12 December 2019
EMA/CHMP/17373/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Akynzeo

International non-proprietary name: netupitant / palonosetron
or fosnetupitant / palonosetron

Procedure No. EMEA/H/C/003728/X/0018

Note

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

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List of abbreviations

5-HT3	5 Hydroxytryptamine 3
ADME	absorption, distribution, metabolism and elimination
ASMF	Active Substance Master File = Drug Master File
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the plasma concentration versus time curve
BCRP	breast cancer resistance protein
BE	bioequivalence
BID	twice daily
BMI	body mass index
bpm	beats per minute
CI	confidence interval
CHMP	Committee for Medicinal Products for Human Use
CINV	chemotherapy-induced nausea and vomiting
CL	clearance
CK (MB)	creatine kinase (MB isozyme)
Cmax	maximum concentration
CMH	Cochran Mantel Haenszel
CNS	central nervous system
CPP	Critical process parameter
CQA	Critical Quality Attribute
CR	complete response
CRO	contract research organization
CLCR	creatinine clearance
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTD (eCTD)	Common Technical Document (electronic CTD)
CTZ	chemoreceptor trigger zone
CV	coefficient of variation
CYP	Cytochrome P450
EC	European Commission
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Disodium edetate dihydrate
EMA	European Medicines Agency
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FLIE	Functional Living Index-Emesis
GC	Gas Chromatography
GCP	Good Clinical Practice
GI	gastrointestinal
HEC	highly emetogenic chemotherapy
HPLC	High performance liquid chromatography
HPLC/MS/MS	high-performance liquid chromatography with tandem mass spectrometry
HR	heart rate
HV	healthy volunteer(s)
IC	Ion chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
ITT	intent to treat
IV	intravenous
IV NEPA FDC	IV netupitant-palonosetron fixed dose combination
KF	Karl Fischer titration
LDPE	Low density polyethylene

LLOQ	lower limit of quantification
LVEF	left ventricular ejection fraction
MAA	Marketing Authorization Application
MEC	moderately emetogenic chemotherapy
MedDRA	Medical Dictionary for Regulatory Activities
MFAS	modified full analysis set
MRP2	multidrug resistance associated protein
MS	Mass spectrometry
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NETU	netupitant
NEPA	Netupitant-palonosetron
NK1	neurokinin 1
NMR	Nuclear magnetic resonance
OAT	organic anion transporter
OATP	organic anion-transporting peptide
PALO	palonosetron
PD	pharmacodynamic
PDE	Permitted daily exposure
PET	positron emission tomography
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetics
PNET	fosnetupitant
PO	oral (per os)
PP	per protocol
PR	interval time (in seconds) from the beginning of the P wave to the beginning of the QRS complex
PT	preferred term(s)
PU	Polyurethane
QA	quality assurance
QRS	duration for depolarization of the ventricles
QT	time between the start of the Q wave and the end of the T wave (ECG measurement)
QTcB	QT corrected for heart rate using Bazett's formula
QTcF	QT corrected for heart rate using Fridericia's formula
RA	receptor antagonist
RAUC	ratio of AUC0-inf fosnetupitant/netupitant or metabolite/netupitant
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAWP	Scientific Advice Working Party
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	standard deviation
SOC	System Organ Class
SmPC	Summary of Product Characteristics
t1/2	half life
TEAE	treatment-emergent adverse event
tmax	time of maximum concentration
UV	Ultraviolet
VAS	visual analog scale
Vz	volume of distribution
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

Helsinn Birex Pharmaceuticals Limited submitted on 7 November 2018 extensions of the marketing authorisation.

The MAH applied for an addition of a new route of administration for intravenous use for Akynzeo, associated with a change in active substance (fosnetupitant, a pro-drug of netupitant), new pharmaceutical form (powder for concentrate for solution for infusion) and a new strength (fosnetupitant/palonosetron 235 mg/0.25 mg).

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (1) point a and (2) points (c) (d) (e) - Extensions of marketing authorisations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0344/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0344/2018 was not yet completed as some measures were deferred.

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 MAH 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.

Scientific advice

The MAH received Scientific advice from the CHMP on 28 April 2016 (EMEA/H/SA/2048/2/2016/II). The Scientific advice pertained to clinical aspects:

- The adequacy of the clinical plan to support the fixed dose combination in the proposed indication
- The approach to demonstrating equivalent efficacy and safety of netupitant and its derivative.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Peter Kiely Co-Rapporteur: Alexandre Moreau (Jean-Michel Race)

The application was received by the EMA on	7 November 2018
The procedure started on	29 November 2018

The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 February 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	19 February 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 February 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 March 2019
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	28 March 2019
The MAH submitted the responses to the CHMP consolidated List of Questions on	18 July 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	20 August 2019
The PRAC Rapporteur circulated the Assessment Report on the responses to the List of Questions to all PRAC members on	22 August 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 September 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	19 September 2019
The MAH submitted the responses to the CHMP List of Outstanding Issues on	14 October 2019
The PRAC Rapporteur circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	18 October 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all PRAC members on	30 October 2019
The CHMP agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	14 November 2019
The MAH submitted the responses to the CHMP List of Outstanding Issues on	20 November 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all PRAC members on	26 November 2019
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 on	12 December 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Akynzeo is currently licensed in adults as an oral capsule for the prevention of acute and delayed vomiting associated with both a) moderately and b) highly emetogenic cancer chemotherapy. The current application is a line extension for the intravenous formulation with the same indications.

2.1.2. Epidemiology

Chemotherapy induced nausea and vomiting (CINV) is a common adverse drug reaction and one of the most feared reactions for patients.

2.1.3. Biologic features; Aetiology and pathogenesis

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.

2.1.4. Clinical presentation, diagnosis

If severe enough, CINV can lead to dehydration, malnutrition, impaired renal function, metabolic alkalosis and aspiration pneumonia. Ensuring that patients can be as comfortable as possible during their regimens is crucial. Hence the role of anti-emetics in this clinical setting is preventative and an integrated part of the supportive care of cancer patients. 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-HT3 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-HT3 receptor antagonists (RAs).

2.1.5. Management

Ensuring that patients can be as comfortable as possible during their regimens is crucial. Hence the role of anti-emetics in this clinical setting is preventative and an integrated part of the supportive care of cancer patients. 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.

Patients receiving HEC regimens or MEC regimens with anthracycline combined with cyclophosphamide should be treated with a combination of a 5-HT3 RA, NK1 RA and a systemic corticosteroid.

About the product

Akynzeo is currently licensed in adults as an oral capsule containing palonosetron and netupitant for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy and moderately emetogenic cancer chemotherapy.

The proposed intravenous palonosetron-fosnetupitant fixed combination (Combination or FDC) is composed of palonosetron - (ALOXI) - a registered 5-HT3 RA, and fosnetupitant, a prodrug of netupitant, which is a NK1 receptor antagonist.

Netupitant is practically insoluble in neutral or basic aqueous media and only very slightly soluble at acidic pH. Therefore, formulation or reconstitution into an aqueous solution was not possible. To circumvent this issue, a pro-drug approach was taken, using fosnetupitant which hydrolyzes rapidly following administration, exposing patients to the same therapeutic moiety *in vivo*, i.e. netupitant.

Palonosetron is a well-known potent and selective 5-HT3 receptor antagonist with demonstrated efficacy by the intravenous (I.V.) and oral route for the prevention of nausea and vomiting associated with cancer therapy.

The oral hard capsules formulation of Akynzeo was approved in the EU through the Centralised Procedure on 27th May 2015 (EU/1/15/1001/001).

Type of Application and aspects on development

The MAH received Scientific advice from the CHMP on 28 April 2016 (EMEA/H/SA/2048/2/2016/II) as described above.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for concentrate for solution for infusion containing 0.25 mg palonosetron (as hydrochloride salt) and 235 mg of fosnetupitant (as chloride hydrochloride salt).

Other ingredients are: edetate disodium dihydrate, mannitol, sodium hydroxide, hydrochloric acid and water for injections.

The product is available in single-dose flint glass vials with rubber stoppers and aluminium cap seals as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Palonosetron

This application is a line extension and contains the same active substance, palonosetron hydrochloride, used to manufacture the already-approved hard capsules. The information presented by the applicant in the ASMF and full dossier for palonosetron hydrochloride is the same as was already assessed in the original submission, and subsequent variations. The active substance is sourced from the same manufacturer, manufactured with the same process and released in accordance with the same active substance specifications.

Fosnetupitant Chloride Hydrochloride

The original dossier for the hard capsules contains netupitant as the second active substance. However, netupitant is only very slightly soluble in water and thus, not suitable for administration in aqueous solution. Therefore, the applicant adopted a pro-drug approach, with the much more soluble fosnetupitant chloride hydrochloride as the second active substance in the powder for concentrate for solution for infusion. The applicant submitted data demonstrating that in vivo, fosnetupitant is rapidly metabolised to netupitant, thus exposing patients to the same therapeutic moiety. As a result, a new ASMF for fosnetupitant chloride hydrochloride was submitted with the line extension.

General information

The chemical name of fosnetupitant chloride hydrochloride is 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-*N*,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium chloride hydrochloride is corresponding to the molecular formula $C_{31}H_{37}Cl_2N_4O_5P$. It has a relative molecular mass of 761.53 g/mol and the following structure:

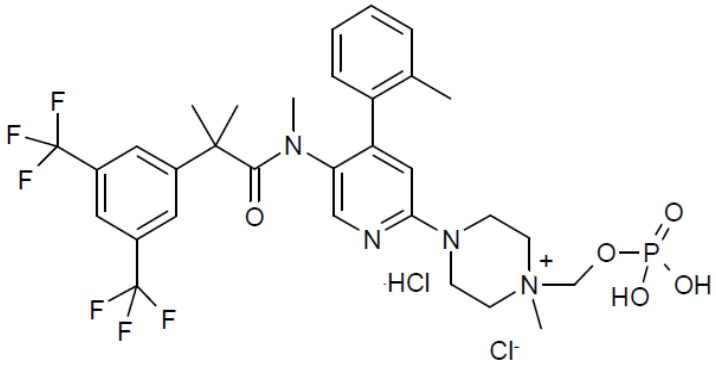


Figure 1: Active substance structure

The chemical structure of fosnetupitant chloride hydrochloride was elucidated by a combination of ^{1}H and ^{13}C NMR spectroscopy, infrared spectroscopy, mass spectrometry and elemental analysis. The active substance is achiral.

The solid state properties of the active substance were measured by gravimetric vapour sorption and x-ray powder diffraction (XRPD). It is a white to off-white to yellowish, crystalline, hygroscopic solid. Three polymorphic forms have been identified following extensive screening, requiring isolation from different solvent mixtures. Fosnetupitant chloride hydrochloride is always isolated as form I following the commercial manufacturing process. Since it is dissolved and lyophilised during finished product manufacture, particle size and polymorphic form are not considered critical quality attributes (CQAs) of the active substance and are not included in the specification.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. Five different manufacturers are responsible for various steps in the manufacturing process.

Fosnetupitant chloride hydrochloride is synthesized in ten main steps using well defined starting materials with acceptable specifications. The synthesis is the same as in the netupitant ASMF but with the addition of the steps to add the phosphonooxymethyl group. Initially, the applicant proposed to remove some of the earlier steps from the fosnetupitant ASMF. However, these were reinstated during the procedure to resolve a CHMP major objection.

The synthetic process uses a convergent strategy with the phosphate group being introduced via a third starting material. During this part of the synthesis, a mutagenic intermediate (05-PNET), which can dimerise to form a second mutagenic substance (05-PNET.i1), is employed. The process is able to purge these impurities but since they are mutagenic and used late in the process, they are nonetheless controlled in the active substance specification.

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

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. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in double low density polyethylene (LDPE) bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended. A desiccant unit is placed within the outer bag and this is further stored within a heat-sealed Mylar/aluminium bag, within a metal drum.

Specification

The active substance specification includes tests for appearance (visual), identity (IR, HPLC), assay (HPLC), chloride content (titration), impurities (HPLC), purity (HPLC), genotoxic impurities (HPLC-MS and IC), residual solvents and base (GC), water content (KF), iodide content (IC), ammonium content (IC), and microbiology (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. Fosnetupitant is a prodrug of the principal impurity, 14-NETU, so from a toxicological viewpoint, its presence in the finished product has no impact. However, given its low solubility, an upper limit of 1% has been set in order to avoid precipitation problems during formulation and reconstitution. Limits for iodide and ammonium have been adequately justified. The limits for chloromethyl chlorosulfate, and two other genotoxic impurities have been set in line with the ICH M7 guidance. Their tests and limits were added to the dossier during the procedure in response to a CHMP major objection, on the basis that class 1 and class 2 mutagenic impurities should be controlled by specification. Fosnetupitant chloride hydrochloride is always isolated as form I, controlled by the crystallisation solvent, so no test for polymorphic form is deemed necessary. Similarly, particle size doesn’t need to be controlled so no test is needed. Based on the result of the risk assessment according to ICH Q3D (see finished product section) and subsequent testing where no metal was detected above 30% of its permitted daily exposure (PDE), a test for elemental impurities is not mandated.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 9 batches ranging from pilot to production scale of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 6 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (5±3 ºC), 24 months under intermediate 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, chloride content, purity, assay, related substances, polymorphic form, and microbiology (annually). The analytical methods used were the same as for release. All parameters remained within specification throughout the study under each set of conditions. The only obvious trend was a small increase in one impurity which remained well below its qualified limit.

Photostability testing following the ICH guideline Q1B was performed on 1 batch, indicating that fosnetupitant is photosensitive.

Forced degradation studies were also carried out in solid state (high temperature and/or humidity) and in aqueous solution (acid, base, peroxide, variable temperature). In the solid phase, the higher the temperature and humidity, the more degradation was observed. In solution, degradation was observed under all conditions, more so under acidic and neutral conditions. Peak purity testing was conducted by diode array on the main active substance peak, which was spectrally pure, thus indicating that the HPLC method is stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 30 months at 5±3 ºC in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is a lyophilised powder intended for reconstitution and parenteral administration. Each vial contains 235 mg fosnetupitant (260 mg of fosnetupitant chloride hydrochloride) and 0.25 mg Palonosetron (0.28 mg of palonosetron hydrochloride).

The current application is a line extension of the already-authorised Azynzeo hard capsules, containing 300 mg netupitant and 0.5 mg Palonosetron. The aim of development was an injectable formulation. Netupitant is practically insoluble in neutral or basic aqueous media and only very slightly soluble at acidic pH. Therefore, formulation or reconstitution into an aqueous solution was not possible. To circumvent this issue, a pro-drug approach was taken, with fosnetupitant as active substance instead of netupitant. Fosnetupitant hydrolyzes rapidly following administration, exposing patients to the same therapeutic moiety *in vivo*, i.e. netupitant.

In order to allow rapid reconstitution, development of a lyophilized powder was proposed. This also keeps all excipients and both active substances in the solid phase and thus, minimises the potential for incompatibilities. Given the instability of fosnetupitant with regards to hydrolysis, an injectable aqueous solution was initially thought to be too difficult to develop.

A suitable formulation was developed, taking into account the stability and physicochemical properties of the active substances. Adequate controls were developed during manufacturing and a suitable container closure system was selected to allow a stable formulation in which fosnetupitant chloride hydrochloride is sufficiently soluble for an injectable solution. Palonosetron is freely soluble in aqueous media, and sufficiently stable, considering the process controls in place.

Fosnetupitant contains a phosphate group as part of the pro-drug section. Phosphate salts with divalent cations, such as Ca^{2+} and Mg^{2+} found in the commonly used reconstitution medium, lactated Ringer's solution, are known to be insoluble. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

Fosnetupitant is sensitive to heat as demonstrated by attempts to sterilise the bulk solution prior to lyophilisation. Furthermore, lyophilised powders don't typically respond well to heat. Therefore, terminal sterilisation was not considered viable. Sterile filtration followed by aseptic processing was therefore selected as the best method for ensuring sterility. Based on the argumentation and data provided, this is considered justified. Filter integrity has been checked, as well as compatibility and bacterial retention capability which were all satisfactory. An extractables study identified several compounds, but based on toxicological evaluation and the levels at which they are present, no risk to patients can be reasonably considered.

The lyophilisation process was optimised in terms of temperature, pressure and duration in order to minimise degradation and ensure an elegant cake is produced, as well as preventing mannitol crystallising as a hemi-hydrate which would increase the amount of water present in the resultant powder. A 3% overfill is added to each vial to allow withdrawal and administration of the full dose as per the label claim.

The recommended reconstitution solvents are 5% glucose solution and 0.9% saline solution. Reconstitution in these media gives a final pH of 7-9 which is slightly basic, as required to prevent fosnetupitant degradation, but also within the acceptable range for parenteral administration. Solutions were demonstrated to be stable for up to 24 hrs without any observed precipitation. Osmolality was also within the desired range. Furthermore, the finished product was demonstrated to be stable under standard clinical setting when exposed to ambient temperature and artificial light, for up to 24 hours.

Compatibility with plastic materials associated with common delivery kit was also investigated. Samples reconstituted in either 5% glucose or 0.9% saline were exposed to equipment made from various common plastic administration set materials. Samples were further exposed to artificial light. Samples were tested for colour and clarity of solution, pH and assay and impurities of each active substance. No anomalous results were observed for any of the samples except for new impurities in the polyurethane (PU) samples. Further investigation identified leachables present in reconstituted solutions exposed to PU for 1 day. However, they are also released in smaller quantity in glucose or saline solutions without the finished product. Moreover, it was argued that the contact time of the reconstituted product with these materials will be much shorter (a few minutes) in clinical practice and as such, no risk to patients is expected. Based on the levels of impurities present, this was accepted by CHMP.

The primary packaging is flint glass vials with perfluoropolymer-coated rubber stoppers and aluminium cap seals. The materials comply 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. As the finished product is photosensitive, the vials are stored in an outer carton which offers suitable protection.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: compounding, bioburden-reducing and sterile filtrations, filling into vials and partial stoppering, lyophilisation and crimping. The process is considered to be a non-standard manufacturing process due to the aseptic steps.

Major steps of the manufacturing process have been validated on four production scale batches of finished product. The following activities were validated and relevant reports provided: equipment and container closure sterilisation, weighing and dispensing of active substance and excipients, compounding, bioburden-reducing filtration, sterilising filtration, filling and stoppering, lyophilisation, crimping and visual inspection. Media fill studies were conducted and used to assign validated hold times at various points and these have been acceptably justified. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Critical process parameters (CPPs) have been defined – in particular, those applied to the sterilising filtration and lyophilisation steps have been thoroughly discussed. The IPCs are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (powder, container and reconstituted solution (visual), reconstitution time, fosnetupitant identity (HPLC, UV), assay (HPLC) and impurities (HPLC), palonosetron identity (HPLC, UV), assay (HPLC) and impurities (HLPC), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.), pH of reconstituted solution (Ph. Eur.), sub-visible particles (Ph. Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.). The container closure integrity check (visual) is performed as an IPC.

The limits for impurities have been adequately justified based on batch data. The limits for impurities is justified in that netupitant is the therapeutic moiety which is limited such that it does not cause precipitation and the others are pro-drugs which also hydrolys *in vivo*. Palonosetron is present in a much lower amount than fosnetupitant so the higher impurity limits are justified.

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data was provided demonstrating that each relevant elemental impurity was not detected above 30% of its PDE. Based on the risk assessment and batch data, it was concluded that it is not necessary to include any elemental impurity controls.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for three production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from three production scale batches of finished product stored for up to 24 months under long term conditions (5±3 ºC) and for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance (powder, container and reconstituted solution), reconstitution time, fosnetupitant assay and impurities, palonosetron assay and impurities, water content, pH of reconstituted solution, sub-visible particles, sterility, bacterial endotoxins and container closure integrity. The analytical procedures used are stability indicating. No significant changes were observed to any of the measured parameters, and for the most part, no obvious trends were observed. There is a slight increase in netupitant formation and water content, though both are well within the specification limits.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples were stored either in the primary vial, the vial within the secondary carton or the vial wrapped in aluminium foil as a dark control. Degradation was observed in the vial alone, but not in either of the other sample formats. Therefore, the finished product is considered to be photosensitive but the secondary carton provides adequate protection.

An in-use stability study was conducted on samples following reconstitution in either 5% glucose or 0.9% saline, which are indicated to be the solvents of choice in the SmPC. Samples were stored for up to 24 hrs without any significant degradation or precipitation. Furthermore, a microbiological challenge study was performed, indicating that the diluted product has bacteriostatic or bactericidal properties. As a result, the reconstituted product is deemed stable for up to 24 hrs at 25 °C. The following text is included in section 6.3 of the SmPC:

"*Store the reconstituted and diluted solution below 25 °C. The product should be diluted immediately after reconstitution. Chemical, physical and microbiological in-use stability after reconstitution and dilution has been demonstrated for 24 hours at 25 °C. Other in-use storage times and conditions are the responsibility of the user*."

Based on available stability data, the proposed shelf-life of 30 months in a refrigerator (2-8 °C), with the vial in the outer carton to protect from light, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

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. The major objections raised in relation to the starting materials and mutagenic impurities have been satisfactorily addressed.

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.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Oral AKynzeo is a fixed combination of 300 mg netupitant, a substance P/neurokinin 1 (NK1) receptor antagonist, and 0.5 mg palonosetron, a serotonin-3 (5-HT3) receptor antagonist. The characteristics of the drugs supported the development as a fixed-dose combination since their mechanism of action is exerted on different neuropathways (5-HT3 receptors and NK1 receptors) and both drugs show a

similar pharmacokinetic profile in terms of extended plasma half-life representing a rational and clinically-appropriate choice of antiemetic drugs.

Fosnetupitant is the netupitant prodrug which has been developed to improve the solubility of netupitant and obtain a viable IV formulation. As fosnetupitant is rapidly converted to netupitant in vivo following IV administration, the pharmacology of fosnetupitant is mainly attributable to netupitant. The applicant has performed a bridging non-clinical development program for fosnetupitant and for fosnetupitant in combination with palonosetron.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Fosnetupitant and netupitant binding profiles on various neurotransmitters/enzymes were characterized. Netupitant is classified as high affinity NK1 receptor antagonist (pKi 9.0) and has approximately 1000-fold selectivity when compared to hNK2 and hNK3 receptors.

The investigations on fosnetupitant revealed that it conferred more than 50% inhibition on the following receptor binding ligand activities: hNK1 agonist ligand (IC50 < 0.28nM), hNK3 antagonist and agonist ligands (IC50 = 0.8 µM and IC50 =0.42 µM, respectively), h5HT6 agonist (IC50 =6.3 µM), Ca++ channel (diltiazem site) antagonist (IC50 =2 µM) and Ca++ channel (verapamil site) antagonist (IC50 =5.4 µM).

In vitro pharmacology of fosnetupitant was provided as published literature Ruzza et al., (2015). Considering that the applicant considers that the pharmacology of fosnetupitant is entirely attributable to its conversion to netupitant, the differences observed in substance P calcium mobilisation are interesting. Fosnetupitant possesses a three-fold higher affinity for the NK1 receptor and faster kinetics of interaction than netupitant. However, it is noted that different pharmacological properties can be attributed to fosnetupitant in vitro and in vivo. In vivo it appears that rapid conversion to netupitant occurs. Therefore, the in vivo pharmacological effects of fosnetupitant are likely due and attributable to netupitant.

In vivo, netupitant and fosnetupitant were able to counteract SP induced nociceptive behaviour with superimposable efficacy and potency. In addition, based on the short half-life measured for fosnetupitant in mice (a few minutes), it can be accepted that the pharmacological effects of Pronetupitant can be interpreted as due to its conversion to Netupitant. Therefore, the studies presented for Netupitant alone in the initial approved MAA dossier for Akynzeo are also relevant for Pronetupitant.

The in vivo effects of fosnetupitant and netupitant were evaluated in the scratching, biting, andlicking responses elicited by Substance P (SP) injected i.t. in mice. The two compounds at 10 and 1 but not at 0.1 mg/kg were able to significantly counteract the nociceptive behaviour induced by SP in a similar and dose dependent manner. Therefore, the two compounds exhibited a similar efficacy and potency in this test.

Due to the rapid conversion of fosnetupitant to netupitant (T1/2 was less than 12 minutes and the netupitant plasma peak concentration was reached in less than 3 min (Tmax), see 2.6.4 Pharmacokinetics Written Summary) and to fact that the applicant considers the pharmacological effects of fosnetupitant can be entirely interpreted as due to its conversion to netupitant study in vivo studies in emesis models were not conducted with fosnetupitant or the fosnetupitant + palonosetron IV fixed dose combination. This is accepted.

Secondary pharmacodynamic studies

One study was carried out using the combination of fosnetupitant and palonosetron, to investigate the possible effects of the combination on cardiovascular function. In the telemetered dog study the intravenous administration of the combination (fosnetupitant + palonosetron) for 2 weeks did not induce any effect on arterial blood pressure, heart rate and body temperature. However, alterations in atrio-ventricular conduction, ventricular depolarisation and repolarisation characterised by increases in PR, PQ, QT interval and QRS complex durations, ST segment, QT corrected QTc and QT shift were observed in the high-dose group (13.2/6 mg/kg/day). There were no effects on QT at low (1.32/1 mg/kg/day) and mid-dose (3.95/3 mg/kg/day) levels. Changes in QT and QRS complex were attributed to the main netupitant metabolite, M1, and it was noted that plasma exposure of M1 is higher in dog when compared to human. Therefore, these findings may not directly correlate with human toxicity.

Safety pharmacology programme

Fosnetupitant did not induce changes on behavioural, neurological or autonomic functions in rats at doses up to 39.47 mg/kg. Treatment with fosnetupitant at all dose levels did not produce any proconvulsant or anticonvulsant activity in the rat in the metrazol test.

Fosnetupitant up to 30 μM possesses no liability for prolonging QT in the hERG expressed in HEK cells. Intravenous administration of fosnetupitant at doses of 1.32, 3.95 and 13.2 mg/kg once daily for 2 consecutive weeks did not induce any alteration of toxicological significance on haemodynamic and electrocardiographic parameters of the conscious dog.

Alterations observed in some of renal function parameters could be considered transient and of no toxicological relevance to renal function. Fosnetupitant affected GI motility at the high dose (79 mg/kg IV) in a similar manner to the reference compound, atropine. This is unlikely to be of biological relevance considering the expected therapeutic dose in human (235 mg IV). There were no changes of toxicological significance in respiratory parameters.

Studies investigating the abuse liability of netupitant and palonosetron were presented. Given that fosnetupitant is rapidly converted to netupitant and that the main pharmacological action of fosnetupitant is attributed to netupitant these studies can be accepted in support of the lack of abuse liability of the fosnetupitant/palonosetron combination.

One study was carried out using the combination of fosnetupitant and palonosetron, to investigate the possible effects of the combination on cardiovascular function. In the telemetered dog study the intravenous administration of the combination (fosnetupitant + palonosetron) for 2 weeks did not induce any effect on arterial blood pressure, heart rate and body temperature. However, alterations in atrio-ventricular conduction, ventricular depolarisation and repolarisation characterised by increases in PR, PQ, QT interval and QRS complex durations, ST segment, QT corrected QTc and QT shift were observed in the high-dose group (13.2/6 mg/kg/day). There were no effects on QT at low (1.32/1 mg/kg/day) and mid-dose (3.95/3 mg/kg/day) levels. Changes in QT and QRS complex were attributed to the main netupitant metabolite, M1, and it was noted that plasma exposure of M1 is higher in dog when compared to human. Therefore, these findings may not directly correlate with human toxicity.

2.3.3. Pharmacokinetics

The pharmacokinetics of fosnetupitant and fosnetupitant + palonosetron IV fixed dose combination (IV NEPA FDC), were characterised consistent with EU Guideline EMEA/CHMP/SWP/258498/2005. Netupitant studies have been submitted for the hard capsules, and previously assessed.

The pharmacokinetics of fosnetupitant was investigated in rat, dog and monkey. Studies were conducted to determine absorption, metabolism, distribution and excretion of fosnetupitant. Pharmacokinetic studies following IV single dose administration in preclinical species indicated that fosnetupitant was rapidly and quantitatively converted to netupitant with no excretion of unchanged prodrug in urine and faeces.

The applicant has developed LC/MS/MS, UPLC-MS-MS and HPLC methods to determine the concentration of fosnetupitant, netupitant and its major metabolites M1, M2, and M3 in rat, monkey, dog and rabbit plasma, and dog heart and rat brain. The lower limit of quantification of fosnetupitant is 3 ng/mL in rat, dog, monkey and rabbit plasma and the lower limit of quantification of netupitant is 5 ng/mL in rat, dog, monkey and rabbit plasma

In all studies fosnetupitant appears to be rapidly converted to netupitant, showing Cmax at the first sampling time, as fosnetupitant. Netupitant was detected in plasma up to 168 hours (median tlast) and its AUC, about 200-fold higher than that of fosnetupitant, represents the 34% of drug related material in plasma exposure to netupitant and its main metabolites are comparable with equivalent doses of netupitant and fosnetupitant.

The human plasma protein binding of fosnetupitant was 92.14% at 1 µM and 94.86% at 10 µM.. The mean blood to plasma concentration ratio in humans was in the range 0.4-0.6 (mean concentration ratios of all the concentrations tested), suggesting that fosnetupitant was mainly distributed in plasma than in the red blood cells. However, no studies on protein binding with rat and dog plasma have been reported for fosnetupitant. In preliminary experiments, following a single intravenous administration in rats and dogs, fosnetupitant was rapidly converted to the active drug, netupitant: the low half-life was estimated at 28 min in rats and 12 min in dogs. Therefore, in preliminary experiments performed, fosnetupitant, incubated in rat plasma, was degraded too quickly to make an accurate measurement of plasma protein binding. In rats, plasma concentrations of netupitant (14-Netu), metabolites M1, M2 and M3 were almost similar in animals receiving the pro-drug (fosnetupitant) and in those receiving the active drug (netupitant), thereby indicating the rapid hydrolysis of fosnetupitant to netupitant. A large netupitant concentration difference was detected in the brain, during the first 8 hours after administration, between groups dosed with fosnetupitant and netupitant. The Cmax of netupitant observed in animals receiving fosnetupitant was approximately 1/10 with respect to the animals treated with netupitant. The brain concentration of fosnetupitant was near the low limit of quantification of the analytical method and the brain/plasma concentration ratio at Tmax was 0.045%, which showed the low permeability blood brain barrier to pro-drug. Only metabolites M1 and M3 were detected in rat brain.

Fosnetupitant and metabolite M2 were not detectable in the heart in dog studies. Netupitant and metabolites M1 and M3 were measurable in the heart. Metabolite M1 demonstrated accumulation, with the ratio between heart concentrations on D30 and plasma concentration 48h following the last administration ranging from 4.5 to 8.3. M1 was almost completely eliminated by the end of the treatment free period.

The rat brain concentration of fosnetupitant, after single dose administration, was near the low limit of quantification of the analytical method and it was detectable only in the first minutes after administration, showing the low blood brain barrier permeability to prodrug. Only netupitant and its

metabolites M1 and M3 were detected in rat brain and dog heart tissues after single and multiple day administration of fosnetupitant.

In in vitro studies, rapid hydrolysis of fosnetupitant with subsequent release of netupitant was demonstrated in human liver, lung, kidney and intestine S9 fraction in the presence and in the absence of NADPH. Since conversion of fosnetupitant to netupitant can occur in the absence of NADPH, it is not thought to involve the CYP450 family of enzymes.

Netupitant is then extensively metabolized to three major active metabolites: desmethyl derivative, M1; N-oxide derivative, M2; OH-methyl derivative, M3. In preclinical species administered with fosnetupitant, rat and dog, plasma exposure to netupitant and to its three main circulating metabolites, M1, M2 and M3, were comparable with the exposures measured after direct intravenous or oral administration of equivalent doses of netupitant.

In both rat and dog, excretion was predominantly by the faecal route, with over 80% of the administered dose recovered in faeces. Less than 0.6% and 1.2% of dose was recovered in the urine in rats and dogs respectively. In dogs administered fosnetupitant 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 IV dosing, with 10% of the dose remaining in the carcass.

The CYP450 inhibition potential of fosnetupitant was evaluated in human liver microsomes (HLM). In the range of concentrations tested (0.3-1000 µM), fosnetupitant was a moderate to weak inhibitor of CYP2C9 (IC50 = 27.9 µM), CYP2C19 (IC50 = 46.1 µM), CYP2C8 (IC50 = 56.7 µM), CYP2B6 (IC50 = 106.8 µM), CYP1A2 (IC50 = 208.4 µM), CYP2D6 (IC50 = 217.2 µM) andCYP3A4 (IC50 = 196.8 µM and 299.2 with midazolam and testosterone substrates, respectively).

In addition, fosnetupitant did not show TDI potential of CYP3A4 and CYP2C9 in the concentrations range from 0.3 to 300 µM, up to 30 minutes of pre-incubation time.

Possible interactions of fosnetupitant with human ABC (efflux) transporters and the human uptake (SLC) transporters were studied in vitro. Fosnetupitant was a moderate inhibitor of OATP1B3 (IC50 = 17.34 µM), OATP1B1 (IC50 = 19.01 µM), MATE1 (IC50 = 29.48 µM), MDR1 (47% Inh. at 50 µM) and a substrate for the uptake transporters OATP1B1 and OATP1B3.

However, given that fosnetupitant is rapidly metabolised to netupitant in vivo interactions between netupitant and CYP450 enzymes or transporters may be more clinically relevant. Netupitant in vitro and in vivo DDI studies have been performed as part of the AKYNZEO® hard capsules registration program.

2.3.4. Toxicology

Toxicology studies focused on the characterization of fosnetupitant and fosnetupitant + palonosetron IV fixed dose combination (IV NEPA FDC), consistent with EU Guideline EMEA/CHMP/SWP/258498/2005 on non-clinical development of fixed combination medicinal product.

Toxicology studies with netupitant alone and as fixed combination with palonosetron were previously assessed during the initial MAA procedure.

Single dose toxicity

Single dose toxicology studies were not carried out. A variety of repeat dose toxicity studies were carried out by the applicant for fosnetupitant (non-pivotal and pivotal) and fosnetupitant and palonestran in combination (pivotal).

Repeat Dose Toxicity

The main toxicity findings in rats was mild centrilobular liver hypertrophy for males and females treated with the high dose. In the 4-week study these changes consisted of dose-related centrilobular hypertrophy associated with increased cytoplasmic eosinophilia, of moderate degree in the high dose group males and of mild degree in the high dose group females and mid-dose group males. This change was correlated with trend of increased liver weight. Liver weights resumed to control levels after the recovery period. No phospholipidosis was observed in toxicology studies in rat with fosnetupitant up to 39.47 mg/kg/day (equivalent to 30 mg/kg/day of netupitant). Absence of phospholipidosis signs was also noted in a 2-week and 4-week studies in dogs administered up to 13.16 mg/kg/day (10 mg/kg/day of netupitant).

In dogs treated with fosnetupitant treatment-related changes were noted in the thymus of three males and one female of the high-dose group following microscopic examination, which consisted of mild atrophy of the thymic cortex, characterised by depletion of lymphocytes. No treatment related changes were noted after the recovery period.

In the pivotal combination study CNS effects were seen after repeated treatment and were likely due to the high dose of palonosetron. Intravenous administration of fosnetupitant- palonosetron combination resulted in adverse effects at the injections sites at the high-dose combination and in changes in cardiovascular parameters at the mid and high dose combination. Fosnetupitant did not show any evidence of QT prolongation in in-vitro (hERG channel study) and in-vivo studies in dogs. In a 2-week and 4-week toxicology study in dogs and in the 2-week telemetered dog study QT prolongation was not observed up to 13.16 mg/kg. The QT prolongation observed with the IV combination fosnetupitant/palonosetron at high doses was seen also in oral combination (netupitant/palonosetron) but only after repeated administration.

TK data from two IV fosnetupitant toxicology studies involving rats and dogs in which fosnetupitant was administered IV for 14 days were presented by the applicant. For IV fosnetupitant and oral netupitant, toxicokinetic data from these rat and dog studies demonstrate that substantial netupitant exposure was achieved. Based on the rapid conversion the T1/2 was less than 12 minutes and on the netupitant plasma peak concentration was reached in less than 3 min (Tmax), the toxicology profile of fosnetupitant can be attribute mainly to netupitant.

No phospholipidosis was observed in toxicology studies in rat with fosnetupitant up to 39.47 mg/kg/day (equivalent to 30 mg/kg/day of netupitant). Absence of phospholipidosis signs was also noted in a 2-week and 4-week studies in dogs administered up to 13.16 mg/kg/day (10 mg/kg/day of netupitant).

Genotoxicity

The genotoxicity of fosnetupitant has been studied with respect to gene mutations in bacteria and mammalian cells and chromosomal aberrations in-vitro and in-vivo. Additionally, tests of primary DNA damage in-vitro and malignant cell transformation have been conducted. Fosnetupitant does not show mutagenic activity or potential for chromosomal damage. It does not induce structural chromosomal aberrations in human lymphocytes, and when administered to rats by intravenous injection, does not induce micronuclei in polychromatic erythrocytes.

Various genotoxic impurities have also been tested for mutagenic potential. Chloromethyl chlorosulphate, 05-PNET and 05-PNET.i1 are considered to be mutagenic and therefore in line with ICH M7 their presence in batches must be documented.

Carcinogenicity

No carcinogenicity studies were carried out and this is considered acceptable given the short duration of treatment.

Reproduction toxicity

Fosnetupitant had no relevant effects on fertility up to 39.47 mg/kg/day. Studies conducted in order to assess the potential for embryofoetal developmental toxicity were carried out in both rats and rabbits. Effects in embryofetal development were observed mainly at high dose level. In the rat studies no malformations were detected in the foetuses of the low and mid-dose groups (3.95 and 13.16 mg/kg/day respectively). One foetus with malformation (hindlimb malrotated) and one dead foetus were observed in the high dose group. Skeletal examination of foetuses demonstrated that no ossification of pubis was detected in 6 foetuses of the high dose group (39.47 mg/kg/day).

For studies in rabbits there were no treatment-related effects for the skeletal examination of fetuses at any dose level. A slight increase in intrauterine deaths was recorded in treated groups with statistically significance in the mid- and high dose groups (6.25 and 12.5 mg/kg/day respectively).

In the pre and post-natal development study the main effect was a decrease in body weight for the females of F0 generation receiving the high dose (39.47 mg/kg/day). Reduction in body weight was also observed for the F1 generation of the high dose group. The mid dosage of 13.16 mg/kg/day was considered the NOAEL for dams and pups of F0 and F1 generations, in terms of development of the conceptus and the offspring. No effects were noted in the reproductive performance of F1 generation. For the F2 there were no relevant effects, only a delay the pre-weaning test (startle response to sound) was noted in the high dose group.

The applicant attributes the toxicology profile of fosnetupitant to netupitant, due to the rapid conversion of fosnetupitant to netupitant, however there are differences in the outcome of the EFD studies of fosnetupitant compared to the studies carried out for netupitant:

- Netupitant; cleft palate occurred, in rats, in three foetuses from a single litter at 100 mg/kg, and in rabbits in the pilot study at 30 mg/kg.
- Fosnetupitant; In rat studies at skeletal examination of foetuses, no ossification of pubis was detected in 6 foetuses of the high dose group distributed in 3 different litters. In rabbits an increase in intrauterine deaths was recorded in treated groups with statistically significance in the mid- and high dose groups (6.25 and 12.5 mg/kg/day respectively).

Although there were apparent differences in the outcome of the EFD studies of fosnetupitant compared to the studies carried out with netupitant, the relevant findings were mainly related to the bone formation (cleft palate and ossification of pubis). As demonstrated in the literature, the absence of Substance P results in a slight reduction of bone resorption rate but concomitantly in a critical reduction of bone formation and mineralization rate. Therefore, the absence of substance P could be relevant during bone formation and therefore have an impact on embryo-foetal development. Effects related to bone formation, probably as a result of effects on Substance P, are common to both netupitant and fosnetupitant, and these manifested in different ways in the different studies.

Local tolerance

Local tolerance studies conducted in order to assess the tolerance to fosnetupitant in animal models showed a good tolerability of the intravenous combination.

Other toxicity studies

Fosnetupitant was not antigenic in guinea pigs. Fosnetupitant is classified as phototoxic. Even though the results achieved with fosnetupitant and netupitant were very similar, netupitant was classed as

non-phototoxic in a previous assessment. This is due to changes in the criteria for classification introduced in the latest guideline for phototoxicity (OECD guideline 432).

2.3.5. Ecotoxicity/environmental risk assessment

The available data suggest that the fixed dose combination of fosnetupitant/palonestron is not expected to pose a risk to the environment.

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

- determination of a log Kow for fosnetupitant using method OECD 123

2.3.6. Discussion on non-clinical aspects

Non-clinical studies indicate that palonosetron, only at very high concentrations, may block ion channels involved in ventricular de- and re-polarisation and prolong action potential duration. Degeneration of seminiferous epithelium was associated with palonosetron following a one month oral repeat dose toxicity study in rats. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Only limited data from animal studies are available regarding the placental transfer (see SmPC section 4.6).

Palonosetron is not mutagenic. High doses of palonosetron (each dose causing at least 15 times the human therapeutic exposure) 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 of the high doses employed and since the medicinal product is intended for single application in humans, these findings are not considered relevant for clinical use.

Non-clinical studies indicate that netupitant and its metabolites and the combination with palonosetron only at very high concentrations may block ion channels involved in ventricular de- and re-polarisation and prolong action potential duration. Reproductive studies in animals with netupitant do not indicate direct or indirect harmful effects with respect to fertility, parturition or postnatal development. An increased incidence of positional foetal abnormalities of the limbs and paws, fused sternebrae and agenesis of accessory lung lobe were observed following daily administration of netupitant in rabbits at 10 mg/kg/day and higher during the period of organogenesis. In a pilot dose range finding study in rabbits, cleft palate, microphtalmia and aphakia were observed in four foetuses from one litter in the 30 mg/kg/day group. The relevance of these findings in humans is unknown. No data from animal studies with netupitant are available regarding placental transfer and lactation. Netupitant is not mutagenic.

Effects in non-clinical studies based on safety pharmacology and single and repeated dose toxicity were observed only at exposures considered in excess of the maximum human exposure, indicating little relevance to clinical use. Phospholipidosis (foamy macrophages) has been observed with the administration of netupitant after repeated administration in rats and dogs. The effects were reversible or partially reversible after the recovery period. The significance of these findings in humans is unknown.

The pharmacology of fosnetupitant has been studied in in vitro and in vivo models to characterize its activity as an NK1 receptor antagonist. Safety pharmacology studies were also conducted.

Fosnetupitant and netupitant binding profiles on various neurotransmitters/enzymes were characterized. Netupitant is classified as high affinity NK1 receptor antagonist (pKi 9.0) and has approximately 1000-fold selectivity when compared to hNK2 and hNK3 receptors.

In vitro, fosnetupitant possesses a three-fold higher affinity for the NK1 receptor and faster kinetics of interaction than netupitant. This may prevent conversion of a portion of fosnetupitant to netupitant. In CHO cells fosnetupitant appears to be more potent than netupitant at every time point tested when both are used at 100 nM (Ruzza et al., 2015). However, different pharmacological properties can be attributed to fosnetupitant in vitro and in vivo. In vivo it appears that rapid conversion to netupitant occurs. Therefore, the in vivo pharmacological effects of fosnetupitant are likely due and attributable to netupitant.

The in vivo effects of fosnetupitant and netupitant were evaluated in the scratching, biting, and licking responses elicited by Substance P (SP) injected i.t. in mice. Therefore, the pharmacological effects of fosnetupitant can be generally interpreted as due to its conversion to netupitant

Safety pharmacology studies and abuse liability studies were also conducted. No effects on CNS and on respiratory functions have been observed with fosnetupitant. Fosnetupitant up to 30 μM possesses no liability for prolonging QT in the hERG expressed in HEK cells. In a 2-week and 4-week toxicology study in dogs and in the 2-week telemetered dog study QT prolongation was not observed up to 13.16 mg/kg.

In rat, dog and monkey, after intravenous administration, fosnetupitant was quickly converted to netupitant. Netupitant was then extensively metabolized to three major active metabolites: desmethyl derivative, M1; N-oxide derivative, M2; OH-methyl derivative, M3. The administered dose of fosnetupitant was almost quantitatively converted to netupitant that was eliminated by biliary excretion and hepatic metabolism (mainly mediated by CYP3A and lesser extent by CYP2C9 and CYP2D6 in humans). In rat and dog the unchanged prodrug was no excreted in urine and feaces.

Based on in vitro data and the in silico predictions, a relevant clinical interaction of fosnetupitant with co-administered drugs is considered unlikely.

In 2-week and 4-week toxicology studies with fosnetupitant in rats, the main change observed was mild centrilobular liver hypertrophy for males and females treated mainly with the high dose. This change was correlated with a trend of increased liver weight. Liver weight resumed to control levels after the recovery period.

Phospholipidosis, observed with oral netupitant administration, was not observed in toxicology studies in rat with fosnetupitant up to 39.47 mg/kg/day (equivalent to 30 mg/kg/day of netupitant). Absence of phospholipidosis signs was also noted in a 2-week and 4-week studies in dogs administered up to 13.16 mg/kg/day (10 mg/kg/day of netupitant). This may be related to the different route of administration.

Fosnetupitant does not show mutagenic activity or potential for chromosomal damage.

Fosnetupitant had no relevant effects on fertility up to 39.47 mg/kg/day. Studies conducted in order to assess the potential for embryofoetal developmental toxicity were carried out in both rats and rabbits. Effects in embryofetal development were observed mainly at high dose level. In the rat studies no malformations were detected in the foetuses of the low and mid-dose groups (3.95 and 13.16 mg/kg/day respectively). One foetus with malformation (hindlimb malrotated) and one dead foetus were observed in the high dose group. At skeletal examination of foetuses, no ossification of pubis was detected in 6 foetuses of the high dose group (39.47 mg/kg/day).

For studies in rabbits there were no treatment-related effects for the skeletal examination of fetuses at any dose level. A slight increase in intrauterine deaths was recorded in treated groups with statistically significance in the mid- and high dose groups (6.25 and 12.5 mg/kg/day respectively).

The toxicology profile of fosnetupitant to netupitant, is attributed to the rapid conversion of fosnetupitant to netupitant, however there are differences in the outcome of the EFD studies of

fosnetupitant compared to the studies carried out for netupitant. For netupitant, cleft palate occurred, in rats, in three foetuses from a single litter at 100 mg/kg, and in rabbits in the pilot study at 30 mg/kg. These effects are all related to bone formation. Substance P is known to play a role in bone formation, therefore, effects on bone formation are common to both netupitant and fosnetupitant, manifested in different ways, and are probably due to effects of netupitant and fosnetupitant on Substance P.

In the pre and post-natal development study the main effect was a decrease in body weight for the females of F0 generation receiving the high dose (39.47 mg/kg/day). Reduction in body weight was also observed for the F1 generation of the high dose group. The mid dosage of 13.16 mg/kg/day was considered the NOAEL for dams and pups of F0 and F1 generations. No effects were noted in the reproductive performance of F1 generation. For the F2 there were no relevant effects, only a delay the preweaning test (startle response to sound) was noted in the high dose group.

Fosnetupitant does not induce eye and dermal irritation. Neither does it induce dermal sensitisation nor active and passive anaphylaxis in vivo.

Fosnetupitant is well tolerated when administered intravenously. Local tolerance results in animal models showed a good tolerability of the intravenous combination.

Intravenous and Intra-arterial administration in rabbits has showed very slight to mild erythema; no changes were noted at microscopic examination. Paravenous administration (a non-intended clinical route/misapplication) in rabbits: for the clinical signs very slight to mild erythema and very slight oedema were observed. At microscopic examination chronic inflammation (from mild to moderate), epidermal hyperplasia (from minimal to mild) of dermis were reported.

Fosnetupitant is classified as phototoxic (see also discussion on Clinical Safety). Even though the results achieved with fosnetupitant and netupitant were very similar, netupitant was classed as non-phototoxic in a previous assessment. This is due to changes in the criteria for classification introduced in the latest guideline for phototoxicity (OECD guideline 432).

The available data suggest that the fixed dose combination of fosnetupitant/palonestron is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical aspects of this line extension have been sufficiently described.

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

- determination of a log Kow for fosnetupitant using method OECD 123

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The MAH 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.

- Tabular overview of clinical studies

Table 1: Tabular listing of clinical studies submitted within this application

Study Type Study No.	Study Objective(s)	Study Design	Key inclusion criteria	Sample Size Gender Age Range (yrs)	Treatment	Study Location
Comparative bioavailability and bioequivalence						
PNET-12-23	Safety/ Fosnetupitant / netupitant Frel IV	Three-part double-blind (within dose cohorts) study	Healthy subjects	160 HVs SAD/SAD-CO; 80 P-CO; 40 F-CO: 40 158 subjects (94M, 64F) received treatment (Safety and PK Set) 18-45 yrs	Part 1: parallel group single ascending dose (SAD) with a crossover extension (SAD CO) (where applicable); Part 2: a pilot crossover part (P-CO), Part 3: final crossover part (F-CO). All parts were performed under	[Module 5.3.1.2, Report PNET-12-32]
Patient PK and initial tolerability study reports						
NEPA-15-19	PK/safety study	Open label, multicenter study with single administration of IV fosnetupitant/palonosetr on (260 mg/0.25 mg) fixed-dose combination, in association with oral dexamethasone, in cancer patients prior to receiving a cycle of HEC	Cancer patients (HEC)	24 (11M, 13F) 42-76 yrs	Single IV IV NEPA FDC 260 mg/0.25 mg	[Module 5.3.3.4, Report NEPA-15-19]
Extrinsic factor PK study reports						
PNET-13-63	PK/Safety drug interaction study with dexamethasone	Single-centre phase 1 open label, 3-period, 4-treatment, cross-over study using an incomplete block design. Pro-Netu administered at 3 dose levels (130 mg, 195 mg and 260 mg) with increasing drug concentration in the infusion solution (2.6 mg/ml, 3.9 mg/ml and 5.2 mg/ml, respectively) to healthy male and female subjects receiving concomitant administration of oral dexamethasone	Healthy subjects	30 (20M, 10F) 23-45 yrs	**Trt A**: oral dex regimen + IV 50 ml 5% glucose infusion over 30 min **Trt B**: oral dex regimen + IV 50 ml fosnetupitant 130 mg infusion over 30 min (2.6 mg/mL) **Trt C**: oral dex regimen + IV 50 ml fosnetupitant 195 mg infusion over 30 min (3.9 mg/mL) **Trt D**: oral dex regimen + IV 50 ml fosnetupitant 260 mg infusion over 30 min (5.2 mg/mL). The dex regimen was: 20 mg/day on Day 1, then 8 mg twice a day (b.i.d.) [16 mg/day] on Days 2, 3 and 4.	[Module 5.3.3.4, Report PNET-13-63]
Phase 3 studies						
PALO-15-17	Provide demonstration of the efficacy contribution of the palonosetron component to the IV NEPA FDC, by establishing non-inferiority [CR acute period (0-24 hr)] of the palonosetron IV infusion vs. IV bolus	Double-blind, randomized (1:1) active-controlled parallel group study	Cancer patients (HEC)	440 (295 M, 145 F) 25-79 yrs	PALO IV 30 min infusion vs. PALO IV 30 sec bolus	[Module 5.3.5.1, PALO-15-17]
NEPA-15-18	Provide safety information and descriptive efficacy information of the IV NEPA FDC	Double-blind, randomized (1:1) active-controlled parallel group study	Cancer patients (HEC)	404 (214 M, 190 F) 25-82 yrs	IV NEPA FDC vs. Oral Akynzeo	[Module 5.3.5.1, NEPA-15-18]

F=female; FDC=fixed dose combination; HEC= highly emetogenic chemotherapy; IV=intravenous; M=male; MEC=moderately emetogenic chemotherapy; PD=pharmacodynamic; PK=pharmacokinetic; PO=oral.

2.4.2. Pharmacokinetics

This is an application for an extension to the existing oral Akynzeo Marketing Authorisation to include IV NEPA FDC, an intravenous fixed dose combination of fosnetupitant (or pro-netupitant) and

palonosetron. Fosnetupitant is a water soluble phosphorylated pro-drug of netupitant rapidly converted to netupitant *in vivo* following IV administration. A pro-drug of netupitant was developed in order to ameliorate the local tolerability compared to the original IV formulation of netupitant.

The proposed indication for IV NEPA FDC (in adults) is the same as oral Akynzeo®:

- *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 clinical pharmacology program for the IV NEPA FDC includes one safety and pharmacokinetic (PK) dose escalation study (PNET-12-23) and two additional studies; a drug-drug interaction study with dexamethasone (PNET-13-63) conducted with fosnetupitant only, and a PK study in cancer patients following administration of the proposed commercial IV NEPA FDC (NEPA-15-19).

An *in silico* physiologically based pharmacokinetic (PBPK) modelling study was also conducted to predict the *in vivo* impact of fosnetupitant interactions with CYP isoforms and efflux/uptake transporters observed *in vitro* on the PK profile of relevant drug substrates (PNET-16-29).

Methods

Analytical methods

Table 4 contains a summary of the bioanalytical methods for the quantification of fosnetupitant, netupitant and its metabolites M1, M2 and M3, in human plasma. Table 5 overviews the method for palonosetron and M9 quantification in human plasma.

All methods underwent pre-study validation. The bioanalytical assays showed good overall performance and the results obtained were of the required quality and integrity. Sample handling was acceptable. Certificates of Analysis for reference standards were provided. The bioanalysis of PK samples and incurred samples reanalysis (ISR) samples were conducted in accordance with the principles of Good Laboratory Practice (GLP). The bioanalytical procedures of the laboratories were GLP certified.

Pharmacokinetic data analysis

PK parameters were calculated from plasma concentrations of fosnetupitant (pro-netupitant), netupitant, netupitant metabolites M1, M2 and M3, and palonosetron by non-compartmental methods using SAS software (Versions 9.2, 9.3 and 9.4).

Statistical methods

In study PNET-12-23, an analysis of variance (ANOVA) model on log transformed data was used to estimate the relative availability factor of netupitant from IV pro-netupitant versus oral netupitant (from the FDC) and its variability. This was obtained by fitting the following linear model (using SAS PROC MIXED): log (AUC/dose) = Treatment + Dose + Period + Sequence + Subject(Sequence) + Error. The antilog of the estimate of the treatment's effect difference (IV – oral) was the estimate of the relative availability factor.

In study PNET-13-63, log-transformed exposure parameters for dexamethasone given alone (IMP 2) and co-administered with pro-netupitant (IMP 1 + IMP 2) were analysed using a mixed model ANOVA with fixed factors for period and treatment and a random factor for subject. The parametric point estimators for the ratios (IMP 1 + IMP 2)/IMP 2 and the 90% confidence intervals (CI) were calculated using the adjusted least squares means from the ANOVA of log-transformed data with subsequent

exponential transformation. Results were then exponential back-transformed to obtain point estimators (i.e., geometric mean ratio) and 90% CI as percent.

Absorption

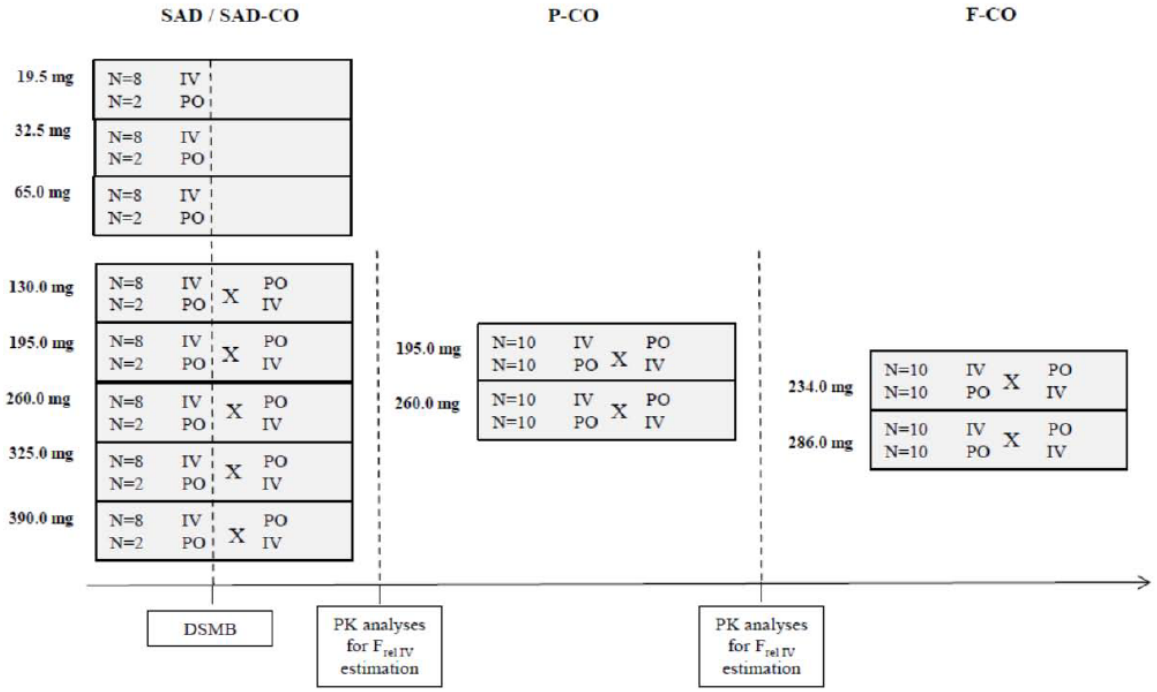
Fosnetupitant/palonosetron FDC is administered intravenously. Therefore, absolute bioavailability of combined drugs is complete (100%).

Bioequivalence

Study PNET-12-23 was a Phase I, double-blind, controlled, parallel groups, unbalanced single ascending dose study to assess the safety of intravenously administered pro-netupitant combined with crossover study extensions to estimate the dose of intravenous pro-netupitant yielding equivalent drug exposure as oral netupitant 300 mg/palonosetron 0.5 mg fixed dose combination in healthy male and female adult volunteers.

A total of 160 subjects were randomized into the study, of which 130 subjects were randomised to the crossover treatment.

Figure 2: Overview of the study design and distribution of subjects by dose and study parts



The subjects received either an IV infusion of pro-netupitant (together with the oral placebo capsule), or the oral netupitant 300 mg/palonosetron 0.5 mg FDC capsule (together with the IV placebo infusion). The duration of the infusion was 30 min for all dose cohorts. Crossover administrations in the same subject were separated by a washout phase of at least 4 weeks.

During the study, 20 blood samples (5 mL) for the analysis of pro-netupitant, netupitant and its 3 main metabolites (M1, M2, M3) were taken at the following times: at predose, t_{mid} [15 min after start of infusion (a.s.i)], t_{end} (30 min a.s.i), and 40 min, 50 min, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96 and 120 h a.s.i.

PK parameters

Pro-netupitant was rapidly converted into netupitant after IV administration, resulting in a limited systemic exposure to the pro-drug and a short elimination half-life. The apparent terminal elimination

half-life of pro-netupitant ranged from 0.05 h to 1.24 h in the dosing interval from 32.5 mg to 390 mg. At 260 mg, the mean half-life was 0.956 h.

Peak netupitant concentrations were observed at the end of infusion for all dose levels. The elimination of netupitant was slow with a mean apparent terminal elimination half-life ranging from 35 h to 55 h for all doses. The mean half-life for the 260 mg dose was 36.1 h.

Netupitant metabolites were detected early within 1 h from start of pro-netupitant infusion. All 3 metabolites were eliminated slowly and M1 showed a longer elimination half-life (mean t1/2 ~58 h to 194 h) compared to M2 (mean t/2 ~6h to 7 h) and M3 (mean t1/2 ~32 h to 69 h).

Comparison of main PK parameters of netupitant and metabolites after 260 mg IV pro-netupitant and 300 mg oral netupitant

The exposure to netupitant after IV administration of 260 mg pro-netupitant (mean AUC0-last of 12014 h·µg/L and mean AUC0-inf of 13854 h·µg/L) was comparable to the mean systemic exposure to netupitant after oral administration of 300 mg netupitant (mean AUC0-last of 11317 h·µg/L and mean AUC0-inf of 13899 h·µg/L). Cmax for netupitant after 260 mg IV fosnetupitant (840.8 µg/L) was ~1.76 times the Cmax after 300 mg oral netupitant (477.3 µg/L). The mean elimination half-life for netupitant after 260 mg IV fosnetupitant (36.1 h) was ~1.65 times shorter than the half-life after 300 mg oral netupitant (51.6 h).

After IV administration of 260 mg pro-netupitant, the mean exposure to M1 was lower (mean AUC0-last of 2326 h·µg/L and mean AUC0-inf of 4070 h·µg/L) compared to the mean M1 exposure after oral administration of 300 mg netupitant (mean AUC0-last of 3057 h·µg/L and mean AUC0-inf of 4819 h·µg/L). The exposure to M2 after oral administration of 300 mg netupitant (mean AUC0-last of 2640 h·µg/L and mean AUC0-inf of 2993 h·µg/L) was comparable to the exposure to M2 after IV administration of 260 mg pro-netupitant (mean AUC0-last of 2583 h·µg/L and mean AUC0-inf of 2935 h·µg/L). The exposure to M3 after IV administration of 260 mg pro-netupitant (mean AUC0-last of 3454 h·µg/L and mean AUC0-inf of 4313 h·µg/L) was slightly lower than the exposure to M3 after oral administration of 300 mg netupitant (mean AUC0-last of 3783 h·µg/L and mean AUC0-inf of 4620 h·µg/L).

Relative availability

Table 2: ANOVA results from the primary analysis

Treatment Dose	Estimated $F_{rel\ IV}$	95% CI of $F_{rel\ IV}$		IV pro-netupitant dose equivalent to 300 mg netupitant [mg]	90% CI of equivalent IV pro-netupitant dose [mg]	
130 mg	1.28	0.95	1.72	235.01	184.88	298.74
195 mg (S)	1.24	1.04	1.48	241.62	209.75	278.33
195 mg (P)	1.12	0.98	1.29	267.57	238.92	299.66
195 mg (S+P)#	1.14	1.03	1.26	263.82	242.64	286.85
234 mg (F)	1.15	0.97	1.38	259.97	224.41	301.16
260 mg (S)	1.02	0.86	1.21	294.53	256.22	338.56
260 mg (P)	1.02	0.89	1.15	295.47	266.24	327.91
260 mg (S+P)#	1.02	0.93	1.12	293.04	271.62	316.14
286 mg (F)	1.32	1.05	1.65	228.07	189.68	274.22
325 mg	1.30	0.80	2.09	231.54	157.76	339.82
390 mg	1.51	1.03	2.22	198.20	145.85	269.35
Cumulated	1.17	1.09	1.24	257.06	243.66	271.20

#:cumulated data of SAD-CO and P-CO cohort
CI: confidence interval, $F_{rel\ IV}$: relative availability factor of IV netupitant, F: final crossover (F-CO) part, P: pilot crossover (P-CO) part, S: single ascending dose crossover (SAD-CO) part, S+P: SAD-CO + P-CO part

Based on the primary analysis estimate for Frel,IV of 1.17 (95% CI 1.09, 1.24), an IV dose of 257 mg (90% CI 243.7, 271.2 mg) pro-netupitant (rounded to 260 mg) is equivalent to the oral 300 mg netupitant dose.

Distribution

After a single 260mg 30-min IV infusion of fosnetupitant single agent, mean volume of distribution [Vz (%CV)] for fosnetupitant in healthy subjects was 124.2 L (60.94%) (Study PNET-12-23, n=30). After a single 30-min intravenous infusion of 260mg fosnetupitant/0.25mg palonosetron FDC, mean Vz (%CV) for fosnetupitant and palonosetron FDC in cancer patients were 295.79 L (180.73%) and 593.89 L (40.21%), respectively (Study NEPA-15-19, n=24).

Fosnetupitant plasma protein binding was determined by equilibrium dialysis. For fosnetupitant, the overall mean % bound was 93.5% (Study PNET-15-90).

Elimination

Terminal half-life (t1/2)

After a single 30-min intravenous infusion of 260mg fosnetupitant alone in HVs (Study PNET-12-23) or in combination with 0.25mg palonosetron in cancer patients (Study NEPA-15-19), the mean t1/2 (CV%) values for fosnetupitant, netupitant, metabolites M1, M2, M3 and palonosetron (patients only) are provided in the table below.

Table 3: PK parameters for fosnetupitant, netupitant, metabolites M1, M2, M3 and palonosetron

$t_{1/2}$ (h) Mean (CV%)	Study PNET-12-23 HVs, n=30	Study NEPA-15-19 Patients, n=24
Fosnetupitant	0.956 (57.80)	0.75 (53.5)
Netupitant	36.05 (18.90)	143.73 (50.49)
Metabolite M1	89.34 (53.06)	159.54 (45.52)
Metabolite M2	36.09 (68.62)	136.40 (78.49)
Metabolite M3	47.32 (48.04)	111.40 (48.59)
Palonosetron	Not available	58.42 (46.56)

The longer netupitant and metabolite t1/2 observed in cancer patients compared to healthy subjects is attributed to the different time intervals in which the half-life values were assessed in these studies.

Clearance (CL)

After a single 30-min IV infusion of 260mg fosnetupitant alone in HVs (Study PNET-12-23) or in combination with 0.25mg palonosetron in cancer patients (Study NEPA-15-19), the mean CL (CV%) values for fosnetupitant and palonosetron (patients only) are provided in the table below.

Table 4: mean CL for fosnetupitant, and palonosetron

CL (L/h) Mean (CV%)	Study PNET-12-23 HVs, n=30	Study NEPA-15-19 Patients, n=24
Fosnetupitant	90.05 (14.73)	249.08 (108.30)
Palonosetron	Not available	7.61 (33.96)

The higher clearance of fosnetupitant in cancer patients compared to healthy subjects suggests faster fosnetupitant biotransformation to netupitant in patients as compared to healthy subjects.

Metabolism and excretion

The primary elimination route for fosnetupitant is metabolism. Fosnetupitant is rapidly and completely hydrolysed to netupitant by non-CYP450 hydrolytic enzymes. Netupitant is then primarily eliminated by CYP3A4-mediated metabolism, giving rise to secondary metabolites M1 (desmethylnetupitant), M2 (netupitant-N-oxide), and M3 (OH-methyl-netupitant). Renal clearance accounts for less than 5% of total clearance. After oral administration of radiolabeled netupitant, 86.5% of administered radioactivity was excreted via the faeces in 30 days post-dose.

The primary elimination route for palonosetron is via the kidneys. After a single intravenous dose of radiolabeled palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine, with unchanged palonosetron representing approximately 40% of the administered dose.

Dose proportionality

In healthy subjects (study PNET-12-23), dose-normalized mean Cmax values and AUC0-inf for fosnetupitant were similar for all dose levels. Dose-normalized mean Cmax values for netupitant were similar for all dose levels, while dose-normalized mean AUC0-inf values of netupitant were variable and slightly supra-proportional with dose increase.

Figure 3 dose-normalized mean Cmax values for fosnetupitant

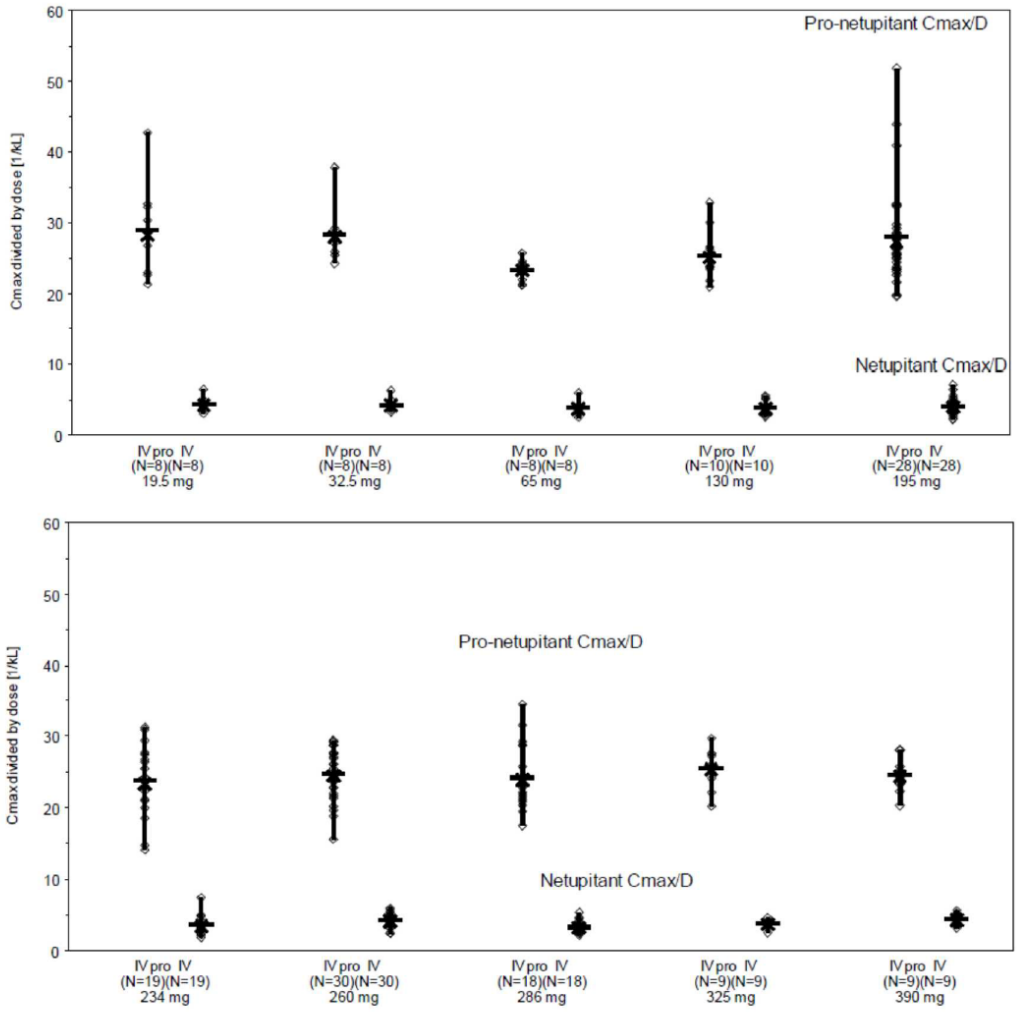
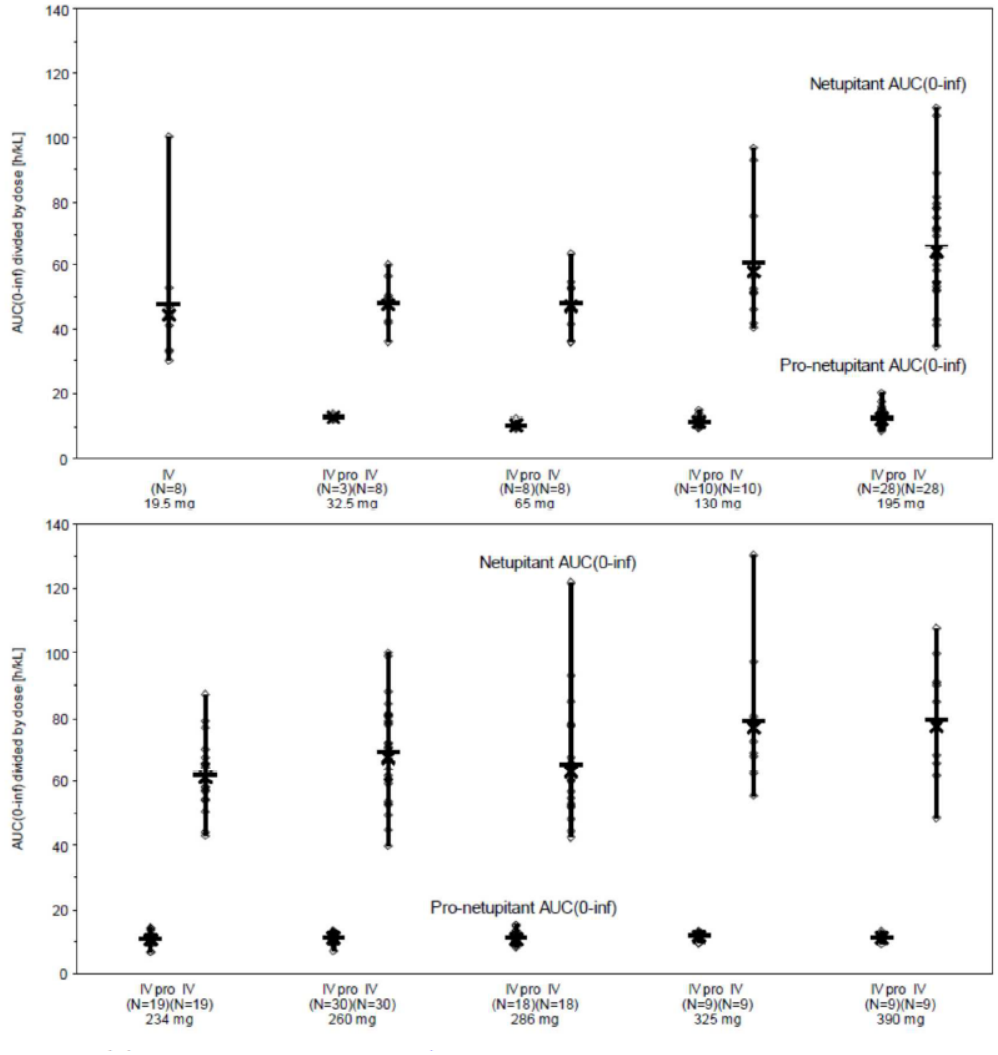


Figure 4 dose-normalized mean AUC0-inf for fosnetupitant



Inter-individual variability

In healthy subjects (study PNET-12-23), inter-individual PK parameter variability was low for fosnetupitant, with CV% for Cmax and AUC parameters <25%. Inter-individual variability for netupitant was also reasonably low, with CV% for Cmax and AUC parameters between 14 and 36%.

In cancer patients (study PNET-15-19), inter-individual PK parameter variability was moderate for fosnetupitant, with CV% for Cmax and AUC parameters around 45%. Inter-individual variability for netupitant was reasonably low, with CV% for Cmax and AUC parameters between 23 and 28%.

Pharmacokinetics in target population

Study NEPA-15-19 was a Phase 1, open label study to evaluate the pharmacokinetic profile and safety of IV fosnetupitant/palonosetron (260 mg/0.25 mg) fixed-dose combination administered for the prevention of chemotherapy-induced nausea and vomiting in cancer patients receiving a single cycle of highly emetogenic chemotherapy (HEC).

Study patients received a 30-min IV infusion of IV NEPA FCD (260 mg/ 0.25mg) on Day 1, together with 12 mg oral dexamethasone, before the start of HEC. Oral dexamethasone 8 mg/day was also administered on Days 2 to 4, immediately after PK sampling.

PK samplings were to be performed on Days 1, 2, 3, 4, 5, 7 and 9. Post-dose PK samplings were scheduled at 30 min (tend), 45 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 12 h, 24 h, 48 h, 72 h, 96 h, 144 h, and 192 h after the start of IV NEPA FDC infusion.

PK profiles of fosnetupitant, netupitant, netupitant metabolites M1, M2 and M3, and palonosetron

Fosnetupitant exposure in cancer patients was lower than in healthy volunteers after IV administration of 260 mg fosnetupitant (PNET-12-23), as indicated by the fosnetupitant Cmax [3478.33 (1558.23) ng/mL in patients vs. 6431 (911) ng/mL in healthy subjects] and fosnetupitant AUC∞ [1400.98 (649.04) h*ng/mL in patients vs. 2938 (362) h*ng/mL in healthy subjects]. This suggests faster fosnetupitant biotransformation to netupitant in patients as compared to healthy subjects, a conclusion supported by higher fosnetupitant systemic clearance in patients [249.08 (269.74) L/h vs. 90.1 (13.3) L/h in healthy volunteers] and comparable netupitant exposures (AUC∞) in patients [15588.49 (5022.77) h*ng/mL] and healthy subjects [13854 (2957) h*ng/mL] after 260 mg IV fosnetupitant.

Mean (SD) netupitant exposure (AUC∞) in patients after IV fosnetupitant/palonosetron (260 mg/0.25 mg) fixed-dose combination was 15588.49 (5022.77) h*ng/mL, similar to mean (SD) AUC∞ reported in healthy volunteers after a single 260 mg IV fosnetupitant infusion [13854 (2957) h*ng/mL] (study PNET-12-23). In addition, exposure was similar to that observed in healthy volunteers after oral administration of 300 mg netupitant [13899 (5549) h*ng/mL] (study PNET-12-23). This indicates that in patients, as well as healthy volunteers, a 260 mg IV fosnetupitant dose is comparable to a 300 mg netupitant oral dose.

The mean (SD) netupitant half-life value estimated in this study of 143.7 (72.6) h, was longer than that reported in study PNET-12-23 both after IV fosnetupitant 260 mg [36.1 (6.8) h] and oral netupitant 300 mg [51.6 (30.9) h]. This is attributed to the different time intervals in which the half-life values were assessed (i.e., up to 192 h in the present study NEPA-15-19 and only up to 120 h from administration in study PNET-12-23).

The PK profiles of netupitant metabolites M1, M2 and M3 in patients following the administration of IV fosnetupitant/palonosetron (260 mg/0.25 mg) fixed-dose combination and in healthy subjects after IV administration of 260 mg fosnetupitant (study PNET-12-23) were comparable.

Maximum palonosetron concentrations were observed at the end of infusion (median tmax: 0.58 h). All PK parameters were superimposable to those observed in a previous PK study in healthy subjects in which a 0.25 mg palonosetron dose was administered as an IV bolus (Study PALO-03-05) [mean (SD) AUC∞ 36066 (10727) h*ng/mL and 34800 (11500) h*ng/mL, respectively]. The only exception was Cmax which was lower in this study after 30-min infusion, 823.00 (288.69) ng/mL, as compared to that observed after the IV bolus, 2060 (1260) ng/mL.

Special populations

PK information concerning intrinsic factors was primarily derived from data generated during the oral Akynzeo® program.

- **Impaired renal and hepatic function**

No studies were performed specifically with fosnetupitant in patients with renal impairment or in patients with liver impairment. However, due to the transient exposure of fosnetupitant and subsequent conversion to netupitant, there are no additional warnings considered necessary with the administration of the prodrug compared to the parent compound.

- **Gender**

The impact of gender on the PK of fosnetupitant, netupitant and its metabolites, and palonosetron was studied. After IV administration of 260 mg fosnetupitant in healthy volunteers (Study PNET-12-23), no

clear impact of gender was observed on the main PK parameters for pro-netupitant, netupitant and its metabolites. In cancer patients (Study NEPA-15-19), the PK profiles of pro-netupitant, netupitant and its metabolites, and palonosetron were reasonably similar overall between males and females after IV administration of fosnetupitant/palonosetron (260 mg/0.25 mg) fixed-dose combination. A marginal impact of gender on fosnetupitant and netupitant metabolites PK was observed, with females showing slightly higher exposures.

Interactions

- **In vitro**

In vitro studies using human liver microsomes showed moderate to weak inhibition properties of fosnetupitant towards in particular CYP2C9 and CYP2C19 (Study PNET-15-49). Also, fosnetupitant weakly inhibited the OATP1B1- and OATP1B3-mediated substrate accumulation in HEK293 cells stably expressing the respective transporters in a dose-dependent manner. Fosnetupitant weakly inhibited the MDR1-mediated probe substrate accumulation in a vesicular transport assay performed with inside-out membrane vesicles prepared from cells overexpressing MDR-1 (Study PNET-15-27).

- **In silico**

Study PNET-16-29 was an *in silico* PBPK study, using the Simcyp Population-Based Simulator (Version 15), to evaluate the likely impact of co-administration of pro-netupitant (260 mg) on the exposure (Cmax and AUC) of a CYP2C9 substrate (S-warfarin), a CYP2C19 substrate (omeprazole), an OATP1B1 and OATP1B3 substrate (rosuvastatin) and a P-gp substrate (digoxin).

A minimal PBPK model with a single adjusting compartment was selected over other models based on the optimal comparison between observed and model predicted plasma concentration-time profiles of pro-netupitant following an IV infusion of 260 mg pro-netupitant administered over 30 minutes (Figure 2).

Figure 5 minimal PBPK model with a single adjusting compartment

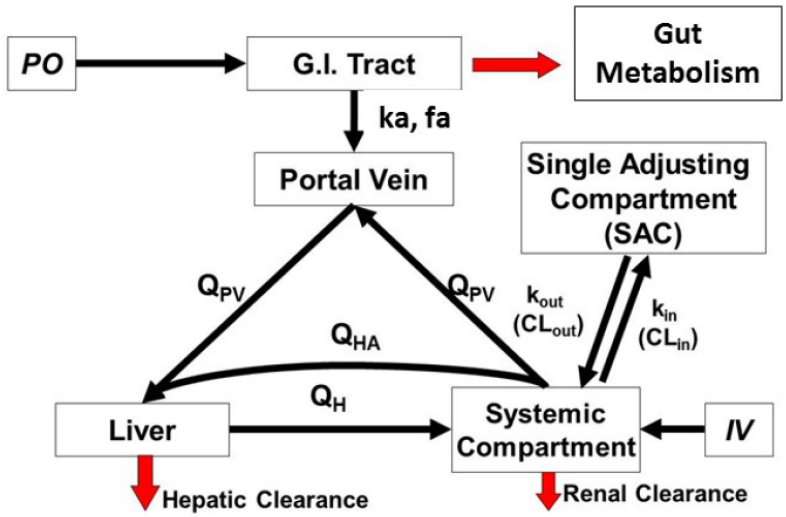


Figure 6 observed and model predicted plasma concentration-time profiles of pro-netupitant

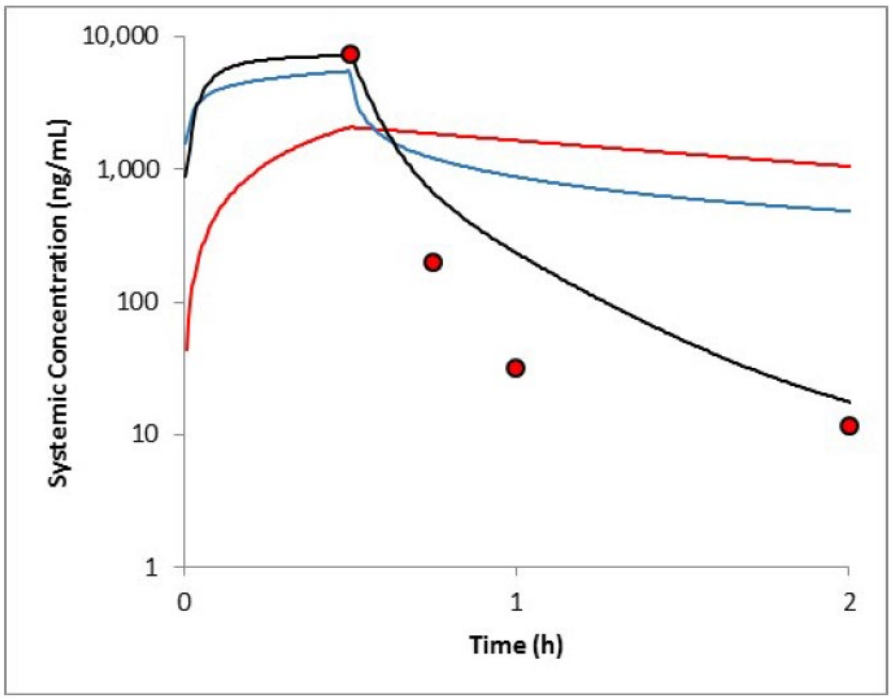


Figure 2 Simulated mean plasma concentration-time profiles (lines) and mean observed concentrations (symbols; n=17; Clinical Study PNET-13-63) for pro-netupitant after an IV infusion of 260 mg administered over 30 minutes. The solid line represents the outcome of the mean data for the simulated population (n=170) using a full PBPK model (blue line), a minimal PBPK model (red line) and a minimal PBPK model with a SAC (black line).

For simulation of plasma concentration-time profiles of pro-netupitant, data from the 17 healthy adult subjects recruited into clinical study PNET-13-63 were used.

In vitro Ki values were used in the model to assess the potential of pro-netupitant as a perpetrator of drug-drug interactions with relevant probe substrates. This involved generating 10 virtual trials of 17 subjects receiving an IV infusion of 260 mg pro-netupitant co-administered with one of the following compounds:

a) A single dose oral dose of 20 mg omeprazole (CYP2C19 substrate)

b) A single oral dose of 10 mg S-warfarin (CYP2C9 substrate)

c) A single oral dose of 20 mg rosuvastatin (OATP1B1 and OATP1B3 substrate)

d) A single oral dose of 0.5 mg digoxin (P-gp substrate)

Simulations were run using the relevant library file for the compound (substrate) within the Simcyp Population-Based Simulator (Version 15). For each compound, sensitivity analyses were performed to assess the impact of a range of Ki values (10-fold lower than the measured *in vitro* value) and hepatic uptake values (1 to 10) on the magnitude of interaction.

Impact of co-administration of pro-netupitant (260 mg) on the exposure of probe substrates

The analysis indicated that, based on *in vitro* Ki estimates for pro-netupitant, there is likely to be negligible interaction between pro-netupitant and CYP2C9 and CYP2C19 substrates and OATP1B1, OATP1B3 and P-gp substrates.

Prediction of the magnitude of interaction with omeprazole (CYP2C19 substrate) indicated no increase in omeprazole exposure, with predicted geometric mean Cmax and AUC ratios of 1.00 and 1.00, respectively. Assuming a CYP2C19 Ki of 2.3 µM (10-fold lower than the *in vitro* value) and a hepatic

uptake of 10 (a scalar of the unbound concentration in the liver relative to that in plasma) for pro-netupitant, the predicted AUC ratio was 1.03.

Prediction of the magnitude of interaction with S-warfarin (CYP2C9 substrate) indicated no increase in S-warfarin exposure, with predicted geometric mean Cmax and AUC ratios of 1.00 and 1.00, respectively. Assuming a CYP2C9 Ki of 1.4 µM (10-fold lower than the *in vitro* value) and a hepatic uptake of 10 for pro-netupitant, the predicted AUC ratio was 1.03.

Prediction of the magnitude of interaction with rosuvastatin (OATP1B1 and OATP1B3 substrate) indicated no increase in rosuvastatin exposure, with predicted geometric mean Cmax and AUC ratios of 1.00 and 1.00, respectively. Assuming an OATP1B1 or OATP1B3 Ki of 0.95 or 0.87 µM (10-fold lower than the *in vitro* values), respectively, and a hepatic uptake of 10 for pro-netupitant, the predicted AUC ratios were 1.00 and 1.00, respectively.

Prediction of the magnitude of interaction with digoxin (P-gp substrate) indicated no significant increase in digoxin exposure, with predicted geometric mean Cmax and AUC ratios of 1.04 and 1.01, respectively. Assuming a hepatic P-gp Ki of 2.5 µM (10-fold lower than the *in vitro* value) and a hepatic uptake of 10, the AUC ratio for digoxin was 1.01. Assuming an intestinal P-gp Ki of 2.5 µM (10-fold lower than the assumed *in vitro* value) and a hepatic uptake of 10 for pro-netupitant, the AUC ratio was 1.04, with an increase in Cmax of 32% (Cmax ratio 1.32) (Figure 21).

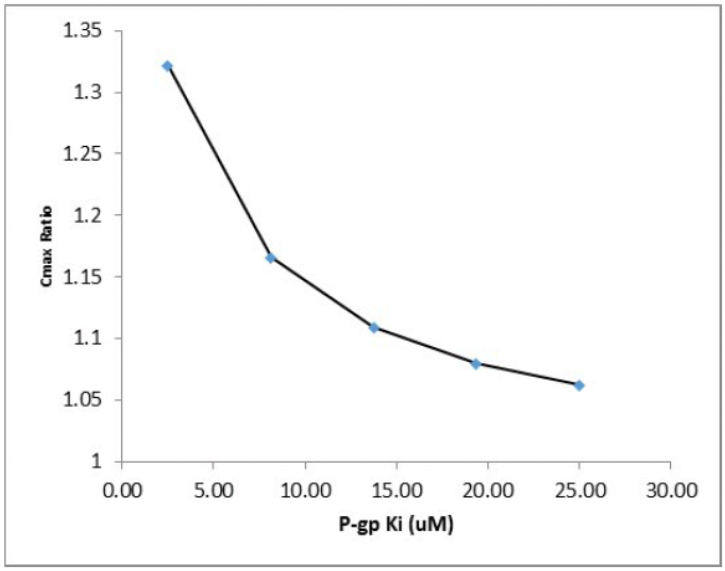


Figure 21 Sensitivity analysis to assess the impact of gut P-gp K_i values for pro-netupitant on the predicted DDI with digoxin (C_{max} ratio) after coadministration of a single oral dose of 0.5 mg digoxin and a single 30-min IV infusion of 260 mg pro-netupitant.

- **In vivo**

Study PNET-13-63 was a randomized three period crossover study in 28 healthy male and female volunteers to assess the effects of IV pro-netupitant infused in 30 minutes on the PK of orally administered dexamethasone.

The pro-netupitant or placebo infusion was given on Day 1. Dexamethasone tablets were given daily on Days 1 to 4.

Pharmacokinetic blood samples for determination of dexamethasone were taken at predose, 30 min, 45 min, then 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, 72, 84, 85, 86, 88, 90, 92, 96, 108 and 120 hours after start of infusion.

Analysis of primary PK parameters of dexamethasone

Table 5 mixed model ANOVA results (Day 1 PK parameters).

Dexamethasone Parameter	Ratio	Point estimate*	90% Confidence interval	
			Lower limit	Upper limit
AUC_{0-24}/D (equal to AUC_{0-t}/D)	B/A	126.55	118.80	134.81
	C/A	149.49	140.52	159.04
	D/A	150.10	140.60	160.25
C_{max}/D	B/A	110.86	100.03	122.87
	C/A	103.46	93.54	114.43
	D/A	96.92	87.15	107.78
C_{min}/D	B/A	275.83	232.62	327.08
	C/A	420.59	355.94	496.98
	D/A	517.75	434.10	617.52

ANOVA model with fixed factors for period and treatment and a random factor for subject.
*Point estimate is the ratio of adjusted geometric means
A: oral dexamethasone plus 5% glucose solution infusion
B: oral dexamethasone plus IV pro-netupitant 130 mg (2.6 mg/mL)
C: oral dexamethasone plus IV pro-netupitant 195 mg (3.9 mg/mL)
D: oral dexamethasone plus IV pro-netupitant 260 mg (5.2 mg/mL)

Table 6 mixed model ANOVA results (Day 4 PK parameters)

Dexamethasone Parameter	Ratio	Point estimate*	90% Confidence interval	
			Lower limit	Upper limit
AUC_{84-108}/D	B/A	172.86	151.16	197.68
	C/A	220.92	193.28	252.50
	D/A	241.54	210.25	277.48
AUC_{84-t}/D	B/A	176.98	154.23	203.10
	C/A	230.71	201.15	264.61
	D/A	254.19	220.47	293.06
C_{max}/D	B/A	140.33	122.16	161.20
	C/A	158.15	137.75	181.57
	D/A	170.25	147.53	196.46
C_{min}/D	B/A	199.86	170.51	234.26
	C/A	282.00	240.73	330.34
	D/A	323.00	274.08	380.65

ANOVA model with fixed factors for period and treatment and a random factor for subject.
*Point estimate is the ratio of adjusted geometric means
A: oral dexamethasone plus 5% glucose solution infusion
B: oral dexamethasone plus IV pro-netupitant 130 mg (2.6 mg/mL)
C: oral dexamethasone plus IV pro-netupitant 195 mg (3.9 mg/mL)
D: oral dexamethasone plus IV pro-netupitant 260 mg (5.2 mg/mL)
Source: Table 14.2.1.5

After administration of dexamethasone alone or with co-administration of IV pro-netupitant, dexamethasone exposure was slightly higher in males than in females. The ANOVA model showed no statistically significant effect for gender or the gender by treatment interaction on dexamethasone PK.

Co-administration of single increasing IV pro-netupitant doses (130 mg, 195 mg, and 260 mg) with oral dexamethasone resulted in a moderate increase of dexamethasone exposure as compared to the exposure achieved after administration of dexamethasone alone.

The extent of the interaction proved to depend on pro-netupitant dose size: dexamethasone exposure was greater after administration of higher pro-netupitant doses. The interaction lasted up to 4 days after pro-netupitant administration.

The extent of dexamethasone exposure increase with 260 mg IV pronetupitant is similar to the one observed when dexamethasone is co-administered with 300 mg oral netupitant (Study NETU-06-07).

The dexamethasone dose reduction to be applied when co-administering IV pro-netupitant 260 mg is the same as of oral Akynzeo®. This means that to warrant a dexamethasone exposure equivalent to that yielded by a standard dexamethasone alone regimen (20 mg on Day 1 followed by 8 mg b.i.d. from Day 2 to 4), the dexamethasone loading and maintenance doses, when the drug is co-administered with pro-netupitant, should be respectively reduced to 12 mg (Day 1) and to 8 mg q.d. (Days 2 to 4).

Exposure relevant for safety evaluation

Table 7 Netupitant exposure following single IV infusion of 260 mg fosnetupitant

Netupitant	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng.h/mL)	$AUC_{0\text{-inf}}$ (ng.h/mL)	t_{max} (h)	$t_{1/2}$ (h)
Patients, I.V. NEPA FDC, 260mg I.V. fosnetupitant (Study NEPA-15-19)					
N	24	24	24	24	24
Mean	590	10724	15588	1.05	143.7
SD	165	2491	5023	1.03	72.6
Median	557	10564	15579	0.56	136.1
Min - Max	310 - 977	5934 - 15495	6151 - 26239	0.52 - 4	57.3 - 385.6
Healthy subjects, 260mg I.V. fosnetupitant (Study PNET-12-23)					
N	30	30	30	30	30
Mean	841	12014	13854	0.62	36.1
SD	173	2340	2957	0.64	6.8
Median	831	11687	13807	0.50	34.9
Min - Max	479 - 1189	7443 - 16537	7947 - 20003	0.5 - 4	26.8 - 52.4
Healthy subjects, 300mg oral netupitant (Study PNET-12-23)					
N	129	129	129	129	129
Mean	477	11317	13899	4.34	51.6
SD	232	4278	5549	1.43	30.9
Median	450	10489	13327	4.00	39.4
Min - Max	85 - 1298	3195 - 26564	3872 - 31789	2 - 12	21.9 - 201.1

2.4.3. Pharmacodynamics

Primary and Secondary pharmacology

No new PD or PK/PD studies were conducted for the IV NEPA FDC program.

Three studies were performed to evaluate the PK and PD effects of netupitant during the oral program development, including an apomorphine challenge study (study NP16602), a NK1 receptor occupancy PET study (study NETU-06-08) and a thorough QT/QTc study (study NETU-07-20). In addition, relationships for cardiac safety and efficacy measures were graphically explored (study NETU-10-02).

Mechanism of action

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

Palonosetron is a 5-HT3 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-HT3 receptors located on vagal afferents to initiate the vomiting reflex.

Primary pharmacology

Results of a positron emission tomography (PET) study, conducted during the oral programme, demonstrated that netupitant is a potent selective NK1 receptor antagonist with continued receptor occupation duration suitable to cover the 120-hour period in chemotherapy induced nausea and vomiting. Based on the PK/PD model, a netupitant plasma concentration of 225 µg/L corresponded to NK1 receptor occupancy (RO) of 90% in striatum.

When model parameters were applied to predict the time course of netupitant RO after IV administration of 260 mg fosnetupitant, the temporal profiles of NK1 occupancy in the different brain regions overlapped those simulated after oral administration of 300 mg netupitant.

Figure 7 temporal profiles of NK1 occupancy in the different brain regions vs those simulated after oral administration of 300 mg netupitant

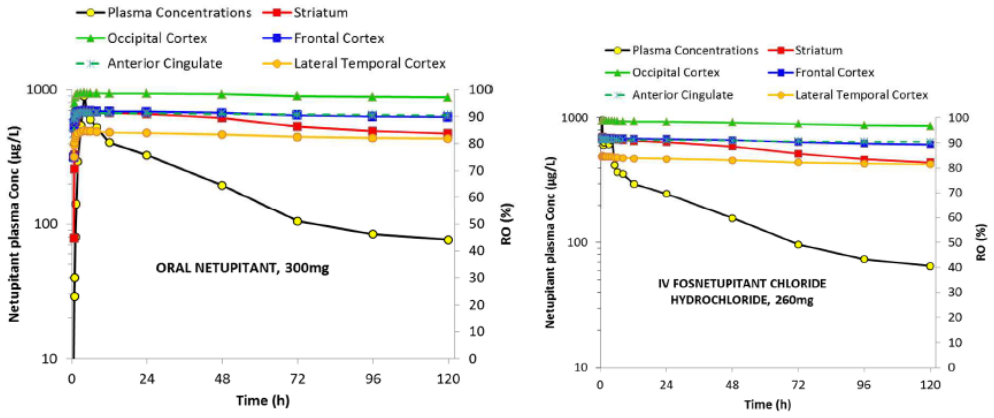


Figure 23: Temporal profiles of model-predicted NK1 receptor occupancy (RO) in different brain regions and mean plasma concentrations observed after oral administration of 300mg netupitant (PNET-12-23, left) and IV administration of 260mg fosnetupitant chloride hydrochloride (PNET-12-23, right)

Secondary pharmacology

A thorough QT study was completed with the oral FDC and demonstrated that the combination of netupitant and palonosetron was safe, well tolerated and had no clinically important effects on heart rate, PR and QRS interval duration, on cardiac morphology or cardiac repolarization when administered in male and female healthy volunteers.

Relationship between plasma concentration and effect

In an apomorphine challenge study, conducted during the oral programme, netupitant appeared to reduce the incidence of emetic episodes in a concentration-dependent manner. No vomiting was

observed for any subject at netupitant plasma concentrations above 300 ng/mL (450 mg in 5 patients and 300 mg in 1 patient). Subjects with lower netupitant concentrations also experienced less vomiting (50%) than the placebo group (75%).

2.4.4. Discussion on clinical pharmacology

This is an application for an extension to the existing oral Akynzeo Marketing Authorisation to include IV NEPA FDC, an intravenous fixed dose combination of fosnetupitant (or pro-netupitant) and palonosetron. Fosnetupitant is a water soluble phosphorylated pro-drug of netupitant rapidly converted to netupitant *in vivo* following IV administration.

The clinical pharmacology program for the IV NEPA FDC included one safety and pharmacokinetic (PK) dose escalation study (PNET-12-23) and two additional studies; a PK study in cancer patients following administration of the proposed commercial IV NEPA FDC (NEPA-15-19), and a drug-drug interaction study with dexamethasone conducted with fosnetupitant only (PNET-13-63).

An *in silico* physiologically based pharmacokinetic (PBPK) modelling study was also conducted to predict the *in vivo* impact of fosnetupitant interactions with CYP isoforms and efflux/uptake transporters observed *in vitro* on the PK profile of relevant drug substrates (PNET-16-29).

Study PNET-12-23 was a dose escalation study in healthy subjects assessing the safety of IV pro-netupitant from 19.5 to 390 mg, combined with crossover study extensions with oral Akynzeo to estimate the dose of IV pro-netupitant yielding a netupitant exposure equivalent to that provided by 300 mg oral netupitant (target dose of oral netupitant component within the combination).

The design and methodology of the study is considered acceptable from a PK perspective.

Pro-netupitant was shown to be rapidly converted to netupitant after IV administration. Peak netupitant concentrations were observed at the end of the 30-minute infusion for all dose levels.

The pharmacokinetic objective of major interest was the estimation of the relative availability factor (Frel,IV) for netupitant when given in form of IV pro-netupitant in comparison to the oral netupitant 300 mg/palonosetron 0.5 mg FDC. The primary target value to estimate exposure was the AUC0-inf based on plasma concentrations of netupitant.

A relative availability factor of 1.17 (95%CI 1.09, 1.24) for netupitant, based on dose-normalised AUC0-inf ANOVA estimates after IV pro-netupitant and oral netupitant administration, was observed when all crossover dose cohorts were considered. An IV pro-netupitant dose of 257 mg (rounded to 260 mg) was therefore identified as the dose that yields a netupitant exposure equivalent to that provided by a 300 mg dose of oral netupitant.

As there was some concern of reduced efficacy in the delayed phase (see Clinical Section), the applicant provided 90% CIs for the ratio of the geometric means for AUC0-24h, AUC24-120h, and Cmin at 120 hrs of netupitant for 260 mg IV pro-netupitant vs 300 mg oral netupitant. The results demonstrated bioequivalence between IV pro-netupitant and oral netupitant for these time intervals.

The results also showed slightly lower exposure to netupitant metabolites for the proposed IV pro-netupitant dose of 260 mg compared to the oral netupitant 300 mg dose. Therefore, the applicant provided 90% CI for the ratio of the geometric means for AUC0-inf, AUC0-last and Cmax of netupitant metabolites (M1, M2, and M3) for 260 mg IV pro-netupitant vs 300 mg oral netupitant. These showed slightly higher exposures to netupitant metabolites following oral netupitant vs IV fosnetupitant. It was shown that this difference in metabolite exposures was unlikely to have a clinically relevant impact on drug safety and efficacy.

Study NEPA-15-19 was a dense sampling PK study with IV NEPA FDC (260 mg fosnetupitant/0.25 mg palonosetron) to characterize the PK profile of unchanged fosnetupitant, netupitant and its metabolites M1, M2 and M3, and palonosetron in cancer patients. 24 adult cancer patients receiving highly emetogenic chemotherapy received a single administration of IV NEPA FDC infused over 30 minutes, together with oral dexamethasone. The design and methodology of this study is considered acceptable from a PK perspective.

Fosnetupitant exposure in cancer patients appeared to be lower than in healthy volunteers, suggesting faster fosnetupitant biotransformation to netupitant in patients as compared to healthy subjects. This is supported by the higher fosnetupitant clearance observed in patients but comparable netupitant exposures in patients and healthy subjects.

Netupitant exposure in cancer patients after 260 mg IV fosnetupitant administration was shown to be similar to that reported in healthy volunteers after a single 260 mg IV fosnetupitant infusion and to that observed in healthy volunteers after oral administration of 300 mg netupitant (study PNET-12-23). This supports previous evidence showing that a 260 mg IV fosnetupitant dose yields a netupitant exposure comparable to that of a 300 mg netupitant oral dose.

Palonosetron PK profile was comparable to that observed in healthy subjects in which a 0.25 mg palonosetron dose was administered as an IV bolus (study PALO-03-05), with the exception of Cmax which was lower after 30-min infusion (823 ng/mL) as compared to the IV bolus (2060 ng/mL).

Study PNET-13-63 assessed the effects of IV pro-netupitant infused in 30 minutes at 3 different dosages on the PK of orally administered dexamethasone (20 mg on Day 1 followed by 8 mg b.i.d. on Days 2, 3, and 4) in healthy male and female subjects.

A mixed model ANOVA, with fixed factors for period and treatment and a random factor for subject, was applied to dose-normalized pharmacokinetic parameters of dexamethasone given alone and co-administered with different doses of pro-netupitant, to assess the effect of pro-netupitant on dexamethasone PK. Furthermore, the gender by treatment interaction was tested using an ANOVA model with the additional fixed factors for gender as well as the gender by treatment interaction.

The design and methodology of this study is considered acceptable and the applicant's conclusions are supported.

This study demonstrated that co-administration of pro-netupitant and dexamethasone increases dexamethasone exposure in a dose dependent manner. Drug-drug interaction occurred on Day 1 and lasted at least until Day 4. The results indicate a need for dose adjustment of dexamethasone when it is co-administered with pro-netupitant.

On Day 1, at the dose of 260 mg pro-netupitant, dexamethasone AUC and Cmin increased approximately of 1.5- and 5.2-folds, respectively, as compared to the parameter values observed with dexamethasone given alone. On Day 4, at the dose of 260 mg pro-netupitant, the point estimates of treatment comparisons for dose-normalized dexamethasone AUC and Cmin increased approximately of 2.5 and 3.2 folds, respectively, as compared to the parameter values observed with dexamethasone given alone.

It is agreed that the extent of dexamethasone exposure increase with 260 mg IV pro-netupitant, the recommended pro-netupitant dose for Phase 3 studies and intended for registration, is similar to the one observed when dexamethasone is co-administered with 300 mg oral netupitant (Study NETU-06-07).

Study PNET-16-29 was an in silico PBPK study to evaluate drug-drug interactions with pro-netupitant.

The PBPK model, based on *in vitro* and *in vivo* data for pro-netupitant, was developed to simulate plasma concentration-time profiles and exposure levels of pro-netupitant after a single IV dose of 260 mg infused over 30 minutes. *In vitro* Ki values were then used to assess the potential of pro-netupitant as a perpetrator of drug-drug interactions with relevant probe substrates: omeprazole (CYP2C19 substrate), S-warfarin (CYP2C9 substrate), rosuvastatin (OATP1B1 and OATP1B3 substrate), and digoxin (P-gp substrate).

Due to the uncertainty of *in vitro* Ki values, sensitivity analyses were conducted to assess the impact of reducing *in vitro* Ki values for pro-netupitant by 10-fold. In addition, hepatic uptake was increased from 1 to 10 (representing the worst case scenario), to assess the effect on the predicted magnitude of the interaction.

The results indicated that an interaction between pro-netupitant and CYP2C9, CYP2C19, OATP1B1, OATP1B3, and P-gp substrates is unlikely.

Currently, PBPK modelling and simulation is acceptable by EU Regulators for predicting either lack of enzyme inhibition (presently, fosnetupitant on CYP2C9 or CYP2C19) by a perpetrator (source: EMA Guidelines on DDI investigations and Guideline on the qualification and reporting of PBPK modelling and simulation) or enzyme inhibition by a moderate inhibitor when data with a strong one are known, and not acceptable for transporter-mediated interactions. Therefore, the Applicant applied the basic method for predicting potential clinically relevant DDI with OATP1B1 and OATP1B3 substrates by using the formulation proposed for R value calculation stemming from the **"**FDA Draft Guidance for Industry *In Vitro Metabolism- and Transporter Mediated Drug-Drug Interaction Studies, CDER, October 2017 – Clinical Pharmacology* ". The results indicated that *in vivo* interactions between fosnetupitant and substrates of OATP1B1/3 transporters are unlikely.

The PBPK model was not adequate for CYP2C19 as only 2 omeprazole studies were provided to qualify the model. Therefore, the applicant focused the in silico DDI evaluation between fosnetupitant and CYP2C substrates mainly on CYP2C9, and then extrapolated results from CYP2C9 to CYP2C19. The analysis indicated that, based on in vitro Ki estimates for fosnetupitant, interaction between fosnetupitant and CYP2C9 and CYP2C19 substrates is unlikely of clinical relevance.

Several studies were performed to evaluate the PK/PD effects of netupitant for the original MAA for oral Akynzeo. These included an apomorphine challenge study, a NK1 receptor occupancy PET study and a thorough QT/QTc study. In addition, relationships for cardiac safety and efficacy measures were explored graphically.

No new PD or PK/PD studies were conducted in the clinical pharmacology program for the IV NEPA FDC, which is acceptable. Simulations support the similarity of the netupitant interaction kinetics with NK1 receptors following administration of 260 mg IV fosnetupitant and 300 mg oral netupitant.

2.4.5. Conclusions on clinical pharmacology

The PK of fosnetupitant, netupitant, M1, M2, M3, and palonosetron were studied and characterised for this application. An IV dose of 260 mg was demonstrated to yield a netupitant exposure equivalent to that provided by a 300 mg dose of oral netupitant

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

- The MAH will perform an in vitro study assessing the ability of fosnetupitant to inhibit all UGTs of interest (i.e. UGT1A1, 1A3, 1A4, 1A6, 1A9, and 2B7.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

The presented efficacy studies are Phase 3. The doses were established in the studies and discussed in section 2 clinical pharmacology.

2.5.2. Main study(ies)

The applicant has submitted 2 Phase 3 clinical efficacy studies (PALO-15017 & NEPA-15-18) however neither would be considered pivotal but more supportive along with bioequivalence study, PNET-12-23 for efficacy PK bridging.

The 2 main clinical efficacy studies will be presented under separate subheadings.

Study number PALO-15-17

A phase 3, single-dose, multicentre, randomised, double-blind, parallel group study to assess the efficacy and safety of palonosetron 0.25 mg administered as a 30-minute IV infusion compared to palonosetron 0.25 mg administered as a 30-second IV bolus for the prevention of chemotherapy-induced nausea and vomiting in cancer patients receiving highly emetogenic chemotherapy.

The objective of the non-inferiority study, PAOL-15-17 was to demonstrate the efficacy of the palonosetron 0.25 mg component of the combination when administered as a 30-min IV infusion and therefore its contribution to the efficacy of the combination product.

Date of the study report: 18th Feb 2017. First patient enrolled: 30th Sep 2015 and last patient completed: 9th Mar 2016. Protocol final version 3 dated 25th January 2016.

Study number NEPA-15-18

A phase 3 multicentre, multinational, randomised, active-controlled, double-blind, double-dummy, parallel group, stratified study assessing the safety of the intravenous FDC in comparison to the oral FDC of Akynzeo.

The primary objective of the study was to assess safety between the 2 formulations. Descriptive efficacy results were secondary objectives for this particular study.

Date of the study report: 17th Mar 2017. First patient enrolled: 17th Nov 2015 and last patient Completed: 2nd Aug 2016

Study PALO-15-17

Study PALO-15017 is a multicentre, randomised, double-blind, double dummy parallel group, stratified study that assessed the efficacy, safety and tolerability of a single-dose of palonosetron 0.25 mg administered as a 30-min IV infusion versus a single-dose of palonosetron 0.25 mg administered as a 30-sec IV bolus, each administered with oral dexamethasone prior to highly emetogenic chemotherapy HEC.

- **Study participants**

Adult chemotherapy naïve patients (male and female patients) with a diagnosis of malignant solid tumour requiring a first treatment with one of the reference HEC regimens. The main characteristics of the population selected for this study were similar to those of the PALO-99-05 study, the pivotal efficacy trial that supported approval of 30- sec IV bolus of palonosetron 0.25 mg. The administration

of the reference HEC was not to extend beyond 4 h on study Day 1 and patients that were scheduled to receive MEC or HEC from Day 2 to Day 5 were excluded.

A total of 441 patients were randomised, and 440 (99.8%) received study treatment. 225 participants were treated with the 30 minute palonosetron infusion IMP and 215 with the 30 second bolus palonosetron control.

- **Treatments**

Test drug: palonosetron 0.25 mg (as 50 mL solution for IV infusion), was to be administered as a 30-min (±5) IV infusion on Day 1. The IV infusion was to start 30 min prior to and was to be completed before the start of the reference HEC administration.

Control drug: palonosetron 0.25 mg (as 5 mL solution for IV bolus), was to be administered as a 30-sec IV bolus on Day 1. The IV bolus was to be administered 30 min before the start of the reference HEC administration.

For blinding purposes, a double-dummy technique was to be applied. Patients were to receive placebos for test and control drugs, as applicable.

The following time windows were defined (as per protocol version 3.0) for the administration of test drug (palonosetron IV infusion) and its placebo, and control drug (palonosetron IV bolus) and its placebo, on Day 1:

- Palonosetron (or placebo) 30-sec IV bolus: to be performed within 5 min from the oral dexamethasone administration
- Palonosetron (or placebo) 30(±5)-min IV infusion: to be started within 5 min from the palonosetron (or placebo) IV bolus administration, between 40-25 min before the start of reference chemotherapy administration

- **Objectives**

The primary objective:

to demonstrate the non-inferiority of a single IV dose of palonosetron 0.25 mg administered as a 30-min IV infusion with oral dexamethasone versus a single IV dose of palonosetron 0.25 mg administered as a 30-sec IV bolus with oral dexamethasone, in terms of proportion of patients with complete response (CR) in the acute phase (0-24 h after start of reference HEC) of CINV.

The secondary efficacy objectives of this study was to demonstrate a) a CR in the delayed and overall phases, b) the proportion of patients with no emetic episodes in the acute, delayed and overall phases and c) the proportion of patients with no use of rescue medication in the acute, delayed and overall phases.

The secondary safety objectives were to evaluate the safety of a single dose of palonosetron 0.25 mg administered as a 30-min IV infusion with oral dexamethasone for the prevention of HEC-induced nausea and vomiting.

- **Outcomes/endpoints**

The primary efficacy endpoint was the proportion of patients with a complete response (CR), defined as no emetic episodes and no rescue medication, in the acute phase of CINV.

The secondary efficacy endpoints were defined as follows:

- The proportion of patients with CR during the delayed and overall phases of CINV

- The proportion of patients with no emetic episodes during the acute, delayed and overall phases of CINV
- The proportion of patients with no rescue medication during the acute, delayed and overall phases of CINV.

Table 8 ***Efficacy endpoints in study PALO-15-17 and study NEPA-15-18***

Table 7 Primary and Secondary Efficacy Endpoints in Clinical Trials

Trial Code	**Primary Endpoint**	**Secondary Endpoint (s)**
PALO-15-17	Complete Response: acute phase	Complete Response: delayed and overall phases Emetic Episodes: acute, delayed and overall phases Rescue Medication: acute, delayed and overall phases
NEPA-15-18	N/A	Complete response: acute, delayed and overall phases Emetic Episodes: acute, delayed and overall phases Rescue Medication: acute, delayed and overall phases No Significant Nausea: acute, delayed and overall phases

Source: Module 5.3.5.1 [PALO-15-17, Section 9.7.1.4; NEPA-15-18, Section 9.7.1.4]
Acute phase = 0-24 h; Delayed phase = 25-120 h; Overall phase = 0-120 h
N/A = not applicable; Study NEPA-15-18 was a safety study

- **Sample size**

The number of patients to be randomised in the study was planned to be 440, equally distributed in the two treatment groups (220 patients/group). Patients were to be randomised according to a randomization ratio 1:1, stratified by gender and country.

The sample size was based on the assumption of a CR rate in the acute (0-24 h) phase of 80% in both groups. The non-inferiority margin was set at -15%. For a two-sided test of difference using Type I error equal to 0.01, a sample size of 212 evaluable patients per group was needed to ensure 90% power (nQuery + nTerim 3.0, module PTEO-1). The sample size was increased to 220 per group, to ensure an adequate number of evaluable patients.

No interim analysis was planned for this study.

- **Randomisation**

Patients that satisfied the inclusion and exclusion criteria were randomised into one of the two treatment arms, in a balanced design (1:1) according to specific procedures using the IWRS. Treatment assignment was managed through a static central blocked randomisation stratified by gender (male, female) and country. The randomisation scheme was meant to be reproducible and prepared prior to study start via a computerized system by the IWRS vendor. A master randomisation copy was to be filed securely by this vendor and the Sponsor in a manner that ensured the blind was properly maintained throughout the trial. The biostatistician involved in the creation of the randomisation lists did not take part in the study activities.

- **Blinding (masking)**

The blinding of the study medications was guaranteed by the use of identical placebos to the respective active drugs (double-dummy technique). When palonosetron 0.25 mg was to be administered as 30-min IV infusion, a 30-sec IV bolus of placebo was to be administered (Group 1). Conversely, when palonosetron 0.25 mg was administered as a 30-sec IV bolus, a 30-min infusion of placebo was to be administered (Group 2). Therefore, each patient was to receive a 30-sec IV bolus and a 30-min IV infusion, one of which contained the active IMP while the other was a placebo.

No blinding was required for dexamethasone, which was administered at the same dose and posology in both treatment groups.

Due to the blinded study design, neither the Sponsor, nor the pharmacist, the Investigator, the patient, or the CRO knew which treatment was administered. The monitor who checked the drug accountability forms was also blinded with regard to the treatment administered. The Investigator had the possibility to unblind the study treatment in case of an emergency situation, when he/she considered it essential to know what treatments the patient had received. The IWRS was to promptly notify, in a blinded fashion, the Sponsor and the Clinical Monitor when a treatment code had been unblinded by the Investigator.

- **Statistical methods**

The full analysis set (FAS) included all randomised patients who received the HEC regimen and active study drug (including partial infusion). Following the intent-to-treat principle, patients were assigned to the treatment group to which they were randomised. The FAS was used for demography, other baseline characteristics and all efficacy analyses.

The per protocol (PP) Population included all patients from the FAS who completed the 0-24 h study period with no major protocol violations, i.e., those believed to potentially affect the primary efficacy endpoint. The PP Population was used for demography, other baseline characteristics, and for the primary efficacy analysis.

All protocol violations (e.g., wrong inclusion, poor compliance, missing diaries, forbidden concomitant medications and mis-randomisations) were to be reviewed and discussed case by case during the blind data review meeting and decisions were to be described in the blind data review document/minutes which were to be finalized prior to database lock.

A blind data review meeting including but not limited to the definition of analysis populations was held on the 6th & 7th Jun 2016.

No interim analysis was planned for this study.

The approach followed for this non-inferiority study was the fixed-margin method. Taking into account that the current study was to address a change in the duration of infusion (from 30-sec bolus to 30-min infusion) for a widely used treatment approved for HEC CINV, the proposed non-inferiority margin of 15% was considered adequate and conservative by the applicant.

Regarding multiplicity, there was one single primary endpoint for confirmatory analysis. Since all the secondary efficacy endpoints in the acute phase of CINV were intended to provide supportive evidence related to the primary objective only and in the delayed and overall phases of CINV were intended to provide additional clinical characterization of treatment effect, no adjustment for multiplicity was planned and results were interpreted in a descriptive manner only.

Three phases were defined for the efficacy evaluation. The acute phase of CINV was to start at 'time 0', which was the start of the reference HEC administration and last for the first 24 h. The delayed

phase of CINV was to start at >24 h after the start of reference HEC administration until 120 h. The overall phase of CINV was to start from time 0 till 120 h after the start of HEC administration.

Due to the short observation period (24 h for the primary efficacy endpoint and a maximum of 120 h for all the other efficacy assessments) and based on a previous Sponsor's studies with a very similar design and in the same setting (HEC), a very low number of dropouts and minimal missing data was expected.

Any patients who did not provide data about occurrence of emetic episodes and rescue medication intake or did not provide a full set of these data throughout the 24 h after HEC administration were to be considered as treatment failures (i.e., non-responders) for the primary efficacy analysis. A patient was to be considered as having CR only if there was documented evidence of both no occurrence of emetic episodes and no rescue medication intake. Otherwise the patient was to be considered a failure. The percentage of responders was to be calculated using the FAS population as denominator.

Gender and country were identified as the factors expected to influence the primary efficacy endpoint. These factors were to be taken into consideration for randomisation and for the analyses however treatment by gender and country interactions was to be explored but not included in the primary analysis model. In case significant interactions (i.e., p-value ≤0.100) were found, additional investigational analyses could have been run in order to understand the reason for the heterogeneity. A logistic regression model was to be used to investigate the interactions between treatment and stratification factors (gender or country). The Chi-square Wald test was to be used to test the significance of the interaction terms.

Non-significance of interaction terms between treatment and factor would indicate that these data do not suggest any evidence that the treatment affects the response differently in each of the type presented by that variable. In case of significant interactions (i.e: p-value ≤0.100), further investigation were to be conducted to understand the reason of heterogeneity.

There was one change to the planned analyses that the applicant regarded as minor; the calculation of non-stratified (crude) risk difference and relative 95% CI according to Newcombe-Wilson method was added to the efficacy endpoints. This was implemented in the final SAP version 5.1 dated 13th June 2016.

Study NEPA-15-18

A phase 3, multicentre, randomized, double-blind, active control study to evaluate the safety and efficacy of IV pro-netupitant/palonosetron (260 mg/0.25 mg) combination for the prevention of chemotherapy-induced nausea and vomiting in repeated chemotherapy cycles in patients receiving highly emetogenic chemotherapy.

- **Study participants & Treatments**

The study participants consisted of female and male adult patients that were chemotherapy-naïve with a diagnosis of malignant solid tumour. Each participant was recruited if they required treatment for at least 4 cycles with the pre-defined reference HEC (mainly cisplatin) to be administered on Day 1 of each chemotherapy cycle. Participants were excluded if they were scheduled to receive MEC or HEC from day 2 to Day 5 of the cycle or had a poor performance status (ECOG > 2).

The control drug, oral netupitant/palonosetron (300 mg/0.50 mg) FDC and the test drug, intravenous 30minute infusion fosnetupitant/palonosetron (260 mg/0.25 mg) FDC were administered on Day 1 of each cycle (60 minutes and 30 minutes respectively) prior to the start of the chemotherapy. The 30-min IV infusion was to be completed before starting chemotherapy administration.

For blinding purposes, the double-dummy technique was applied. Patients were to be administered with placebos for test and control treatments, as applicable.

The selection of doses for the IV infusion are based on the approved IV bolus dose of palonosetron and the results of the PK study in healthy volunteers PNET-12-23 that was discussed in the clinical pharmacology section above.

- **Objectives**

Safety and tolerability are the primary objectives of the trial. The secondary objective of this study was to describe the efficacy of a single dose of IV NEPA FDC (260 mg/0.25 mg) infused over 30 min with oral dexamethasone during the acute (0-24 h), delayed (>24-120 h) and overall (0-120 h) phases of initial and repeated cycles of HEC (4 cycles in total).

In contrast to the non-inferiority study PALO-15-17, efficacy endpoints are defined as CR (no emetic episodes and no rescue medication) during the acute & delayed phases but also the overall phase as an endpoint. Nausea assessment has also been described using the visual analogue scale (VAS).

All patients were to be asked to document in a patient diary details of their emetic episodes during the 120 h following the start of chemotherapy cycle. These details included:

- Each episode of retching or vomiting
- Date of each retching or vomiting episode
- Exact time of onset of each retching or vomiting episode

Each emetic episode, as well as date and start time of occurrence was to be documented on the eCRF in accordance with the patient diary records.

- **Statistical methods**

The assessment and description of efficacy was a secondary objective of the study. Only descriptive statistics were planned for the efficacy endpoints. All efficacy analyses were performed on the FAS. In contrast to the non-inferiority study PALO-15-17, there was no per protocol (PP) set analysis.

At each cycle, for each phase (acute, delayed, and overall), numbers and percentages (including 95% confidence interval [CI] using the Wilson score method) of patients with CR, with no emetic episodes, with no rescue medications, and with no significant nausea were summarized by treatment and by treatment and gender.

Differences between groups in response rate and 95% CI for difference were analysed using Newcombe-Wilson's method and also the stratum-adjusted Cochran-Mantel- Haenszel (CMH) method for the risk difference. Gender and country were used as strata.

Results were interpreted only in a descriptive manner.

Since nausea intensity was assessed daily by VAS, for the endpoint referred to "patients with no significant nausea" in the delayed and overall phases, the maximum VAS value in the relevant phase was considered (i.e., the maximum VAS value for Day 2 to 5 for delayed phase and for Day 1 to 5 for the overall phase). Data collected on the patient diaries were also listed, as well as the calculated variable for CR. The recorded emetic episodes were also listed by treatment group.

The efficacy analyses were performed for the full analysis set (FAS) for both PALO-15-17 and NEPA 15-18. In the non-inferiority study PALO-15-17, primary efficacy analysis was also performed on the Per Protocol (PP) population. For this development program, the FAS population included patients who were randomised, received the reference chemotherapy regimen and study drug.

Results

Table 9: Patient demographics

Table 5 Patient Demographics- Cycle 1 –HEC Trials (Safety population)

	PALO-15-17 (N=440) n (%)	NEPA-15-18 (N =404) n (%)
Gender , n (%)		
Male	295 (67.0)	214 (53.0)
Female	145 (33.0)	190 (47.0)
Age (years)		
Mean (SD)	59.4 (8.6)	59.5 (10.2)
Median	60.0	61.0
Min-max	25-79	25-82
Race , n (%)		
White	440 (100.0)	401 (99.3)
Black	-	2 (0.5)
Asian	-	1 (0.2)
ECOG performance status, n (%)		
Grade 0	206 (46.8)	164 (40.6)
Grade 1	220 (50.0)	230 (56.9)
Grade 2	14 (3.2)	10 (2.5)

Source: CSRs [Module 5.3.5.1, PALO-15-17, Tables 6 and 7, NEPA-15-18 Tables 6 and 7]

Eastern Cooperative Oncology Group Performance Status:

Grade 0: Fully active, able to carry on all pre-disease performance without restriction.

Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light orsedentary nature, e.g. light house work, office work.

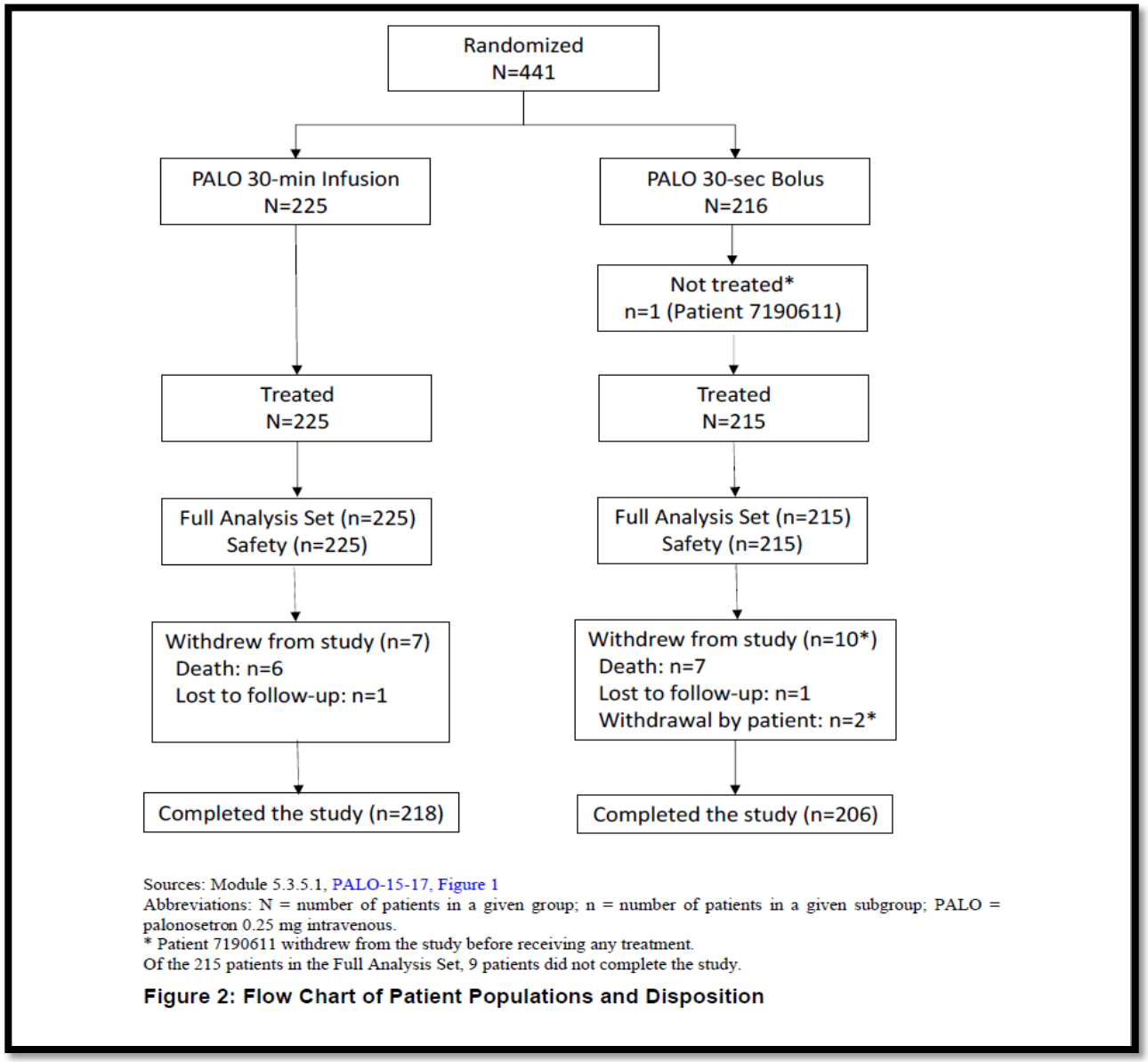
Grade 2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.

Abbreviations: ECOG=Eastern Cooperative Oncology Group; FDC=Fixed Dose Combination; max=maximum; min=minimum; N=Number of patients in group; n=number of patients with data; SD=Standard Deviation.

Over half of the participants in each trial had a primary cancer diagnosis of lung cancer and cisplatin was the most commonly administered HEC in both trials (approx. 96% participants received cisplatin in both studies).

- **Participant flow**

Figure 8: Study PALO-15-17 participant flow



Sources: Module 5.3.5.1, PALO-15-17, Figure 1
Abbreviations: N = number of patients in a given group; n = number of patients in a given subgroup; PALO = palonosetron 0.25 mg intravenous.
* Patient 7190611 withdrew from the study before receiving any treatment.
Of the 215 patients in the Full Analysis Set, 9 patients did not complete the study.

Figure 2: Flow Chart of Patient Populations and Disposition

- **Recruitment**

The first patient was enrolled on the 30th Sep 2015 with the last patient completed on the 9th Mar 2016. A total of 76 study centres were activated for patient recruitment in 9 countries. The study period was 5 months with a maximum total study duration per patient of 37 days, including up to 14 days screening period, 6 (+2) days of study evaluation period (of which 4 days on active treatment), and a follow-up visit or a telephone call on Day 21 (±2). A total of 441 participants were randomised in study PALO-15-17.

- **Conduct of study**

2 protocol amendments were made to study PALO-15-17 with the latest protocol version 3.0, dated 25th January 2016.

Major protocol deviations are summarized in Table 4 of the study report. All patients with major protocol deviations were excluded from the PP Population, as previously described in statistical methods.

There were major protocol deviations in 15 (3.4%) patients in the FAS: 11 (4.9%) in the infusion group and 4 (1.9%) in the bolus group. The most common major protocol deviation (affecting 9 [2.0%] patients) referred to "dexamethasone not administered within the time window on the morning of Day 2". All remaining major protocol deviations either referred to an HEC dosage outside of the reference range (3 [0.7%] patients) or to the use of medication with potential anti-emetic effects within 24 h after starting the reference HEC (3 [0.7%] patients).

- **Baseline data**

The safety population was comprised 295 (67.0%) male patients and 145 (33.0%) female patients, equally distributed between treatment groups (gender was a stratification factor).

In terms of race, all (100%) patients in the Safety Population were Caucasian (white).

The applicant also presented other demographics ECOG status, smoker, alcohol consumption, medical & cancer history, priori and concomitant medication and reference chemotherapy.

An overview of all randomized patients by gender and country is shown below. The greatest proportion of patients were enrolled in the Russian Federation (30.4%), followed by Hungary (22.2%), Romania (20.6%), and the Republic of Georgia (9.5%). Gender is balanced in both arms but more males (67% versus 33%) were enrolled into the study compared to females.

PALO-15-17
Table 14.1.1.4 Strata: Number of Patients by Gender and Country - All Randomized Patients

		IV PALO Infusion (N=225) n (%)	IV PALO Bolus (N=216) n (%)	Overall (N=441) n (%)
By Gender	Patients - Male	151 (67.1)	145 (67.1)	296 (67.1)
	Patients - Female	74 (32.9)	71 (32.9)	145 (32.9)
By Country	Patients from Belarus	9 (4.0)	6 (2.8)	15 (3.4)
	Patients from Bosnia and Herzegovina	3 (1.3)	2 (0.9)	5 (1.1)
	Patients from Bulgaria	19 (8.4)	19 (8.8)	38 (8.6)
	Patients from Georgia (Republic)	21 (9.3)	21 (9.7)	42 (9.5)
	Patients from Greece	7 (3.1)	7 (3.2)	14 (3.2)
	Patients from Hungary	50 (22.2)	48 (22.2)	98 (22.2)
	Patients from Lithuania	2 (0.9)	2 (0.9)	4 (0.9)
	Patients from Romania	46 (20.4)	45 (20.8)	91 (20.6)
	Patients from Russian Federation	68 (30.2)	66 (30.6)	134 (30.4)

- **Numbers analysed**

The FAS included 440 (99.8%) patients who were treated with the study drug and received HEC (225 [100%] patients in the infusion group, and 215 [99.5%] in the bolus group). The PP Population included 425 (96.4%) patients (214 [95.1%] patients in the infusion group and 211 [97.7%] patients in the bolus group).

A total of 16 (3.6%) randomized patients was excluded from the PP Population due to major protocol violations: 11 (4.9%) patients in the infusion group and 4 (1.9%) patients in the bolus group; in addition, one patient in the bolus group was not treated and was, therefore, excluded from the FAS.

Table 5 Patient Disposition (Population: All Randomized Patients)

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus	Total
	N = 225	N = 216	N = 441
	n (%)	n (%)	n (%)
FAS / Safety Population	225 (100)	215 (99.5)	440 (99.8)
Per-Protocol population	214 (95.1)	211 (97.7)	425 (96.4)
Reason for exclusion from PP Population:			
Major protocol deviation	11 (4.9)	4 (1.9)	15 (3.4)
Not in FAS	0	1 (0.5)	1 (0.2)

Sources: Summary Tables 14.1.1.1 and 14.1.1.2
Abbreviations: FAS = Full Analysis Set; IV = intravenous; N = number of patients in a given group; n = number of patients in a given subgroup; PP = Per-Protocol.

Outcomes and estimation

Table 10 Non-inferiority analyses of CR in the acute phase for both the FAS and PP Populations

Palonosetron 0.25 mg IV	30-min Infusion		30-sec Bolus
Full Analysis Set	N = 225		N = 215
Responder, n (%)	186 (82.7)		186 (86.5)
[95% confidence interval][a]	[77.2, 87.1]		[81.3, 90.4]
CMH risk difference % (Infusion – Bolus) [99% CI][b]		-3.8 [-12.2; 4.7]	
P-value [b]		p<0.001	
Per-Protocol Population	N = 214		N = 211
Responder, n (%)	177 (82.7)		182 (86.3)
[95% confidence interval][a]	[77.1, 87.2]		[81.0, 90.3]
CMH risk difference % (Infusion – Bolus) [99% CI][b]		-3.4 [-12.0; 5.2]	
P-value [b]		p<0.001	

Source: Summary Tables 14.2.1.1, 14.2.1.2, 14.2.1.3, and 14.2.1.4
Abbreviations: CMH = Cochran-Mantel-Haenszel; CI = confidence interval; IV = intravenous; N = number of patients in a given group; n = number of patients in a given subgroup.
(a) Wilson score method confidence interval.
(b) CMH stratum-adjusted method for difference in proportions, stratified by gender and country according to Koch et al. and O'Gorman et al. The non-inferiority margin is set to 15%. P-value associated with non-inferiority testing.

Table 11: CR in the delayed and overall phases for the FAS - palonosetron 0.25 mg administered as a 30-min IV

Palonosetron 0.25 mg IV	30-min Infusion		30-sec Bolus
	N = 225		N = 215
Delayed Phase (>24-120 h)			
Responder, n (%)	170 (75.6)		165 (76.7)
[95% confidence interval][a]	[69.5; 80.7]		[70.7; 81.9]
CMH risk difference % (Infusion – Bolus) [95% CI][b]		-1.2 [-8.7; 6.3]	
Overall Phase (0-120 h)			
Responder, n (%)	150 (66.7)		156 (72.6)
[95% confidence interval][a]	[60.3; 72.5]		[66.2; 78.1]
CMH risk difference % (Infusion – Bolus) [95% CI][b]		-6.0 [-14.1; 2.1]	

Source: Summary Table 14.2.2.1
Abbreviations: CMH = Cochran-Mantel-Haenszel; CI = confidence interval; IV = intravenous; N = number of patients in a given group; n = number of patients in a given subgroup.
(a) Wilson score method confidence interval.
(b) CMH stratum-adjusted method for difference in proportions, stratified by gender and country according to Koch et al. and O'Gorman et al.

Table 12: secondary efficacy endpoints : proportion of patients with no emetic episodes & no rescue medication in the acute, delayed, and overall phases- Results for the FAS

Palonosetron 0.25 mg IV	**30-min Infusion** N = 225		**30-sec Bolus** N = 215
Acute Phase (0-24 h)			
Responder, n (%)	186 (82.7)		190 (88.4)
[95% confidence interval][a]	[77.2; 87.1]		[83.4; 92.0]
CMH risk difference % (Infusion – Bolus) [95% CI][b]		-5.6 [-11.9; 0.6]	
Delayed Phase (>24-120 h)			
Responder, n (%)	176 (78.2)		168 (78.1)
[95% confidence interval][a]	[72.4; 83.1]		[72.1; 83.1]
CMH risk difference % (Infusion – Bolus) [95% CI][b]		0.1 [-7.2; 7.4]	
Overall Phase (0-120 h)			
Responder, n (%)	155 (68.9)		160 (74.4)
[95% confidence interval][a]	[62.6; 74.6]		[68.2; 79.8]
CMH risk difference % (Infusion – Bolus) [95% CI][b]		-5.6 [-13.6; 2.4]	

Source: Summary Table 14.2.2.2.
Abbreviations: CMH = Cochran-Mantel-Haenszel; CI = confidence interval; IV = intravenous; N = number of patients in a given group; n = number of patients in a given subgroup.
(a) Wilson score method confidence interval.
(b) CMH stratum-adjusted method for difference in proportions, stratified by gender and country according to Koch et al. and O'Gorman et al.

Table 16 No Rescue Medication in the Acute, Delayed, and Overall Phases (Population: Full Analysis Set)

Palonosetron 0.25 mg IV	30-min Infusion		30-sec Bolus
	N = 225		N = 215
Acute Phase (0-24 h)			
Responder, n (%)	200 (88.9)		195 (90.7)
[95% confidence interval][a]	[84.1; 92.4]		[86.1; 93.9]
CMH risk difference % (Infusion – Bolus) [95% CI][b]		-1.7 [-7.0; 3.7]	
Delayed Phase (>24-120 h)			
Responder, n (%)	183 (81.3)		176 (81.9)
[95% confidence interval][a]	[75.7; 85.9]		[76.2; 86.4]
CMH risk difference % (Infusion – Bolus) [95% CI][b]		-0.7 [-7.6; 6.3]	
Overall Phase (0-120 h)			
Responder, n (%)	173 (76.9)		169 (78.6)
[95% confidence interval][a]	[71.0; 81.9]		[72.6; 83.6]
CMH risk difference % (Infusion – Bolus) [95% CI][b]		-2.0 [-9.3;5.4]	

Source: Summary Table 14.2.2.5
Abbreviations: CMH = Cochran-Mantel-Haenszel; IV = intravenous; N = number of patients in a given group; n = number of patients in a given subgroup.
(a) Wilson score method confidence interval.
(b) CMH stratum-adjusted method for difference in proportions, stratified by gender and country according to Koch et al. and O'Gorman et al.

Ancillary analyses

Subgroup analyses in studies PALO-15-17 and NEPA-15-18 were performed on selected endpoints based on stratification factors which were the same for both trials; gender and country.

Table 13 differences in response between gender, the difference being greater with the intravenous formulation compared to the oral formulation.

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Table 14.2.1.3 Subgroup analysis: Complete Response in each phase by Cycle and by Gender - FAS
Subgroup: Male

Cycle	Phase	IV NEPA FDC (N=203) n (%) [95%CI]	Oral NEPA FDC (N=201) n (%) [95%CI]	Treatment Difference % [95%CI] Without strata adjustment	With strata adjustment
Patients with a Complete Response					
Cycle 1	Number of evaluable patients in cycle	107	107		
	Acute Phase (0-24 hours)	106 (99.1) [94.9;99.8]	103 (96.3) [90.8;98.5]	2.8 [-1.9; 8.3]	2.8 [-1.1; 6.7]
	Delayed Phase (>24-120 hours)	91 (85.0) [77.1;90.6]	99 (92.5) [85.9;96.2]	-7.5 [-16.2; 1.1]	-7.5 [-15.5; 0.5]
	Overall (0-120 hours)	90 (84.1) [76.0;89.8]	98 (91.6) [84.8;95.5]	-7.5 [-16.5; 1.4]	-7.5 [-15.8; 0.8]
Cycle 2	Number of evaluable patients in cycle	92	96		
	Acute Phase (0-24 hours)	88 (95.7) [89.3;98.3]	91 (94.8) [88.4;97.8]	0.9 [-6.1; 7.8]	0.7 [-5.2; 6.7]
	Delayed Phase (>24-120 hours)	79 (85.9) [77.3;91.6]	89 (92.7) [85.7;96.4]	-6.8 [-16.2; 2.2]	-6.3 [-14.4; 1.8]
	Overall (0-120 hours)	77 (83.7) [74.8;89.9]	87 (90.6) [83.1;95.0]	-6.9 [-16.8; 2.8]	-6.4 [-15.3; 2.6]
Cycle 3	Number of evaluable patients in cycle	80	80		
	Acute Phase (0-24 hours)	79 (98.8) [93.3;99.8]	78 (97.5) [91.3;99.3]	1.3 [-4.5; 7.5]	1.4 [-2.9; 5.7]
	Delayed Phase (>24-120 hours)	74 (92.5) [84.6;96.5]	74 (92.5) [84.6;96.5]	0.0 [-8.9; 8.9]	1.4 [-5.6; 8.3]
	Overall (0-120 hours)	73 (91.3) [83.0;95.7]	74 (92.5) [84.6;96.5]	-1.3 [-10.4; 7.8]	0.1 [-7.1; 7.4]
Cycle 4	Number of evaluable patients in cycle	57	62		
	Acute Phase (0-24 hours)	53 (93.0) [83.3;97.2]	62 (100) [94.2; 100]	-7.0 [-16.7; 0.2]	-6.5 [-12.4; -0.6]
	Delayed Phase (>24-120 hours)	51 (89.5) [78.9;95.1]	62 (100) [94.2; 100]	-10.5 [-21.1; -2.4]	-8.5 [-15.3; -1.6]
	Overall (0-120 hours)	50 (87.7) [76.8;93.9]	62 (100) [94.2; 100]	-12.3 [-23.2; -3.8]	-10.0 [-17.2; -2.8]

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Table 14.2.1.3 Subgroup analysis: Complete Response in each phase by Cycle and by Gender - FAS
Subgroup: Female

Cycle	Phase	IV NEPA FDC (N=203) n (%) [95%CI]	Oral NEPA FDC (N=201) n (%) [95%CI]	Treatment Difference % [95%CI] Without strata adjustment	With strata adjustment
Patients with a Complete Response					
Cycle 1	Number of evaluable patients in cycle	96	94		
	Acute Phase (0-24 hours)	82 (85.4) [77.0;91.1]	79 (84.0) [75.3;90.1]	1.4 [-9.0; 11.8]	1.7 [-8.0; 11.4]
	Delayed Phase (>24-120 hours)	68 (70.8) [61.1;79.0]	77 (81.9) [72.9;88.4]	-11.1 [-22.8; 1.0]	-10.7 [-22.1; 0.6]
	Overall (0-120 hours)	66 (68.8) [58.9;77.1]	71 (75.5) [66.0;83.1]	-6.8 [-19.2; 6.0]	-6.7 [-18.5; 5.0]
Cycle 2	Number of evaluable patients in cycle	87	80		
	Acute Phase (0-24 hours)	73 (83.9) [74.8;90.2]	68 (85.0) [75.6;91.2]	-1.1 [-12.1; 10.2]	0.1 [-10.5; 10.7]
	Delayed Phase (>24-120 hours)	68 (78.2) [68.4;85.5]	68 (85.0) [75.6;91.2]	-6.8 [-18.4; 5.1]	-6.4 [-17.5; 4.6]
	Overall (0-120 hours)	66 (75.9) [65.9;83.6]	64 (80.0) [70.0;87.3]	-4.1 [-16.5; 8.6]	-4.1 [-16.1; 7.8]
Cycle 3	Number of evaluable patients in cycle	83	70		
	Acute Phase (0-24 hours)	72 (86.7) [77.8;92.4]	66 (94.3) [86.2;97.8]	-7.5 [-17.1; 2.3]	-6.6 [-15.4; 2.3]
	Delayed Phase (>24-120 hours)	66 (79.5) [69.6;86.8]	61 (87.1) [77.3;93.1]	-7.6 [-19.2; 4.6]	-6.1 [-16.7; 4.4]
	Overall (0-120 hours)	64 (77.1) [67.0;84.8]	59 (84.3) [74.0;91.0]	-7.2 [-19.3; 5.7]	-5.2 [-16.5; 6.0]
Cycle 4	Number of evaluable patients in cycle	65	55		
	Acute Phase (0-24 hours)	57 (87.7) [77.5;93.6]	54 (98.2) [90.4;99.7]	-10.5 [-20.7; -0.7]	-7.6 [-15.4; 0.2]
	Delayed Phase (>24-120 hours)	54 (83.1) [72.2;90.3]	53 (96.4) [87.7;99.0]	-13.3 [-24.5; -2.0]	-10.7 [-20.1; -1.3]
	Overall (0-120 hours)	52 (80.0) [68.7;87.9]	52 (94.5) [85.1;98.1]	-14.5 [-26.4; -2.3]	-12.2 [-22.9; -1.4]

Treatment by factor interaction was tested only in the efficacy study (PALO-15-17). No treatment-by-gender or treatment-by-country interactions were detected although the study may not have been sufficiently powered to detect such differences.

All subgroup analyses were exploratory and results need to be interpreted with caution due to small numbers in some groups.

Table 14: CR in study NEPA-15-18 males / females:

Table 15: CR in the overall phase in study NEPA-15-18 - FAS

	Males		Females	
	N	Treatment Difference NEPA IV minus Oral [95%CI]	N	Treatment Difference NEPA IV minus Oral [95%CI]
Cycle 1	214	-7.5 [-15.8; 0.8]	190	-6.7 [-18.5; 5.0]
Cycle 2	188	-6.4 [-15.3; 2.6]	167	-4.1 [-16.1; 7.8]
Cycle 3	160	0.1 [-7.1; 7.4]	153	-5.2 [-16.5; 6.0]
Cycle 4	119	-10.0 [-17.2; -2.8]	120	-12.2 [-22.9; -1.4]

Source: Table 14.2.1.3 – study NEPA-15-18
Note: The 95%CI for the difference in proportions is calculated with strata adjustment using the Cochran-Mantel-Haensel method with country as strata

Table 15: ***main efficacy results- summary***

Table 27: Results of Efficacy Studies in IV FDC Program

Study	Treatment Arm	# Treated/FAS	Complete Response (%)			difference and 99% CI for primary endpoint (for non-inferiority trial)	Statistical Test
			Acute	Delayed	Overall		
PALO-15-17	Palo 0.25 mg IV 30 min infusion Palo 0.25 mg IV 30 sec bolus	225/225 215/215	82.7 86.5	75.6 76.7	66.7 72.6	-3.8[-12.2, 4.7] p<0.001	CR in acute phase (primary endpoint) CMH risk difference % (infusion – bolus) [99% CI]. Stratum adjusted method for difference in proportions, stratified by gender and country. NI margin set to 15%. P value associated with non-inferiority testing.
NEPA-15-18	Cycle 1 IV FDC (260/0.25 mg) Oral FDC (300/0.50mg)	 203/203 201/201	 92.6 90.5	 78.3 87.6	 76.8 84.1	 N/A	N/A Efficacy was a secondary objective, no formal statistical test performed.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16. Summary of efficacy for trial NEPA-15-18

Title: A phase 3, multicentre, randomised, double-blind, active control study to evaluate the safety and efficacy of IV fosnetupitant/palonosetron (260 mg/0.25 mg) combination for the prevention of chemotherapy-induced nausea and vomiting in repeated chemotherapy cycles in patients receiving highly emetogenic chemotherapy..	
Study identifier	Study Number : NEPA-15-18 Eudra CT Number : 2015-001800-74

Design	Multicentre, multinational, randomized, active-controlled, double-blind, double-dummy, parallel group, stratified study evaluating the safety and efficacy of a single dose of IV NEPA FDC (260 mg/0.25 mg) infused in 30 min, with oral dexamethasone, prior to initial and repeated cycles of HEC. The control group was oral netupitant/palonosetron (300 mg/0.50 mg) fixed-dose combination (Oral NEPA FDC) administered orally 60 min before start of reference HEC.		
	Duration of main phase: Duration of screening period: Follow-up visit or a telephone call:	14 weeks. 7-14 days	
Hypothesis	descriptive statistics for the efficacy endpoints		
Treatments groups	Test group	IV fosnetupitant/palonosetron (260 mg/0.25 mg) fixed-dose combination (IV NEPA FDC).	
	Control group	oral netupitant/palonosetron (300 mg/0.50 mg) fixed-dose combination (Oral NEPA FDC).	
Endpoints and definitions	CRR acute phase	proportion of patients with complete response (CR) (no emetic episodes and no rescue medication) during the acute phase (0-24 h after the start of reference chemotherapy)	
	CRR delayed phase.	proportion of patients with complete response (CR) (no emetic episodes and no rescue medication) during delayed phase (>24- 120 h after the start of reference chemotherapy)	
	CRR overall phase	proportion of patients with complete response (CR) (no emetic episodes and no rescue medication) during the overall phase (0-120 h after the start of reference chemotherapy)	
	Absence of emesis	- Rate of patients with no emetic episode during the • acute(0-24 h), • delayed(>24-120 h),	
		Rate of patients with no rescue medication during the : • acute(0-24 h), • delayed(>24-120 h), • overall (0-120h) phases	
Database lock			
Results and Analysis			

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set (FAS) Per protocol <time point>			
Descriptive statistics and estimate variability	Treatment group	Test group 30-min infusion	Control group 30-sec IV bolus	Treatment Difference % [95%CI] Without strata adjustment[a] With strata adjustment[b]
	Cycle 1			
	Number of subject (FAS)	203	201	
	CRR acute phase n (%) 95% IC	188 (92.6) [88.2;95.5]	182 (90.5) [85.7;93.9]	2.1 [-3.5;7.7] 2.3 [-2.7;7.2]
	CRR delayed n (%) 95% IC	159 (78.3) [72.2;83.4]	176 (87.6) [82.3;91.4]	-9.2 [-16.5;-1.9] -9.0 [-15.8;-2.2]
	CRR overall n (%) 95% IC	156 (76.8) [70.6;82.1]	169 (84.1) [78.4;88.5]	-7.2 [-14.9;0.5] -7.1 [-14.2;-0.1]
	Cycle 2			
	Number of subject (FAS)	179	176	
	CRR acute phase n (%) 95% IC	161 (89.9) [84.7;93.5]	159 (90.3) [85.1;93.9]	-0.4 [-6.8;6.0] 0.4 [-5.4;6.3]
	CRR delayed n (%) 95% IC	147 (82.1) [75.9;87.0]	157 (89.2) [83.8;93.0]	-7.1 [-14.4;0.3] -6.4 [-13.1;0.4]
	CRR overall n (%) 95% IC	143 (79.9) [73.4;85.1]	151 (85.8) [79.9;90.2]	-5.9 [-13.7;2.0] -5.3 [-12.7;2.0]
	Cycle 3			
	Number of subject (FAS)	163	150	
	CRR acute phase n (%) 95% IC	151 (92.6) [87.6;95.7]	144 (96.0) [91.5;98.2]	-3.4 [-8.9;2.1] -2.4 [-7.3;2.4]
	CRR delayed n (%) 95% IC	140 (85.9) [79.7;90.4]	135 (90.0) [84.2;93.8]	-4.1 [-11.4;3.3] -2.2 [-8.5;4.0]
	CRR overall n (%) 95% IC	137 (84.0) [77.7;88.9]	133 (88.7) [82.6;92.8]	-4.6 [-12.2;3.1] -2.5 [-9.1;4.2]
	Cycle 4	122		

	Number of subject (FAS)	122	117	
	CRR acute phase n (%) 95% IC	110 (90.2) [83.6;94.3]	116 (99.1) [95.3;99.8]	-9.0 [-15.6;-3.4] -7.0 [-11.9;-2.2]
	CRR delayed n (%) 95% IC	105 (86.1) [78.8;91.1]	115 (98.3) [94.0;99.5]	-12.2 [-19.6;-5.6] -9.6 [-15.4;-3.8]
	CRR overall n (%) 95% IC	102 (83.6) [76.0;89.1]	114 (97.4) [92.7;99.1]	-13.8 [-21.6;-6.6] -11.1 [-17.6;-4.6]
	Cycle 1			
Absence of Emetic Episodes	Number of subject (FAS)	203	201	
	acute phase n (%) 95% IC	193 (95.1) [91.2;97.3]	187 (93.0) [88.6;95.8]	2.0 [-2.7;7.0] 2.4 [-1.8;6.5]
	delayed phase n (%) 95% IC	173 (85.2) [79.7;89.4]	184 (91.5) [86.9;94.7]	-6.3 [-12.7;0.0] -6.2 [-12.0;-0.4]
	overall phase n (%) 95% IC	171 (84.2) [78.6;88.6]	178 (88.6) [83.4;92.3]	--4.3 [-11.1;2.4]* -4.3 [-10.4;1.8]]
Absence of Rescue Medication	acute phase n (%) 95% IC	195 (96.1) [92.4;98.0]	187 (93.0) [88.6;95.8]	3.0 [-1.6;7.8] 3.3 [-0.6;7.3]
	delayed phase n (%) 95% IC	172 (84.7) [79.1;89.0]	184 (91.5) [86.9;94.7]	-6.8 [-13.2;-0.5] -6.9 [-12.9;-1.0]
	overall phase n (%) 95% IC	168 (82.8) [77.0;87.3]	179 (89.1) [84.0;92.7]	-6.3 [-13.1;0.5] -6.0 [-12.3;0.2]
Analysis description	Efficacy objectives were only descriptive			

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is for a line extension to the intravenous formulation of the fixed dose combination Akynzeo. Therefore, the clinical development programme requires to show that this formulation is comparable and bioequivalent to the oral formulation. From an efficacy perspective this has not been robustly demonstrated by the applicant in light of the study designs, namely submitting efficacy studies that are more supportive in nature and relying mainly on the PK-bridge. The study NEPA-15-18 was not designed or powered to examine for differences in clinical efficacy between the oral and IV administration of fixed dose combination Akynzeo.

An "other concern" was raised in the efficacy assessment regarding the absence a powered efficacy study. There were also "other concerns" that required careful consideration by the applicant as they highlighted the shortcomings of the efficacy data presented and lack of adherence to the CHMP scientific advice received.

The applicant emphasises that study NEPA-15-18 was aimed to complement the clinical development programme of IV NEPA FDC, providing additional safety information as per FDA request in light of the higher Cmax of intravenous netupitant observed compared to oral formulation in the bioavailability study PNET-12-23. The applicant references the "bioequivalence plus safety approach" that was accepted by the CHMP for fosaprepitant assessment. However, CHMP scientific advice in relation to Akynzeo emphasised that judging how far PK differences might translate in altered efficacy is the less preferred option from a regulatory perspective.

Regarding study NEPA-15-18, there is little uncertainty that the intravenous formulation is comparable to the oral FDC during the acute phase of CINV. The proportion of patients with no emetic episodes, no rescue medication or no significant nausea in the acute phase was ≥90% for both treatment groups at each cycle. In contrast the response in the delayed phase is not comparable with the worst difference seen in cycle 4.

This difference in results in the delayed phase is relevant in light of the OC raised regarding the shorter half-life in study PNET-12-23 and the scientific advice given in 2016 relating to PK bridging from study PNET-12-23:

"From a scientific perspective, there is concern on whether the advantage established for the oral FDC over the mono-components can be equally assumed for the IV FDC……tmax and t1/2 are considered major determinants of the duration of drug action after dosing; t1/2 of the intravenous formulation seems to be shorter and less variable, compared to the capsules. Correspondingly, the maintenance of the therapeutic concentration in the plasma might be influenced by a shorter t1/2. This could lead to a shortening of the duration of the antiemetic effect. Even if the duration of antiemetic effect of netupitant is probably better correlated with interactions at the receptor level than with plasma half-life, the clinical relevance of the difference in t1/2 remains still unclear and represents an uncertainty factor."

The applicant provided a justification as to why the intravenous formulation half-life was shorter in study PNET-12-23 compared to the oral formulation (exceptionally high individual half-life values but similar median half-lives) and that the differences are unlikely to have impacted the delayed efficacy effects which is acceptable. The applicant has also provided a justification as to how the lower Cmax after the 30min infusion compared to the 10sec bolus does not negatively affect the clinical efficacy of study NEPA-15-18 which is acceptable:

a) Cmax is not primarily related to the antiemetic efficacy of 0.25mg palonosetron and b) study PALO-15-17 demonstrates non-inferiority.

The applicant does emphasise that they did consider the scientific advice in relation to assessing response after subsequent cycles of chemotherapy but did not consider a comparative efficacy study as the pivotal safety study NEPA-15-18 had already started recruiting patients.

The difference in complete response rate especially in the delayed phase was unexpected considering that exposure was equivalent in study PNET-12-23. Moreover, the responses rates in the overall phase were considered as the focus of efficacy measures because the overall phase captures both the acute and delayed phases reflective of the indication. While a definitive explanation cannot be provided by the applicant, a few noteworthy points were raised in terms of the composite endpoint whereby "no emetic episodes" is the most objective component compared to "use of rescue medication" which is left

to the patient's decision. This point is further emphasised in the post hoc analyses that excluded the sites where there was inappropriate use of rescue medication.

Furthermore, in order to support efficacy of IV NEPA FDC in the delayed phase, the applicant provided results from new study (NEPA 17-05) designed to evaluate the safety (primary endpoint) and efficacy (secondary endpoint) of IV NEPA FDC versus PO NEPA FDC for the prevention of CINV in female breast cancer patients receiving anthracycline/cyclophosphamide (AC) chemotherapy (HEC). Descriptive efficacy results showed a lower difference in terms of complete response in the delayed phase between both arms in study NEPA-17-05 compared to study NEPA15-18 (-3.3% [-10.7;4.1] vs -9.2 [-16.5;-1.9] respectively) during cycle 1. However, no definitive conclusions can be made on these studies regarding the efficacy.

The applicant references the SmPC guidelines stating that the descriptive efficacy results presented are not statistically compelling or clinically relevant to include in section 5.1 of the SmPC. Despite this, the CHMP regards this efficacy data (or lack of) as clinically relevant for the prescriber. Informing the clinician that the efficacy results are not interpretable explaining the reasons for not designing a non-inferiority study is clinically relevant. However, given that a) NETU-10-29 (oral FDC versus aprepitant + palonosetron) was also designed similarly with descriptive statistics and b) CHMP did not accept this data to be included in section 5.1 of the SmPC, the issue will not be further pursued.

The imbalance of CR between males and females and the differential of efficacy in women receiving the infusion was further discussed. In study PALO 15-17, patients were stratified by gender in light of the known higher occurrence of CINV in females and the applicant provided a logistic regression model which did not find a gender interaction. Furthermore, the number of female patients were smaller (33%). While a difference between the two strata are expected, any difference between the infusion versus the bolus is not expected. The applicant states that there is no plausible clinical or PK rationales for a lower efficacy of infusion as compared to bolus in females and results should not be over-interpreted.

The gender imbalance between the two studies may be due to the difference in geographical regions (Ukraine not included in study PALO-15-17 where the majority of the patients with ovarian cancer came from) and type of cancer (ovarian cancer, H&N cancer and lung cancer), which seems reasonable as gender was included as a stratification factor at the time of randomization.

While the newly submitted female only study NEPA-17-05 does not show a difference in efficacy between the two types of formulation, the results do not allow draw a firm conclusion on a difference in effectiveness between men and women since only women were included.

Efficacy data and additional analyses

NEPA-15-18 and PALO-15-17 in the presented application both enrolled patients receiving HEC only. NEPA enrolled 53% males while PALO enrolled 67% males. Comparing the proportion of MEC: HEC and Male: Female in studies NEPA-15-18, PALO-15-17 and also the 3 studies from the initial oral formulation application; NETU-10-29, NETU-08-18 and NETU-07-07, the data seem to suggest that males respond better to Akynzeo when receiving HEC than MEC.; females respond similarly to Akynzeo whether receiving HEC or MEC. However, in relation to gender, it is difficult to draw definitive conclusions from this data; the CHMP will not pursue this issue any further.

It is acknowledged that the emetogenic potential of chemotherapy regimen is the most important predictor of CINV risk and therefore studies performed in patients receiving HEC is crucial. In all clinical submitted studies only patients receiving HEC regimens were included. No studies were conducted in the patients receiving MEC. This is in contrast to the studies performed for the oral formulation which included HEC and MEC. As per the EMA Guideline On Non-Clinical and Clinical Development Of

Medicinal Products For The Prevention Of Nausea And Vomiting Associated With Cancer Chemotherapy, studies specifically addressing this issue are expected.

In the clinical overview it was stated: *"If, however, at least non-inferior activity has been shown in a substitution study in case of highly emetogenic therapy and the use of the standard regimen is well documented also in moderately emetogenic chemotherapy, extrapolation as regards activity might be feasible"*

In light of a) the duration of activity of the intravenous formulation and b) the reduced efficacy in the delayed phase in study NEPA-15-18, extrapolation of activity was not considered feasible. Therefore, the applicant was requested to further justify omitting studies in participants receiving MEC. The applicant considers that the IV NEPA FDC line extension was mainly based on a bioequivalence approach considering that fosnetupitant is rapidly and completely converted into netupitant. For this reason, the applicant considers that the data obtained with the oral form are applicable to the injectable form and there is no reason to regard the safety profile in patients receiving MEC any differently. However, one may wonder about the choice of not performing studies in patients receiving a MEC based chemotherapy while the oral form is registered for the prevention of CINV in patients receiving both cisplatin-based HEC chemotherapy or MEC regimen.

There is no unequivocal demonstration of a shorter duration of activity of the intravenous formulation over the initial 120 hours following chemotherapy administration. The applicant provides a justification that a different duration of activity and a reduced efficacy of IV NEPA are not supported by PK/PD results which is accepted. This is further supported in the clinical pharmacology section; the applicant provided 90% CIs for the ratio of the geometric means for AUC0-24h, AUC24-120h, and Cmin at 120 hrs of netupitant for 260 mg IV pro-netupitant vs 300 mg oral netupitant. Bioequivalence between IV pro-netupitant and oral netupitant was demonstrated for these time intervals.

The reduced activity in the delayed phase in study NEPA 15-18 is not fully understood but results submitted by the applicant from study NEPA 17-15 are supportive. Even though both studies were not designed or powered to compare efficacy of IV NEPA FDC vs PO NEPA FDC, the intravenous formulation was demonstrated to be bioequivalent to the oral formulation, therefore the efficacy of IV NEPA FDC can be considered similar and is therefore acceptable.

2.5.4. Conclusions on the clinical efficacy

The pivotal clinical study was primarily designed as a safety study and was not powered for comparative efficacy therefore it is difficult to draw definitive efficacy conclusions from this study. However, given that the overall application adopted a bioequivalence PK efficacy bridging approach with descriptive efficacy data only, these issues will no longer/will be pursued.

2.6. Clinical safety

For this line extension to the authorised oral netupitant-palonosetron fixed-dose combination (NEPA FDC - Akynzeo® hard capsules), safety data is drawn from the oral development program and post marketing since the approval and commercialisation of the oral formulation as well as from the IV NEPA FDC (intravenous netupitant-palonosetron fixed-dose combination) studies.

Safety data for the IV NEPA FDC clinical development program are not integrated due to the design of the development program. There were two trials that administered the IV NEPA FDC in cancer patients (NEPA-15-18, NEPA-15-19), two that administered fosnetupitant alone in healthy volunteers (PNET-12-23, PNET-13-63) and one that employed palonosetron alone (PALO-15-17). No integration of safety data was deemed appropriate for the two studies NEPA-15-18 and NEPA 15-19 in cancer patients due to the clinical and methodological differences in the design and population (phase 3 safety vs. phase 1

PK, controlled vs. single arm, chemo naïve vs. naïve and non-naïve, multicycle vs. single cycle, respectively).

NEPA-15-18

NEPA-15-18 was a Phase 3, multinational, multicenter, randomized, double-blind, double-dummy, active-controlled safety study conducted in chemotherapy-naïve adult male and female patients (ECOG Performance Status of 0, 1, or 2) who were diagnosed with a malignant solid tumour requiring at least 4 cycles of highly emetogenic chemotherapy (HEC). The study was designed to assess the safety and tolerability of a single IV NEPA FDC dose in both initial and repeated cycles of chemotherapy.

Patients were randomised to receive either the IV NEPA FDC or oral Akynzeo®; both treatment arms concomitantly received oral dexamethasone for CINV prophylaxis. Study drugs were administered 30 or 60 minutes prior to the start of the chemotherapy (IV and oral, respectively) on day 1, with oral dexamethasone being administered 30 minutes prior to the start of chemotherapy and also daily on days 2 to 4.

Patients could continue to participate in up to 4 repeated cycles, provided that eligibility criteria were fulfilled.

Safety was the primary objective; it included evaluation of physical examination and vital signs findings, 12-lead ECG results, safety laboratory test results (haematology, blood chemistry, urinalysis), and adverse event monitoring.

A total of 404 patients (203 IV FDC; 201 oral Akynzeo®) were treated in Study NEPA-15-18 and are included in the safety population; of these, approximately 60% went on to complete all 4 cycles.

NEPA-15-19

NEPA-15-19 was a Phase 1, single arm, open label pharmacokinetic and safety study conducted in adult male and female naïve or non-naïve patients scheduled to receive a cycle of HEC. All patients received the IV NEPA FDC (260 mg fosnetupitant/0.25 mg palonosetron) infused over 30 minutes starting from 30 minutes before HEC. Oral dexamethasone was administered on Day 1 and also daily on days 2 to 4.

Pharmacokinetic parameters were calculated from plasma concentrations of fosnetupitant, netupitant, netupitant metabolites (M1, M2 and M3) and palonosetron.

The safety variables evaluated in this study were: treatment-emergent adverse events (TEAEs), physical examination (PE), vital signs, 12-lead electrocardiogram (ECG), laboratory tests (haematology, blood chemistry, and urinalysis).

A total of 36 patients were treated in Study NEPA-15-19 and are included in the safety population.

PNET-12-23

This was a Phase 1, double-blind, controlled, parallel group, single ascending dose study in healthy male and female volunteers to assess the safety of intravenously administered fosnetupitant combined with crossover study extensions to estimate the dose of fosnetupitant yielding netupitant equivalent exposure to that provided by oral netupitant 300 mg/palonosetron 0.5 mg fixed dose combination.

The study was designed in 3 parts, where doses of fosnetupitant ranging from 19.5 mg to 390 mg were administered either as a single dose or in a crossover fashion with oral Akynzeo®. The primary objective was to assess the safety of pro-netupitant administered as a single intravenous (IV) infusion. Safety assessments included, Adverse events (AEs), clinical laboratory test results (haematology, blood chemistry, urinalyses, and blood coagulation), vital signs, 12-lead electrocardiogram results,

physical examination findings. For the local tolerability assessment in addition to laboratory parameters an ultrasonography scanning of dosing and contralateral veins was performed.

A total of 158 healthy subjects were treated with study drug in this trial and included in the safety population.

PNET-13-63

This was a Phase 1, randomized, three-period, four-treatment, incomplete block, crossover study in healthy male and female volunteers designed to evaluate the potential pharmacokinetic interaction between three doses of intravenous fosnetupitant and the oral dexamethasone regimen used for antiemetic prophylaxis.

Safety population of the study includes a total of 30 healthy subjects.

PALO-15-17

PALO-15-17 was a Phase 3, multinational, multicenter, randomized, double-blind, double-dummy, parallel-group study conducted in chemotherapy-naïve adult male and female patients with a malignant solid tumour who were scheduled to have their first cycle of one of the protocol-specified reference HEC regimens. The study was designed to support the IV NEPA FDC program by establishing the non-inferiority of a single intravenous (IV) dose of palonosetron 0.25 mg administered as a 30-minute (min) infusion versus a single IV dose of palonosetron 0.25 (Aloxi®) mg administered as a 30-second (sec) bolus (FDA-approved regimen) prior to HEC. Patients in both treatment arms received oral dexamethasone prior to HEC on day 1, and daily [BID] from days 2 through 4.

Safety was assessed by the evaluation of physical examination and vital signs findings, 12-lead ECG results, safety laboratory test results (haematology, blood chemistry, urinalysis), and adverse event monitoring.

A total of 440 patients (225 in the 30-minute infusion group; 215 in the bolus group) were treated in Study PALO-15-17 and are included in the safety population.

Patient exposure

In study NEPA-15-18, the safety population (all patients who had received at least one dose of active study drug [including partial infusion]) included a total of 404 cancer patients treated in up to 4 cycles. Approximately 60% of patients in NEPA-15-18 completed the 4 cycles. Overall, there were 404 patients treated in Cycle 1, 356 patients treated in Cycle 2, 313 patients treated in Cycle 3, and 239 patients treated in Cycle 4. Patients treated in the IV and oral NEPA groups throughout the 4 cycles were,

- Cycle 1: 203 patients IV NEPA, 201 patients oral NEPA
- Cycle 2: 179 patients IV NEPA, 177 patients oral NEPA
- Cycle 3: 163 patients IV NEPA, 150 patients oral NEPA
- Cycle 4: 122 patients IV NEPA, 117 patients oral NEPA

All patients treated with either IV or oral NEPA FDC also received oral dexamethasone.

Study NEPA 15-19 included 36 cancer patients treated for one cycle. 12 of the patients were mistakenly under-dosed due to incomplete administration of the IV NEPA FDC volume caused by technical issues with the infusion pump detector system however the 12 patients were replaced for PK evaluations and a total of 36 patients was included in the safety population.

Adverse events

The analysis of adverse events was based on treatment-emergent AEs (TEAEs) defined as AEs that began or worsened in severity after the start of the first administration of the study drug through study completion.

NEPA-15-18

Of the 404 patients in the safety population, 343 (84.9%) patients experienced at least one TEAE, and the incidence of TEAEs was similar between the treatment groups: 83.3% of patients in the IV NEPA FDC group and 86.6% of patients in the oral NEPA FDC group.

TEAEs were most commonly reported in body systems that are most often involved with the cytotoxic effects of chemotherapy administration. Overall, throughout the entire study and in both the treatment groups, TEAEs were most commonly reported (>15%) in the following SOCs:

- blood and lymphatic system disorders (46.3%);
- gastrointestinal (GI) disorders (28.0%);
- general disorders and administration site conditions (25.7%);
- investigations (22.5%); and
- skin and subcutaneous tissue disorders (18.1%).

An overview of TEAEs throughout the NEPA-15-18 study is summarised in Table 5 below.

Table 5: Overview of TEAEs Throughout the NEPA-15-18 Study (Population: Safety)

	IV NEPA FDC (N=203) n (%) E	Oral NEPA FDC (N=201) n (%) E	Overall (N=404) n (%) E
Any TEAE	169 (83.3) 808	174 (86.6) 892	343 (84.9) 1700
Study-drug-related TEAE	26 (12.8) 75	23 (11.4) 71	49 (12.1) 146
Dexamethasone-related TEAE	20 (9.9) 33	20 (10.0) 44	40 (9.9) 77
Severe TEAE	86 (42.4) 149	90 (44.8) 188	176 (43.6) 337
Severe study-drug-related TEAE	2 (1.0) 9	3 (1.5) 5	5 (1.2) 14
Severe dexamethasone-related TEAE	3 (1.5) 4	6 (3.0) 12	9 (2.2) 16
Serious TEAE	41 (20.2) 57	43 (21.4) 78	84 (20.8) 135
Serious study-drug-related TEAE	0	0	0
Serious dexamethasone-related TEAE	1 (0.5) 1	5 (2.5) 10	6 (1.5) 11
TEAE leading to death	10 (4.9) 10	14 (7.0) 14	24 (5.9) 24
Study-drug-related TEAE leading to death	0	0	0
Dexamethasone-related TEAE leading to death	1 (0.5) 1	0	1 (0.2) 1
TEAE leading to discontinuation from the study	16 (7.9) 17	20 (10.0) 20	36 (8.9) 37
Study-drug-related TEAE leading to discontinuation from the study	2 (1.0) 2	1 (0.5) 1	3 (0.7) 3
Dexamethasone-related TEAE leading to discontinuation from the study	0	2 (1.0) 2	2 (0.5) 2

Source: Module 5.3.5.1, NEPA-15-18, Table 16

The most frequently reported TEAEs (i.e., those reported by > 5% of patients in either treatment group) were anaemia, leukopenia, neutropenia, thrombocytopenia, constipation, nausea, asthenia,

fatigue, ALT increased, AST increased, blood creatinine increased, decreased appetite, alopecia, headache, and hypertension. These events generally occurred in similar percentages of patients across the IV and oral NEPA groups.

The satisfactory local tolerability observed in Phase 1 studies in healthy subjects with fosnetupitant alone was confirmed in study NEPA-15-18 in cancer patients with IV NEPA FDC. The frequency of TEAEs potentially suggestive of a local tolerability issue (e.g. injection site extravasation, infusion site extravasation, injection site reaction) was small and also reported for the oral treatment group (where a placebo infusion was administered). In addition, the frequency of TEAEs was small (≤ 1.0%) and similar between the two treatment groups for phlebitis and thrombophlebitis. None of these TEAEs were considered by the Investigator as related to treatment with study drug.

TEAEs related to study drug were reported for 26 (12.8%) patients in the IV NEPA FDC group and for 23 (11.4%) patients in the oral NEPA FDC group. Frequency and type of TEAEs were similar in the two treatment groups. The only two events reported in more than 2% of patients in both treatment groups were constipation and ALT increases. Constipation was reported by 13 [6.4%] patients in the IV NEPA FDC group and 12 [6.0%] patients in the oral NEPA FDC group and ALT increases were experienced by 4 patients (2.0%) in each treatment group.

Overall, 47 (11.6%) and 120 (29.7%) patients experienced exclusively mild and moderate (Grades 1 and 2) events, respectively. These events were reported in similar numbers of patients in both treatment groups (Grade 1: 23 [11.3%] patients in the IV NEPA and 24 [11.9%] patients in the Oral NEPA group; Grade 2: 60 [29.6%] patients and 60 [29.9%] in the IV NEPA and Oral NEPA groups, respectively). The pattern of mild and moderate events reflected the overall AE profile of the study; events occurred most frequently in the following SOCs and PTs: Blood and Lymphatic System Disorders (neutropenia, anaemia), Gastrointestinal SOC (nausea, constipation), General Disorders (asthenia, fatigue), and Investigations (AST, ALT and Creatinine increased).

Overall, Grade 3 TEAEs were experienced by 61 (30.0%) patients in the IV NEPA FDC group and 54 (26.9%) patients in the Oral NEPA FDC group, and Grade 4 TEAEs were experienced by 15 (7.4%) patients in the IV NEPA FDC group and 22 (10.9%) patients in the Oral NEPA FDC group. As expected, neutropenia was the most frequent Grade 3/4 TEAE reported during this study (37 [18.2%] patients in the IV NEPA FDC group and 37 [18.4%] patients in the Oral NEPA FDC group). Severe TEAEs were reported for 86 (42.4%) patients in the IV NEPA FDC group and 90 (44.8%) patients in the Oral NEPA FDC group. For IV NEPA FDC, 2 patients (1.0%) experienced severe TEAEs related to study drug and 3 patients (1.5%) experienced severe TEAEs related to dexamethasone. For Oral NEPA FDC, 3 patients (1.5%) experienced severe TEAEs related to study drug and 6 patients (3.0%) experienced severe TEAEs related to dexamethasone.

Table 17: most frequently reported (≥2% of patients in either treatment group) Grade 3- 4 TEAEs

MedDRA System Organ Class MedDRA Preferred Term	IV NEPA FDC (N=203) n (%)		Oral NEPA FDC (N=201) n (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Any Grade 3 or Grade 4 TEAE	61 (30.0)	15 (7.4)	54 (26.9)	22 (10.9)
Blood and lymphatic system disorders	34 (16.7)	12 (5.9)	32 (15.9)	21 (10.4)
Anaemia	5 (2.5)	0	7 (3.5)	1 (0.5)
Leukopenia	6 (3.0)	0	4 (2.0)	3 (1.5)
Neutropenia	28 (13.8)	9 (4.4)	21 (10.4)	16 (8.0)
Thrombocytopenia	0	1 (0.5)	5 (2.5)	2 (1.0)
Investigations	7 (3.4)	2 (1.0)	17 (8.5)	1 (0.5)
Alanine aminotransferase increased	2 (1.0)	0	14 (7.0)	0
Aspartate aminotransferase increased	3 (1.5)	0	5 (2.5)	0

Source: [Module 5.3.5.1, NEPA-15-18, Table 18]
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV NEPA FDC = intravenous fosnetupitant/palonosetron fixed-dose combination; MedDRA = Medical Dictionary for Regulatory Activities, v.18.0; N = number of patients in a given group, n = number of patients in a given subgroup; Oral NEPA FDC = oral netupitant/palonosetron fixed-dose combination; TEAE = treatment-emergent adverse event.

TEAEs leading to study discontinuation were reported for 16 (7.9%) patients in the IV NEPA FDC group and 20 (10.0%) patients in the Oral NEPA FDC group.

The frequency distribution of TEAE severity (CTCAE Grades 1-4) was similar across the treatment groups. TEAEs leading to death were reported for 10 (4.9%) patients in the IV NEPA FDC group and 14 (7.0%) patients in the Oral NEPA FDC group. None of them was assessed as related to study drug.

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

Adverse events of special interest in this study:

1. Electrocardiogram QT prolonged: QT prolongation was identified as an AE of special interest, and changes in QT intervals were monitored closely. Overall, electrocardiogram QT prolonged events were reported for 5 (1.2%) patients, all treated at the same study site. All events were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 and all were non-serious events. The events were assessed as possibly related (2 patients in the IV NEPA FDC group and 1 patient in the Oral NEPA FDC group), probably related (1 patient in the IV NEPA FDC group), and not related (1 patient in the Oral NEPA FDC group) to study drug. Changes for heart rate and all other intervals were small and similar between treatment groups.

2. Constipation: Constipation, a known TEAE observed also with the oral formulation during the clinical development program, was reported for 47 (11.6%) patients overall: 21 (10.3%) patients in the IV NEPA FDC group and 26 (12.9%) patients in the Oral NEPA FDC

group. Only 1 (0.5%) patient in the IV NEPA FDC group had a Grade 3 case of constipation during the study. The event was considered by the Investigator as a non-serious TEAE, not related to treatment with study drug or dexamethasone.

NEPA-15-19

A total of 62 adverse events in 22 (61.1%) patients were TEAEs. The most common (reported in 7 or more patients) occurred in the following SOCs: gastrointestinal disorders (16; 44.4%), general disorders (8; 22.2%) and vascular disorders (7; 19.4%). Specific preferred terms reported in 3 or more patients included constipation (8; 22.2%), nausea (5; 13.9%), peripheral swelling (4;11.1%), asthenia (3; 8.3%) and dizziness (3; 8.3%).

Fourteen (14) of the 62 TEAEs were considered related to the study medication in 8 (22.2%) patients and 5 TEAEs were considered related to dexamethasone in 4 (11.1%) patients.

Table 18

Table 6: Summary of subjects with treatment emergent adverse events NEPA-15-19– Safety population

No. of patients in each category	n (%) E
	N=36
Any TEAE	22 (61.11%) 62
TEAE related to NEPA*	8 (22.22%) 14
TEAE related to dexamethasone*	4 (11.11%) 5
Serious TEAE	0 (0.00%) 0
Severe TEAEs (CTCAE grade >= 3)	0 (0.00%) 0
TEAE leading to withdrawal	0 (0.00%) 0

Source: [Module 5.3.3.2, NEPA-15-19, Table 12.2.3-1]
TEAE(s) = Treatment Emergent Adverse Event(s)
* TEAEs related to a drug are defined as AEs with relationship classified as definite, probable, possible, unassessable or missing.
N – Number of patients; n - Number of patients with at least one adverse event in the category; E - Number of adverse events
"NEPA" = IV NEPA FDC = study drug

All TEAEs reported in this study were either mild or moderate in severity. Fifteen patients (41.7% of safety population) reported exclusively mild TEAEs, while 7 patients (19.4% of the safety population) experienced TEAEs of moderate severity. Moderate intensity events included constipation, nausea, vomiting, asthenia, headache, swelling face, flushing, and hypertension. No patient reported severe or life-threatening (CTC grade ≥3) TEAEs.

PNET-12-23

Overall, 169 TEAEs were observed after drug administration in 80 of the 158 subjects (50.6%). Most of these events (108 events, 63.9%) were assessed as drug-related. All TEAEs were of mild or moderate intensity. No death and no other serious adverse events occurred in this study.

Overview of drug-related treatment-emergent adverse events in total, overall and at a dose of 260 mg pro-netupitant reported by more than 1% of subjects

	S+P-260 mg N=30			Overall IV N=148			Overall Oral N=134			Total N=158		
	n	%	E	n	%	E	n	%	E	n	%	E
TEAE	**10**	**33.3**	**20**	**46**	**31.1**	**83**	**57**	**42.5**	**86**	**80**	**50.6**	**169**
Related TEAEs	**9**	**30.0**	**14**	**34**	**23.0**	**55**	**37**	**27.6**	**53**	**59**	**37.3**	**108**
Gastrointestinal disorders												
Abdominal pain							2	1.5	2	2	1.3	2
Abdominal pain upper				3	2.0	3	5	3.7	6	7	4.4	9
Constipation				2	1.4	2	10	7.5	10	12	7.6	12
Nausea				2	1.4	2	4	3.0	4	4	2.5	6
General disorders and administration site conditions												
Fatigue				6	4.1	6	3	2.2	3	9	5.7	9
Infusion site thrombosis	4	13.3	4	8	5.4	8	2	1.5	2	10	6.3	10
Nervous system disorders												
Dizziness	2	6.7	3	3	2.0	4	3	2.2	3	6	3.8	7
Headache	2	6.7	2	12	8.1	13	17	12.7	20	25	15.8	33

N: Number of subjects in specified group, n: Number of subjects with at least 1 adverse event in the category, %: Percent of Subjects with adverse events, E: Number of adverse events
S: single ascending dose (SAD)/ single ascending dose crossover (SAD-CO) part, P: pilot crossover (P-CO) part
TEAE: treatment-emergent adverse event

Most of the TEAEs observed after treatment with either active IV infusion or active oral drug belonged to the following MedDRA system organ class: General disorders and administration site conditions (56 TEAEs in 40 subjects), Nervous system disorders (50 TEAEs in 34 subjects), and Gastrointestinal disorders (39 TEAEs in 26 subjects). The frequency of subjects with gastrointestinal disorders was higher with the oral formulation compared to the IV formulation (14.9% vs. 6.1%).

The frequency of subjects presenting administration site reactions was only slightly higher with the IV formulation compared to the oral formulation (18.9% vs. 14.9%) due to vessel puncture site thrombosis at the contralateral arm (blood withdrawal arm) observed in both groups. The most frequently reported TEAE after both administration routes was headache. The frequency of subjects with headache was higher with the oral formulation compared to the IV formulation (15.7% vs. 8.1%).

The most frequently reported TEAEs assessed as drug-related were headache (33 events), constipation (12 events), infusion site thrombosis (10 events), abdominal pain upper (9 events), fatigue (9 events), dizziness (7 events), and nausea (6 events). The number of drug-related TEAEs or frequency of subjects with drug-related TEAEs did not increase with ascending pro-netupitant doses. The following drug-related gastrointestinal events occurred mainly after oral administration of netupitant 300 mg/palonosetron 0.5 mg compared to IV pro-netupitant (any dose): constipation (10 and 2 events), abdominal pain upper (6 and 3 events), and nausea (4 and 2 events). Oppositely, the following drug-related adverse events were more frequently observed with the IV pro-netupitant treatment compared to oral netupitant 300 mg/palonosetron 0.5 mg: infusion site thrombosis (8 and 2 events), fatigue (6 and 3 events), and dizziness (4 and 3 events) occurred mainly after IV administration of pro-netupitant.

The most frequently reported drug-related TEAE after the active drug administration following both routes was headache. The frequency of headache adverse events considered as drug-related was lower after IV administration (8.1% of IV treated subjects) compared to oral administration (12.7% of oral treated subjects).

A total of 38 thrombotic events have been observed during the study. These TEAEs were reported with a clearly higher frequency as cases involving the contralateral blood drawing vein (28 events) compared to cases involving the dosing vein (10 events). A total of 8 drug-related TEAEs of infusion

site thrombosis of mild severity were observed after IV administration (1 subject treated with 195 mg, 2 subjects treated with 234 mg, 4 subjects treated with 260 mg, and 1 subject treated with 286 mg). All 8 events recovered. The percentage of subjects with infusion site thrombosis with respect to the number of subjects treated with the respective dose was 3.6% for 195 mg (1 of 28 treated subjects), 10.5% for 234 mg (2 of 19 treated subjects), 13.3% for 260 mg (4 of 30 treated subjects) and 5.6% for 286 mg (1 of 18 treated subjects). No thrombotic events were observed with doses above 286 mg pro-netupitant.

Applicant study report safety summary:

- Single doses of 19.5 mg to 390 mg pro-netupitant were well tolerated after administration via IV infusion, at 2.6 mg/mL concentration over 30 min. The proportion of subjects with drug-related TEAEs or the number of drug-related TEAEs did not increase with ascending pro-netupitant doses.
- Some differences in the safety profile after administration of the IV formulation containing pro-netupitant and the oral FDC containing netupitant and palonosetron may be related to the route of administration and/or to the presence of palonosetron.
- Pro-netupitant was locally well tolerated after IV administration by IV infusion over 30 min at the concentration of 2.6 mg/mL.
- The safety results were in line with the current knowledge about the safety of netupitant.
- No notable effect of the IMP on safety laboratory parameters, vital signs, or ECG became apparent during the study.

PALO-15-17

The incidence of TEAEs was similar between treatment groups: 37.8% in the infusion and 35.8% in the bolus group. Neutropenia and asthenia were the only TEAEs experienced by at least 5% of patients. Severe TEAEs were reported for 16 (7.1%) patients in the infusion group and 18 (8.4%) patients in the bolus group. Serious TEAEs were reported for 15 (6.7%) patients in the infusion group and 12 (5.6%) patients in the bolus group.

Table 23 TEAEs of CTCAE Grade 3 or 4 (Population: Safety)

Palonosetron 0.25 mg IV	**30-min Infusion**		**30-sec**	
MedDRA System Organ Class	N = 225		N = 215	
MedDRA Preferred Term	n (%)		n (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Any TEAE	8 (3.6)	2 (0.9)	9 (4.2)	2 (0.9)
Blood and lymphatic system	**4 (1.8)**	**3 (1.3)**	**6 (2.8)**	**2 (0.9)**

Anaemia	1 (0.4)	0	0	0
Leukopenia	0	1 (0.4)	1 (0.5)	0
Neutropenia	2 (0.9)	3 (1.3)	6 (2.8)	2 (0.9)
Thrombocytopenia	1 (0.4)	1 (0.4)	0	0
Cardiac disorders	**3 (1.3)**	**0**	**0**	**0**
Arrhythmia supraventricular	1 (0.4)	0	0	0
Atrial fibrillation	2 (0.9)	0	0	0
Cardiac arrest	0	1 (0.4)	0	0
Gastrointestinal disorders	**0**	**0**	**0**	**1 (0.5)**
Vomiting	0	0	0	1 (0.5)
Investigations	**1 (0.4)**	**0**	**2 (0.9)**	**0**
Alanine aminotransferase increased	0	0	1 (0.5)	0
Blood creatinine increased	1 (0.4)	0	1 (0.5)	0
Blood urea increased	1 (0.4)	0	1 (0.5)	0
Creatinine renal clearance decreased	0	0	1 (0.5)	0
Monocyte count decreased	0	0	1 (0.5)	0
Metabolism and nutrition disorders	**2 (0.9)**	**1 (0.4)**	**4 (1.9)**	**0**
Dehydration	1 (0.4)	0	1 (0.5)	0
Hyperglycaemia	0	0	2 (0.9)	0
Hypokalaemia	0	1 (0.4)	1 (0.5)	0
Hyponatraemia	2 (0.9)	0	0	0
Musculoskeletal and connective tissue disorders	**0**	**0**	**1 (0.5)**	**0**
Pain in extremity	0	0	1 (0.5)	0
Nervous system disorders	**1 (0.4)**	**0**	**0**	**0**
Syncope	1 (0.4)	0	0	0
Renal and urinary disorders	**1 (0.4)**	**0**	**0**	**0**
Renal failure	1 (0.4)	0	0	0
Respiratory, thoracic and mediastinal disorders	**1 (0.4)**	**1 (0.4)**	**0**	**0**
Dyspnoea	1 (0.4)	1 (0.4)	0	0
Hypoxia	1 (0.4)	0	0	0
Respiratory failure	0	1 (0.4)	0	0
Skin and subcutaneous tissue	**1 (0.4)**	**0**	**0**	**0**
Angioedema	1 (0.4)	0	0	0
Vascular disorders	**3 (1.3)**	**0**	**1 (0.5)**	**0**
Hypertension	2 (0.9)	0	0	0
Hypotension	2 (0.9)	0	0	0
Peripheral circulatory failure	0	0	1 (0.5)	0

Source: Summary Table 14.3.1.3.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; MedDRA = Medical Dictionary of Regulatory Activities, v.18.0; N = number of patients in a given group, n = number of patients in a given subgroup; TEAE = treatment-emergent adverse event.

Note: Only those PTs of CTCAE Grades 3 or 4 are shown. TEAEs of Grade 5 are discussed separately in section 12.3.1.1 Deaths. A complete list of PTs of all grades is provided in the source table.

Overall, 13 patients died: 6 (2.7%) patients in the infusion group and 7 (3.3%) patients in the bolus group.

No patient withdrew from the study due to a TEAE.

TEAEs related to study drug were reported for 8 (3.6%) patients in the infusion group and 3 (1.4%) patients in the bolus group. Only constipation was reported as a TEAE related to study drug for more than 2% of patients in either treatment group; this TEAE was experienced by 5 (2.2%) patients in the infusion group and 2 (0.9%) patients in the bolus group.

One patient in the infusion group experienced 2 severe TEAEs classified as possibly related to study drug (atrial flutter [Grade 5] and dyspnoea [Grade 4]); both events were classified as serious and the event of atrial flutter led to the patient's death (note that this patient's medical history at study entry included atrial flutter).

Table 19 study-drug-related TEAEs (Safety Population)

Table 24 Study-Drug-Related TEAEs (Population: Safety)

Palonosetron 0.25 mg IV MedDRA System Organ Class MedDRA Preferred Term	30-min Infusion N = 225 n (%) Events	30-sec Bolus N = 215 n (%) Events
Any study-drug-related TEAE	8 (3.6) 14	3 (1.4) 4
Cardiac disorders	**3 (1.3) 5**	**0**
Atrial flutter	2 (0.9) 2	0
Bundle branch block right	1 (0.4) 1	0
Palpitations	1 (0.4) 1	0
Tachycardia	1 (0.4) 1	0
Gastrointestinal disorders	**5 (2.2) 5**	**2 (0.9) 3**
Constipation	5 (2.2) 5	2 (0.9) 3
General disorders and administration site conditions	**1 (0.4) 1**	**1 (0.5) 1**
Chest pain	0	1 (0.5) 1
Malaise	1 (0.4) 1	0
Respiratory, thoracic and mediastinal disorders	**2 (0.9) 3**	**0**
Dyspnoea	1 (0.4) 2	0
Hiccups	1 (0.4) 1	0

Source: Summary Table 14.3.1.7
Abbreviations: IV = intravenous; MedDRA = Medical Dictionary of Regulatory Activities, v.18.0; N = number of patients in a given group, n = number of patients in a given subgroup; TEAE = treatment-emergent adverse event.
Note: Study-drug-related TEAEs are TEAEs with a missing relationship or assessed by the Investigator as definite, probable, possible or unassessable.

There were no safety concerns for laboratory parameters. Analysis of ECG data indicated that changes in QTc interval values were observed at a similar frequency in both treatment groups.

Serious adverse events and deaths

NEPA-15-18

Serious adverse events

Serious TEAEs were reported for 41 (20.2%) patients in the IV NEPA FDC group and 43 (21.4%) patients in the Oral NEPA FDC group. The most frequently reported (≥2% of patients in either treatment group) serious TEAEs were those expected in the cancer population under chemotherapy treatment including neutropenia (6 [3.0%] patients in the IV NEPA FDC group and 8 [4.0%] patients in the oral NEPA FDC group), pneumonia (6 [3.0%] patients in the IV NEPA FDC group and 4 [2.0%] patients in the oral NEPA FDC group), thrombocytopenia (1 [0.5%] patient in the IV NEPA FDC group and 4 [2.0%] patients in the oral NEPA FDC group), and anaemia (no patients in the IV NEPA FDC group and 4 [2.0%] patients in the Oral NEPA FDC group).

No serious TEAEs were assessed as related to study drug. One patient (0.5%) in the IV NEPA FDC group experienced serious TEAEs related to dexamethasone, and 5 patients (2.5%) in the Oral NEPA FDC group experienced serious TEAEs related to dexamethasone.

There was no evidence of increased incidences of SAEs with increasing exposure.

Deaths

TEAEs leading to death were reported for 10 (4.9%) patients in the IV NEPA FDC group and 14 (7.0%) patients in the Oral NEPA FDC group. None of them was assessed as related to study drug.

The most frequent preferred terms for patients who died during the NEPA-15-18 study were: sudden death (4 patients; 1 in the IV NEPA group and 3 in the oral NEPA group), pneumonia (2 patients, 1 in each treatment group) and sepsis (2 patients in the oral NEPA group). All other PTs occurred in only one patient.

NEPA-15-19

There were no serious adverse events or deaths in study NEPA-15-19.

PNET-12-23

There were no serious adverse events or deaths in study PNET-12-23.

PALO-15-17

See assessment of this study under heading Adverse Events above.

Laboratory findings

Studies NEPA-15-18 and NEPA-15-19

Routine laboratory tests included haematology, chemistry and urinalysis at screening, day 2 and day 6 of each cycle during the Phase 3 repeated cycles safety study (NEPA-15-18) and were analysed at a central laboratory. For the Phase 1 Study (NEPA-15-19), blood and urine for laboratory evaluations were collected at screening (day 1) and follow up (day 21) and were analysed at the local laboratory of the single site conducting the study.

As expected, in patients receiving chemotherapy over repeated cycles, leukopenia (including neutropenia, monocytopenia and granulocytopenia), anaemia and thrombocytopenia were observed with generally similar reductions in patients receiving the IV NEPA FDC and oral NEPA FDC. 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 repeated cycle exposure.

PNET-12-23

No notable effect of the IMP on safety laboratory parameters were reported.

PALO-15-17

There were no safety concerns for haematology and blood chemistry parameters. The spectrum of laboratory changes observed during the study is typical of laboratory findings detected in the setting of oncologic patients receiving HEC and/or treatment with dexamethasone.

Safety in special populations

Age:

In the safety study NEPA-15-18, a total of 7 IV NEPA treated patients out of 203 (3.4%) were ≥ 75 years of age. Age was evaluated as a post-hoc analysis and did not reveal any differences that would require special consideration.

Gender:

Gender was a stratification factor and was evaluated in study NEPA-15-18. No significant effect was revealed.

Gender did not affect netupitant PK after NEPA IV FDC administration in cancer patients (NEPA-15-19).

Race

As far as race is concerned, 99.3% of patients in the NEPA-15-18 study were white, therefore an analysis by race is not meaningful; however race was evaluated in the oral Akynzeo program. No differences were revealed for patient gender that would require any special consideration.

Renal impairment:

No specific studies were performed to evaluate fosnetupitant in patients with renal impairment. However, due to the transient exposure of fosnetupitant and subsequent conversion to netupitant there are no additional warnings considered necessary with the administration of the prodrug compared to the parent compound.

In healthy volunteers receiving oral netupitant, less than 5% of all drug-related material was excreted in urine and less than 1% of the netupitant dose was eliminated unchanged in the urine. No dosage adjustment for Akynzeo® is necessary in patients with mild to moderate renal impairment. Use of Akynzeo® should be avoided in patients with severe renal impairment or end-stage renal disease.

Hepatic impairment:

No studies were performed specifically with IV fosnetupitant in patients with hepatic impairment.

Following oral Akynzeo® administration, Cmax and total exposure of netupitant (AUC0-inf) were increased in subjects with mild (n=8), moderate (n=8), and severe (n=2) hepatic impairment compared to matching healthy subjects, although there was pronounced individual variability in both hepatically impaired and healthy subjects.

Total palonosetron exposure was also increased in subjects with mild and moderate hepatic impairment compared to matching healthy subjects.

Although the increases were statistically significant, they are of questionable clinical significance as 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. Limited conclusions can be drawn for patients with severe hepatic impairment due to the low number of subjects included in this group.

Based on these data, no dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh score 5-9). Limited data exist in patients with severe hepatic impairment (Child Pugh score ≥10). Use of Akynzeo® should be avoided in patients with severe hepatic impairment.

Pregnancy and lactation:

No cases of pregnancy occurred during the IV NEPA FDC development program. Furthermore, there are no concerning signals or causes for concern in fosnetupitant, netupitant or palonosetron preclinical genotoxicity and reproduction studies at the proposed clinical concentration ranges. However, safety in human pregnancy has not been established for either palonosetron or netupitant, and animal reproduction studies do not always predict human response; the FDC should not be used during pregnancy, unless it is considered essential by the physician.

It is unknown whether netupitant or palonosetron are excreted in breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and the potential for tumorigenicity shown for palonosetron in the rat carcinogenicity study, caution should be exercised if the IV NEPA FDC is to be administered to nursing women. A decision should be made whether to continue/discontinue breast-feeding or to continue/discontinue therapy taking into account the benefit of breast-feeding to the child and the benefit of the IV NEPA FDC to the woman.

Paediatric Population

No safety data are available in paediatric patients. An agreed PIP is provided in Module 1.10.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

A comprehensive evaluation of drug interactions was conducted during the oral Akynzeo® development program. To supplement these studies, *in vitro* and *in vivo* studies with fosnetupitant were conducted during the IV development program.

Drug interactions with the IV NEPA FDC are attributed to the netupitant component, as exposure to fosnetupitant is limited and the prodrug is rapidly converted to netupitant. There are no known drug interactions with palonosetron.

Drug interactions with fosnetupitant were evaluated during the IV NEPA FDC program as follows: 1) a clinical trial in healthy subjects with dexamethasone (PNET-13-63), 2) *in vitro* followed by *in silico* studies with fosnetupitant.

Table 20: Overview of drug interaction studies performed with oral netupitant single agent or in combination with palonosetron during the oral Akynzeo program.

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. The effect lasted for 8 days.	NETU-06-07 NEPA-14-39
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%	

Study PNET-13-63

This was a Phase 1, randomized, three-period, four-treatment, incomplete block, crossover study in healthy male and female volunteers designed to evaluate the potential pharmacokinetic interaction between three doses of intravenous fosnetupitant and the oral dexamethasone regimen used for antiemetic prophylaxis. Safety was a secondary objective.

Safety population of the study includes a total of 30 healthy subjects.

A total of 143 treatment emergent adverse events (TEAEs), all of mild and moderate severity were reported by 25 of the 30 subjects (83.3% of subjects). No serious adverse events occurred and none of the subjects discontinued the study due to an adverse event. Most of the events were considered related to pro-netupitant (98 of 143 events) and dexamethasone (118 of 143 events).

The frequency of subjects with at least one TEAE was generally higher after administration of dexamethasone together with pro-netupitant (between 66.7% after Treatment D and 85.0% of subjects after Treatment C) than after administration of dexamethasone alone (60.7% of subjects). No dose dependency was observed with a similar frequency between Treatments A and D (60.7% and 66.7% of subjects with at least one TEAE, respectively). This was also the case when drug-related TEAEs were considered.

All 3 dose levels of fosnetupitant (130 mg, 195 mg and 260 mg) administered with increasing drug concentration in the infusion solution (2.6 mg/mL, 3.9 mg/mL and 5.2 mg/mL, respectively were well tolerated.

The IV and oral NEPA FDC should be used with caution in patients receiving concomitant medications that are primarily metabolized by CYP3A4 due to the known CYP3A4-mediated drug interactions. Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. Doses adjustment of these agents in clinical trials either in the oral or IV NEPA FDC program were not necessary, and no safety concerns identified in this population. Caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4 that were not studied.

For dexamethasone, the same dose adjustment as that approved for Akynzeo® capsules is proposed for IV NEPA FDC.

Discontinuation due to AES

Study NEPA-15-18

TEAEs leading to study discontinuation were reported for 16 (7.9%) patients in the IV NEPA FDC group and 20 (10.0%) patients in the Oral NEPA FDC group. The most frequently reported TEAEs leading to discontinuation from the study were disease progression (6 [3.0%] patients in each treatment group) and renal failure (3 [1.5%] patients in the IV NEPA FDC group and 1 [0.5%] patient in the oral NEPA FDC group). All other TEAEs leading to discontinuation occurred with a frequency of less than or equal to 1.0% of patients in either treatment group.

Study-drug-related TEAEs leading to discontinuation, were experienced by a total of 3 (0.7%) patients (2 [1.0%] patients in the IV NEPA FDC group and 1 [0.5%] patient in the oral NEPA FDC group).

The PT reported were:

- disease progression (IV NEPA FDC Group, Cycle 2),
- hypersensitivity (oral NEPA FDC group, Cycle 2) and
- hepatic enzymes increased (IV NEPA FDC group, Cycle 1).

  [Module 5.3.5.1, NEPA-15-18, Table 14.3.2.13 and Table 14.3.2.14].

The incidence of adverse events leading to patient withdrawal was similar in the first 3 cycles.

No adverse events leading to withdrawal occurred in cycle 4.

Study NEPA-15-19

No adverse events leading to withdrawal occurred in study NEPA-15-19.

Study PNET-12-23

One subject discontinued the study prematurely due to adverse events prior to first dosing (vasovagal syncope and dizziness). In two other subjects, the infusion of the study drug was interrupted and

restarted during administration of the active product due to adverse events ("swelling around the infusion site" and "strange sensation at infusion site"). Both events were considered to be unlikely related to the study drug.

Study PALO-15-17

No patient withdrew from the study due to a TEAE.

Post marketing experience

As of May 8th, 2018, the IV NEPA FDC has not been marketed yet.

Oral Akynzeo® has been marketed since October 2014. Regular PSURs have been submitted by the sponsor.

Based on sales data, approximately 112,000 patients have been treated with the oral combination worldwide, considering for each patient an average of 6 cycles of chemotherapy preceded by antiemetic prophylaxis with Akynzeo®.

Collectively, there is no evidence of any change in the clinical pattern of Akynzeo® ADRs or of any new qualitative or quantitative safety concern from the 3 and half years post-marketing experience.

2.6.1. Discussion on clinical safety

Safety data for the IV NEPA FDC clinical development program are not integrated due to the design of the development program. There were two trials that administered the IV NEPA FDC in cancer patients (NEPA-15-18, NEPA-15-19), two that administered intravenous fosnetupitant alone in healthy volunteers (PNET-12-23, PNET-13-63) and one that employed intravenous palonosetron alone (PALO-15-17) as outlined above. The focus of safety data presented in the dossier is derived primarily from the pivotal safety study NEPA-15-18 and also the PK study NEPA-15-19 with safety evaluation as a secondary objective. Safety data from studies which administered fosnetupitant or palonosetron as single agents are considered supportive.

A total of 239 cancer patients received at least one dose of the IV NEPA FDC in studies NEPA 15-18 and NEPA 15-19.

Study NEPA-15-18

The most frequently reported TEAEs were anaemia, leukopenia, neutropenia, thrombocytopenia, constipation, nausea, asthenia, fatigue, ALT increased, AST increased, blood creatinine increased, decreased appetite, alopecia, headache, and hypertension. These events generally occurred in similar percentages of patients across the IV and oral NEPA groups.

Anaemia and thrombocytopenia are not seen in section 4.8 of the smPC for the hard capsule Akynzeo formulation however the applicant explains that the most frequently reported (≥2% of patients in either treatment group) serious TEAEs were those expected in the cancer population under chemotherapy treatment including anaemia (no patients in the IV NEPA FDC group and 4 [2.0%] patients in the Oral NEPA FDC group) and thrombocytopenia (1 [0.5%] patient in the IV NEPA FDC group and 4 [2.0%] patients in the oral NEPA FDC group).

The only two events reported in more than 2% of patients in both treatment groups were constipation and ALT increases. Both of these events are listed as possible undesirable effects in the SmPC of the hard capsule Akynzeo formulation at frequencies of common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100) respectively and so are not new to the intravenous formulation.

The satisfactory local tolerability observed in Phase 1 studies in healthy subjects with fosnetupitant alone and further confirmed in study NEPA-15-18 in cancer patients with IV NEPA FDC is reassuring.

The frequency and type of serious adverse events were reported to be similar in the two treatment groups and no serious TEAEs were assessed as related to study drug. It is also noted that the most frequently reported (≥2% of patients in either treatment group) serious TEAEs were those expected in the cancer population under chemotherapy treatment.

TEAEs leading to study discontinuation were reported in similar numbers for both the oral and IV NEPA FDC groups. Increased hepatic enzymes is already listed in section 4.8 of the SmPC of the oral formulation as an uncommon adverse reaction and so is not new to the intravenous formulation.

TEAEs of special interest in this study were captured in the MedDRA PTs "electrocardiogram QT prolonged" and severe (Grade 3 or 4) "constipation".

Electrocardiogram QT prolonged: All events were non-serious events and no relevant differences between IV NEPA FDC and oral NEPA FDC were detected with regard to increased QTc. These results together with the satisfactory results of the thorough QT study completed with the oral FDC indicate a satisfactory cardiac safety profile for the IV NEPA FDC.

Constipation is a known TEAE observed also with the oral formulation during the clinical development program and was reported in similar numbers in both treatment groups.

Study NEPA-15-19

All TEAEs reported in this study were either mild or moderate in severity. Moderate intensity events included constipation, nausea, vomiting, asthenia, headache, swelling face, flushing, and hypertension. No patient reported severe or life-threatening TEAEs.

Most of the TEAEs are mentioned as possible undesirable effects in section 4.8 of the SmPC of the authorised hard capsule Akynzeo formulation except for the occurrence of swelling face/peripheral swelling. In study NEPA-15-19, only one TEAE of peripheral swelling (grade 1) was considered as possibly related to study drug and neither swelling face nor peripheral swelling were reported in the key safety study NEPA-14-18. The applicant therefore does not consider that swelling face or peripheral swelling need to be added to section 4.8 of the SmPC for this formulation.

No adverse events leading to withdrawal and no serious adverse events or deaths were reported in study NEPA-15-19.

Study PNET-12-23

Overall, 169 TEAEs were observed after drug administration in 80 of the 158 subjects (50.6%). Most of these events (108 events, 63.9%) were assessed as drug-related. All TEAEs were of mild or moderate intensity. No death and no other serious adverse events occurred in this study.

In this study, single doses of 19.5 mg to 390 mg pro-netupitant were reported to be well tolerated after administration via IV infusion, at 2.6 mg/mL concentration over 30 min and the proportion of subjects with drug-related TEAEs or the number of drug-related TEAEs did not increase with ascending pro-netupitant doses.

Some differences in the safety profile after administration of the IV pro-netupitant formulation and the oral netupitant and palonosetron FDC were attributed to the route of administration and/or to the presence of palonosetron.

In healthy volunteer studies, infusion site reactions occurred either as infusion site thrombosis or vessel puncture site thrombosis (mostly in PNET-12-23 due to a higher number of subjects). Can this difference be related to different administration pattern (Intravenous versus infusion through an

implantable venous access device)? The Applicant was asked to further discuss this issue comparing with the low number of such events in cancer patient studies. The Applicant clarified that the higher rate of infusion site reactions observed in healthy volunteers compared to patients seems to be related to the use of a particular ultrasound examination technique in volunteers during PNET-12-23 study.

It was noted that the Cmax for netupitant after 260 mg IV pro-netupitant (840.8 ug/L) was ~1.76 times higher than the Cmax after 300 mg oral netupitant (477.3 ug/L) which may have implications for safety. (See section 2.1.3 of this report). The applicant was asked to discuss this. In the response, the Applicant acknowledges that the Cmax of netupitant was higher following the IV NEPA combination infusion compared to the lower Cmax following the oral administration of netupitant/palonosetron and indeed that it was expected to be. As evidence that a higher netupitant Cmax obtained following IV NEPA administration is not expected to adversely affect the safety of IV NEPA compared to oral NEPA the Applicant refers to the satisfactory safety results from studies NEPA-15-18 and NEPA-17-05.

Study PALO-15-17

The incidence of TEAEs was similar between treatment groups which supports the study report conclusion which is that the study demonstrated that slow infusion of palonosetron 0.25 mg represents a safe and effective alternative to the approved bolus infusion for patients with a diagnosis of malignant solid tumour requiring treatment with HEC regimens.

No serious adverse events or deaths were reported in studies NEPA-15-19 or PNET-12-23.

The incidence of serious adverse events and deaths were similar between treatment groups in study PALO-15-17.

In NEPA-15-18, 10 and 14 deaths occurred in NEPA IV infusion and oral NEPA FDC, respectively, and 41 and 43 serious TAEA, respectively. Deaths occurred more frequently in the oral group than in IV infusion group.

From study PALONO-15-17, TEAEs leading to death were reported for 13 patients: 6 (2.7%) patients in the infusion group and 7 (3.3%) patients in the bolus group.

For studies NEPA-15-18 and PALONO-15-17, no summary and no discussion were initially provided by the Applicant, only cross-references towards narratives. Consequently, the Applicant was requested to provide a summary and a discussion of deaths as well as cases of serious adverse events and withdrawal should be provided for each treatment group in the form of a table, separating deaths from serious adverse events and withdrawals. The Applicant provided a summary of cases of deaths and discontinuations with information regarding patient treatments and comorbidities. For all cases, death and discontinuations can be related to the evolution of main disease for which they received fosnetupitant (i.e metastatic cancer) or associated comorbidities and/or can be due to chemotherapy adverse effects.

Based on Studies NEPA-15-18 and NEPA-15-19, there was no obvious indication of treatment-related effects on chemistry or urinalysis parameters across treatment groups.

No notable effect of the IMP on safety laboratory parameters were reported in studies PNET-12-23 and PALO-15-17.

Taking into consideration data from both the oral Akynzeo® program and the IV NEPA studies NEPA-15-18 and NEPA-15-19, no differences were revealed for patient age, race or gender that would require any special consideration.

Taking into consideration data from both the oral Akynzeo® program and the IV NEPA study NEPA-15-18, subgroup analyses based on renal function did not reveal any differences that would require special consideration.

ALT and AST increases were noted to have occurred in 2 (1%) and 3 (1.5%) subjects respectively who received IV NEPA FDC and in 14 (7%) and 5 (2.5%) subjects respectively who received oral NEPA FDC in study NEPA-15-18. It is noted that liver transaminases increased is listed as an uncommon adverse reaction in the proposed SmPC and the SmPC of the oral Akynzeo formulation. Taking into consideration data from both the oral Akynzeo® program and the IV NEPA study NEPA-15-18, no dosage adjustment is proposed for patients with mild to moderate hepatic impairment (Child-Pugh score 5-9). Caution is recommended in patients with severe hepatic impairment (Child Pugh score ≥9).

No cases of pregnancy occurred during the IV NEPA FDC development program. Furthermore, there are no concerning signals or causes for concern in fosnetupitant, netupitant or palonosetron preclinical genotoxicity and reproduction studies at the proposed clinical concentration ranges. However, safety in human pregnancy has not been established for either palonosetron or netupitant, and animal reproduction studies do not always predict human response. Use in pregnancy is proposed to be contraindicated according to the proposed SmpC.

It is unknown whether netupitant or palonosetron are excreted in breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and the potential for tumorigenicity shown for palonosetron in the rat carcinogenicity study, caution should be exercised if the IV NEPA FDC is to be administered to nursing women.

No safety data are available in paediatric patients. Use in the paediatric population is not indicated. The proposed SmPC reflects the fact that no safety data are available in paediatric patients.

Based on the results of study PNET-13-63, the same dose adjustment for dexamethasone as that approved for Akynzeo® capsules is proposed for IV NEPA FDC. As per the oral NEPA FDC SmPC, the proposed IV NEPA FDC SmPC recommends caution in patients receiving concomitant medications that are primarily metabolized by CYP3A4 due to the known CYP3A4-mediated drug interactions. No new safety related drug-drug or other interactions have been identified.

In study NEPA-15-18, TEAEs leading to study discontinuation were reported in similar numbers for both the oral and IV NEPA FDC groups.

There were no adverse events leading to withdrawal occurred in studies NEPA-15-19 and PALO-15-17. Two study drug interruption events reported in study PNET-12-23 were not considered to be related to the study drug.

Fosnetupitant is classified as phototoxic however the Applicant has adequately justified why this is not considered to be clinically relevant considering that: fosnetupitant binds to melanin in the uveal tract and in the eye but not remarkably in the skin; fosnetupitant rapidly disappears from the systemic circulation in humans by hydrolysis to netupitant, which was not indicated as a phototoxic compound; fosnetupitant is given intravenously and no topical application is foreseen; fosnetupitant is not a drug for chronic use. It is administered as a single dose treatment in hospital environment on day 1 of cancer chemotherapy cycles.

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

2.6.2. Conclusions on the clinical safety

The CHMP considers that the safety profile of the IV NEPA FDC has been shown to be similar to the approved oral NEPA FDC Akynzeo.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Torsade de pointes due to QT/QTC prolongation Serotonin syndrome (due to palonosetron) Teratogenic effects
Missing information	Effects in children

Pharmacovigilance plan

No additional pharmacovigilance activities.

Risk minimisation measures

Safety concern	Risk minimisation measures
Torsade de pointes due to QT/QTc prolongation	Routine risk minimisation measures: SmPC Section 4.4 where advice is given for monitoring of patients with conditions leading to QT prolongation PL section 2 Additional risk minimisation measures: No additional risk minimisation measures
Serotonin syndrome (due to palonosetron)	Routine risk minimisation measures: SmPC Section 4.5 SmPC Section 4.4 where advice is given for monitoring of patients with serotonin-syndrome like symptoms. PL section 2 Additional risk minimisation measures: No additional risk minimisation measures
Teratogenic effects	Routine risk minimisation measures: SmPC Section 4.6 PL section 2 Additional risk minimisation measures:

Safety concern	Risk minimisation measures
	No additional risk minimisation measures
Effects in children	Routine risk minimisation measures: SmPC Section 4.2 PL section 2 Additional risk minimisation measures: No additional risk minimisation measures

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.7 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Akynzeo. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Akynzeo is currently licensed in adults as an oral capsule for the prevention of acute and delayed vomiting associated with both a) moderately and b) highly emetogenic cancer chemotherapy. The

current application is a line extension for an intravenous formulation associated with a new strength in the same indications.

3.1.2. Available therapies and unmet medical need

Current treatment options commonly prescribed for CINV include serotonin (5-HT3) receptor antagonists, glucocorticosteroids, benzodiazepines and dopamine receptor antagonists.

The option for clinicians to administer an intravenous formulation of a fixed dose combination anti-emetic drug that acts both on the acute and delayed phase of CINV would be considered beneficial. While there are serotonin and neurokinin 1 receptor antagonists approved in the EU, no intravenous FDC is currently available for patients to receive. In particular neurokinin 1 receptor antagonists have well documented activity against cisplatin induced delayed emesis.

3.1.3. Main clinical studies

The pivotal study for bridging PK with efficacy is PNET-12-23, a clinical bioequivalence study in healthy subjects and the pivotal safety study is NEPA-15-18 in cancer patients receiving up to 4 cycles of highly emetogenic chemotherapy with safety objectives the primary focus and secondary descriptive efficacy endpoints.

The efficacy studies for this application are considered supportive with no pivotal efficacy study per se submitted as part of the clinical development plan. NEPA-15-18 consisted of chemotherapy naïve cancer patients who were starting a highly emetogenic chemotherapy regimen. Patients were randomised to receive either the intravenous or oral formulation of Akynzeo and a corresponding placebo dummy. Patient were assessed for 4 cycles. The primary objectives were safety and tolerability and the secondary objective was to describe the efficacy using complete response, emetic episodes and nausea as endpoints during the acute, delayed and overall phases. However, the study was not powered for non-inferiority.

PALO-15-17 was a non-inferiority study assessing the efficacy in the acute phase of intravenous Palonosetron infusion and bolus injection of Palonosetron in patients receiving highly emetogenic chemotherapy. Safety objectives were secondary. Safety data from two studies where intravenous fosnetupitant was administered alone in healthy volunteers (PNET-12-23, PNET-13-63) and one where intravenous palonosetron was administered alone (PALO-15-17) are considered supportive.

3.2. Favourable effects

Study PALO-15-17 demonstrated that palonosetron administered as a 30minute intravenous infusion was non-inferior in terms of both efficacy and safety to the 30 second bolus injection establishing that it can be used in combination with netupitant as an infusion.

Specifically, this study demonstrated non-inferiority in terms of the proportion of patients reporting CR (defined as no emetic episodes and no rescue medication intake) in the acute phase as a primary efficacy objective and secondary endpoints included a) CR in the delayed and overall phases, b) the proportion of patients with no emetic episodes in the acute, delayed, and overall phases and c) the proportion of patients with no use of rescue medication in the acute, delayed, and overall phases.

In the full analysis set, 186 (82.7%) patients in the infusion group reported CR in the acute phase, as did 186 (86.5%) patients in the bolus group. The difference in proportion between the 30-min infusion and 30-sec bolus treatment groups was -3.8% (99% CI: -12.2%, 4.7%). 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 of -15%, non-inferiority of palonosetron 30-min infusion vs. 30-sec bolus was demonstrated. The p-value associated with non-inferiority testing was <0.001.

Study NEPA-15-18 demonstrated that there was comparable efficacy in terms of a complete response, absence of emetic episodes, absence of rescue medication and nausea control in the acute phase between the oral and intravenous FDC drug. In cycle 1, patients that had no emetic episodes for the overall phases were comparable between the two formulations IV 84.2% and oral 88.6% respectively. Noteworthy, bioequivalence has been demonstrated between the two formulations.

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties about the favourable effects related to the introduction of the new pharmaceutical form and strength for intravenous use.

3.4. Unfavourable effects

Of the 404 patients in the safety population in the pivotal safety study NEPA-15-18, 343 (84.9%) patients experienced at least one TEAE.

The most frequently reported TEAEs (i.e., those reported by > 5% of patients in either treatment group) were anaemia, leukopenia, neutropenia, thrombocytopenia, constipation, nausea, asthenia, fatigue, ALT increased, AST increased, blood creatinine increased, decreased appetite, alopecia, headache, and hypertension.

Overall, 47 (11.6%) and 120 (29.7%) patients experienced exclusively mild and moderate (Grades 1 and 2) events, respectively. These events were reported in similar numbers of patients in both treatment groups (Grade 1: 23 [11.3%] patients in the IV NEPA and 24 [11.9%] patients in the Oral NEPA group; Grade 2: 60 [29.6%] patients and 60 [29.9%] in the IV NEPA and Oral NEPA groups, respectively). The pattern of mild and moderate events reflected the overall AE profile of the study; events occurred most frequently in the following SOCs and PTs: Blood and Lymphatic System Disorders (neutropenia, anaemia), Gastrointestinal SOC (nausea, constipation), General Disorders (asthenia, fatigue), and Investigations (AST, ALT and Creatinine increased).

Overall, Grade 3 TEAEs were experienced by 61 (30.0%) patients in the IV NEPA FDC group and 54 (26.9%) patients in the Oral NEPA FDC group, and Grade 4 TEAEs were experienced by 15 (7.4%) patients in the IV NEPA FDC group and 22 (10.9%) patients in the Oral NEPA FDC group. As expected, neutropenia was the most frequent Grade 3/4 TEAE reported during this study (37 [18.2%] patients in the IV NEPA FDC group and 37 [18.4%] patients in the Oral NEPA FDC group). Severe TEAEs were reported for 86 (42.4%) patients in the IV NEPA FDC group and 90 (44.8%) patients in the Oral NEPA FDC group. For IV NEPA FDC, 2 patients (1.0%) experienced severe TEAEs related to study drug and 3 patients (1.5%) experienced severe TEAEs related to dexamethasone. For Oral NEPA FDC, 3 patients (1.5%) experienced severe TEAEs related to study drug and 6 patients (3.0%) experienced severe TEAEs related to dexamethasone.

The only two events reported in more than 2% of patients in both treatment groups were constipation and ALT increases. Constipation (an adverse event of special interest in this study) was reported by 13 [6.4%] patients in the IV NEPA FDC group and 12 [6.0%] patients in the oral NEPA FDC group and ALT increases were experienced by 4 patients (2.0%) in each treatment group.

TEAEs related to study drug were reported for 26 (12.8%) patients in the IV NEPA FDC group and for 23 (11.4%) patients in the oral NEPA FDC group. Frequency and type of TEAEs were similar in the two treatment groups.

TEAEs leading to study discontinuation were reported for 16 (7.9%) patients in the IV NEPA FDC group and 20 (10.0%) patients in the Oral NEPA FDC group.

TEAEs leading to death were reported for 10 (4.9%) patients in the IV NEPA FDC group and 14 (7.0%) patients in the Oral NEPA FDC group.

3.5. Uncertainties and limitations about unfavourable effects

There are no uncertainties or limitations in the unfavourable effects in relation to this line extension.

3.6. Effects Table

Table 1. Effects Table for the line extension of Akynzeo as an intravenous infusion for the prevention of acute and delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy. (March 2017)

Effect	Short Description	Unit	Treatment IV NEPA	Control Oral NEPA	Uncertainties/ Strength of evidence	References
Favourable Effects **Study NEPA-15-18 - Secondary descriptive efficacy endpoints in patients receiving HEC in the acute, delayed and overall phases**						
Complete Response Cycle 1	no emetic episodes and no rescue medication	%	Acute Phase 92.6% Delayed Phase 78.3% Overall Phase 76.8%	Acute Phase 90.5% Delayed Phase 87.6% Overall Phase 84.1%	Descriptive efficacy results only presented	
No significant nausea Cycle 1	Visual analogue scale	%	90.1% 81.3% 79.3%	93% 89.1% 86.6%	Descriptive efficacy results only presented	
Unfavourable Effects						
Constipation	Incidence of constipation	%	6.4	6.0	Known ADR for this FDC	
ALT increase	Incidence of ALT increase	%	2.0	2.0	Known ADR for this FDC	

Abbreviations:
Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results from clinical study PALO-15-17 showed that 30-minute IV infusion of palonosetron 0.25 mg is non-inferior to a 30-second bolus in patients receiving a highly emetogenic chemotherapy regimen.

The descriptive efficacy results presented in NEPA-15-18 demonstrate comparable control of acute phase CINV in patients receiving HEC between the oral formulation and the intravenous infusion. The results are maintained for the 4 cycles examined. These results are considered to be clinically important and support the overall bioequivalence PK/PD bridging approach taken with this application.

From a PK standpoint, the chosen dose of 260 mg fosnetupitant is justified and results in Netupitant exposures are similar to the ones observed with the oral 300 mg netupitant dose already authorised and marketed. The absence of a powered non-inferiority study comparing NEPA IV FDC to NEPA PO

FDC does not allow to draw any firm conclusion regarding the efficacy of the prevention of nausea and vomiting during the delayed phase in patients receiving highly emetic chemotherapy. However, as the intravenous formulation is regarded as bioequivalent to the oral formulation, therefore the efficacy of IV NEPA FDC can be considered acceptable and overall similar.

No new safety issues have been identified, in overall the safety profile is in line with the well known safety of the oral formulation.

3.7.2. Balance of benefits and risks

Since the intravenous formulation is regarded as bioequivalent and non-inferior to the oral formulation, therefore the efficacy of IV NEPA FDC can be considered acceptable and in line with the already known efficacy of the oral Akynzeo.

The CHMP considers that the safety profile of the IV NEPA FDC has been shown to be similar to the approved oral NEPA FDC Akynzeo.

3.8. Conclusions

The overall B/R of Akynzeo powder for concentrate for solution for infusion' of fosnetupitant and palonosetron of 235 mg/0.25 mg, to be administered intravenously is positive in the approved indications.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Akynzeo 235 mg/0.25 mg, powder for concentrate for solution for infusion for intravenous use is favourable in adult patients in the following indication:

- 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 CHMP therefore recommends the extension of the marketing authorisation for Akynzeo 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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.