer patients receiving cyclophosphamide and either doxorubicin or epirubicin the primary efficacy endpoint (percentage of patients with CR in the delayed phase at cycle 1) during the first chemotherapy cycle was higher in the combination group (76.9%) than the palonosetron alone group (69.5%), with a difference from the palonosetron alone group of 7.4% which can be considered a clinically relevant difference. The superiority of netupitant/palonosetron to palonosetron alone was demonstrated (CMH OR: 1.47 with 95% CI from 1.17 to 1.85; p=0.001). 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). In general, the results of the secondary endpoints consistently supported those of the primary and key secondary endpoints for the delayed and overall phases. The multiple-cycle extension phase confirmed these results showing CR rates being 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.

Uncertainty in the knowledge about the beneficial effects.

The pivotal efficacy trial in the MEC setting (NETU-08-18) almost exclusively recruited patents with a diagnosis of breast cancer treated with an anthracycline plus cyclophosphamide (AC). Recently clinical antiemetic guidelines have given special consideration to patient-related risk factors contributing to the emetogenic potential for patients receiving AC-based chemotherapy rather than solely based on the

emetogenicity of the chemotherapy. The young age and female gender of the population that typically received AC-based chemotherapy may put this group at an increased risk for CINV over what AC chemotherapy alone would suggest. Nevertheless it is taken into consideration by the CHMP that AC chemotherapy has previously served as gold standard of the MEC regimen in antiemetic efficacy pivotal trials' being a "worst-case" emetogenicity representative for MEC chemotherapy and this model is considered to be familiar to clinicians for use to prevent CINV induced by MEC. The indication in the prevention of acute and delayed nausea and vomiting in MEC is therefore considered to be appropriately supported by this clinical trial. Nevertheless relevant information for the prescriber about regimen and study population of this trial was included into the SmPC to highlight this extrapolation of efficacy results.

Risks

Unfavourable effects

Common adverse reactions reported with Akynzeo were headache (3.6%), constipation (3.0%) and fatigue (1.2%). None of these events was serious. The frequency of headache, constipation and fatigue was similar (2.9%, 2.5% and 0.7%, respectively) in patients receiving oral palonosetron 0.5 mg alone.

TEAEs most commonly reported were in blood and lymphatic system disorders and skin and subcutaneous tissue disorders and appeared to occur more frequently in comparison to the comparator groups (palonosetron, aprepitant + ondansetron). Overall, the FDC was well tolerated and many adverse reactions are likely to be associated with either the underlying condition or associated cytotoxic therapies. Similarly SAEs and deaths reflected the patient population and concurrent treatment.

Uncertainty in the knowledge about the unfavourable effects

The FDC demonstrated teratogenic potential in animals showing an increased incidence of some foetal malformations. Considering that alternative treatment options are available, the use of Akynzeo during pregnancy was contraindicated and teratogenicity added as a potential risk to the RMP. Furthermore women with childbearing potential must use effective contraception during use of akynzeo as described in the SmPC.

Almost all patients included in the multi-cycle Phase 3 studies were < 75 years (1821/1862, 97.8%) and only a minority (41/1862, 2.2%) was ≥ 75 years of age. Since also hepatic impairment led to a longer half-life of the active substances and since in elderly subjects the exposure to netupitant and palonosetron was increased compared to younger adults, precautionary statements on the limited experience in this patient population were added to the SmPC.

Netupitant increased exposure to docetaxel (increased AUC 0-t by 37% and C_{max} by 50%). Exposure was also increased to a lesser extent for etoposide (AUC_{0-t} 21%, no change in C_{max}). For cyclophosphamide mean increase in exposure ranged from 8 to 14%. As increased chemotherapy toxicities following administration of netupitant cannot be completely ruled out with orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range precautionary statements for possible increased toxicity were added to the product information to monitor patients for increased toxicity of chemotherapeutic agents that are substrates for CYP3A4.

Benefit-risk balance

Importance of favourable and unfavourable effects

Nausea and vomiting are among the side effects associated with cancer treatment. If nausea and vomiting are not controlled in a cancer patient, serious metabolic problems such as fluid and electrolyte balance disturbances and nutritional status deficiencies can develop. Psychological problems associated with nausea and vomiting may include anxiety and depression. In addition, uncontrolled nausea and vomiting may also lead to the decision by the physician to reduce chemotherapy dose intensity or to the wish by the patient to stop potentially beneficial cancer therapy. The applicant showed within a pivotal study with cancer patients receiving HEC clinical meaningful results of the FDC compared to palonosetron alone in the proportion of patients with complete response in the overall and delayed phase. The additional action of netupitant in particular on the delayed phase was demonstrated.

In a second study in patients receiving cyclophosphamide and either doxorubicin or epirubicin the percentage of patients with CR in the delayed phase at cycle 1 was 7.4% higher for the FDC compared to palonosetron alone giving proof of efficacy in MEC. Efficacy results were generaly supported by the seconday enpoints. The multiple-cycle extension phase confirmed these results showing CR rates being consistently higher for the netupitant/palonosetron FDC than for palonosetron alone in each phase up to cycle 6.

Unfavourable effects observed in the clinical trials mainly reflected toxicities of the concurrent chemotherapy and no significant or unexpected adverse reactions related to the FDC were noted.

Benefit-risk balance

The data from the clinical development programme indicate that Akynzeo is effective in reducing the incidence of acute and delayed nausea and vomiting associated with highly- and moderately- emetogenic chemotherapy, notwithstanding the recent changes to the classification AC based chemotherapy regimens. Efficacy was maintained when used in subsequent chemotherapy cycles.

Akynzeo showed a favourable safety profile with unfavourable effects and uncertainties thereof being balanced with the implemented wordings in the product information.

Discussion on the benefit-risk balance

The applicant could demonstrate in two separate pivotal studies efficacy of oral administration of the FDC netupitant 300 mg plus palonosetron 0.5 mg to prevent acute and delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy.

Results of the pivotal studies show a statistical superiority notably in terms of delayed emesis (primary endpoint) of netupitant plus palonosetron over palonosetron alone in cancer patients receiving cisplatin regimen and a combination of anthracyclines plus cyclophosphamide regimen.

Clinical practice guidelines in oncology recommend that patients receiving HEC regimens or MEC regimens with anthracycline combined with cyclophosphamide should be treated with a combination of a 5-HT_3 RA, NK1 RA and a systemic corticosteroid.

The advantages of this fixed-dose combination include an improvement of the benefit/risk due to an addition of therapeutic activity of the substances particularly in the delayed phase of emesis. Simplification of therapy

by decreasing the number of individual dose units to be taken by the patient may simplify therapy and improve patient compliance.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Akynzeo in the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin - based cancer chemotherapy and the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Not applicable

- **Obligation to complete post-authorisation measures**

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that netupitant is qualified as a new active substance.