Amsterdam, 11 December 2025
EMADOC-1700519818-3001016
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on an extension of marketing authorisation

Akynzeo

International non-proprietary name: Fosnetupitant/Netupitant/Palonosetron

Procedure No. EMA/X/0000258060

Marketing Authorisation Holder (MAH): Helsinn Birex Pharmaceuticals Limited

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EMA PL:	Sotirios Michaleas
EMA PA:	Diego Alvarez
Start of the procedure:	27/03/2025
Date of this report:	11/12/2025

Disclaimer: The template for this report covers different stages of the Line Extension application. Hence some sections of the report might be left blank or might contain guidance text which is not applicable to the intermediate stages of the procedure. In case of withdrawal of the application, the latest intermediate report adopted by the committee will be published on the EMA website. In preparation for this, all non-applicable sections will be removed.

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List of abbreviations

AE	Adverse event
ANOVA	Analysis of variance
API	Active Pharmaceutical Ingredient
ASM	Active Substance Manufacturer
AUC	Area under the curve
BDL	Below the limit of detection
BET	Bacterial endotoxin test
BI	Biological indicator
BW	Body weight
CAT	Committee for Advanced Therapies
CEP	Certificate of suitability
CHMP	Committee for Medicinal Products for Human Use
CINV	Chemotherapy-induced nausea and vomiting
CKC	Cetalkonium chloride
CoA	Certificate of Analysis
COSY	Correlation Spectroscopy;
CQA	Critical quality attribute
CRS	Chemical Reference Standard
CT	Clinical Trial
CTD	Comon technical document
DAD	Diode-array detection
EDQM	European Directorate for the Quality of Medicines
EI	Elemental impurities
EMA	European Medicines Agency
EMA	European Medicines Agency
EO	Ethylene Oxide
EP	European Pharmacopoeia
FDA	Federal Drug Authority
FID	Flame-ion detector
FPS	Finished Product Specifications
FT-IR	Fourier Transformation Infrared Spectroscopy
GC	Gas chromatography
GCP	Good clinical practice
GMP	Good Manufacturing Practice
HCl	Hydrochloric Acid
HMBC	Heteronuclear Multiple Bond Correlation Spectroscopy
HPLC	High performance liquid chromatography
HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
ICH	International Council for Harmonisation

ICH	International conference on harmonisation
IPA	Isopropyl alcohol
IPC	In-process control test
IPC	In process control
IR	Infra-red
IV	Intravenous
KF	Karl Fischer
KL	Knee location
LC	Liquid chromatography
LDPE	low-density polyethylene
LLE	Liquid-liquid extraction
LLOQ	Lower limit of quantification
LoD	Loss on Drying
LOD	Limit of detection
LOQ	Limit of Quantitation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation holder
MCT	Triglycerides, medium-chain
mg	milligrams
MS	Mass spectrometry
ng	nanogram
NLT	Not less than
nm	nanometre
NMT	Not more than
NVR	Non-volatile residue
PD	Pharmacodynamics
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PKS	Pharmacokinetic set
PL	Package Leaflet
ppm	parts per million
PRAC	Pharmacovigilance Risk Assessment Committee
Psi	pressure per square inch
PV	Process Validation
PVDF	Polyvinylidene fluoride
QC	Quality control
QOS	Quality Overall Summary
QP	Qualified Person
RA	Risk Assessment
RH	Relative Humidity
RMP	Risk management plan
RRF	Relative response factor
RRT	Relative retention time

RS	Residual solvents
Rt	Retention time
RT	Room temperature
SAE	Serious adverse event
SAL	Sterility assurance level
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
TAMC	Total aerobic microbial count
TEAE	Treatment emergent adverse event
TTC	Threshold of toxicological concern
TYMC	Total yeast microbial count
US	United states
USP	United States Pharmacopoeia
UV	Ultra violet
WFI	Water for injections
WS	Work Sharing

1. Executive Summary

On 11 December 2025, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the extension of the marketing authorisation for the medicinal product Akynzeo.

The CHMP recommended the approval of one new presentation of Akynzeo 300 mg/0.5 mg oral suspension for use in adults.

The indication for Akynzeo 300 mg/0.5 mg hard capsules, 300 mg/0.5 mg oral suspension, 235 mg/0.25 mg powder for concentrate for solution for infusion and 235 mg/0.25 mg concentrate for solution for infusion remains unchanged and is provided in the summary of product characteristics (SmPC).

Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

This report summarises the scientific review leading to the opinion adopted by the Committee for Medicinal Products for Human Use (CHMP).

2. Administrative/regulatory information and recommendations on the procedure

2.1. Submission of the dossier

On 09/03/2025, Helsinn Birex Pharmaceuticals Limited submitted an extension of the marketing authorisation to introduce a new pharmaceutical form (300 mg/0.5 mg oral suspension).

The MAH applied for the following indications for Akynzeo 300 mg/0.5 mg oral suspension:

- 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.

2.2. Legal basis and dossier content

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, (2) point (d) - Extensions of marketing authorisations.

2.3. Scientific advice and protocol assistance

Not applicable.

2.4. Information on paediatrics

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0132/2024 on the granting of a product-specific waiver for netupitant / palonosetron (Akynzeo), (EMEA-001198-PIP04-23).

2.5. Information on orphan market exclusivity

2.5.1. Similarity with authorised orphan medicinal products

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.

2.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur:	Finbarr Leacy

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur:	Amelia Cupelli

The application was received by the EMA on	09 March 2025
The procedure started on	27 March 2025
The CHMP Rapporteur's first Assessment Report was received on	16 June 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	19 June 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 July 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	24 July 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	09 October 2025
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	12 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
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	11 December 2025

2.7. Final CHMP outcome

2.7.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 2.4. of this report.

2.7.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 2.5. of this report.

2.7.3. Final opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Akynzeo 300 mg/0.5 mg oral suspension is favourable in the following indication(s):

Akynzeo is indicated in adults for the:

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

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

The CHMP therefore recommends the extension(s) of the marketing authorisation for Akynzeo 300 mg/0.5 mg oral suspension, subject to the conditions described in the following sections.

2.7.4. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

2.7.5. Other conditions and requirements of the marketing authorisation

2.7.5.1. 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.

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

2.7.6.1. Risk management plan (RMP)

The marketing authorisation holder (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.

2.7.6.2. Additional risk minimisation measures

None

2.7.6.3. Obligation to conduct post-authorisation measures

None

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

Not applicable.

3. Introduction

Therapeutic Context

Akynzeo is a fixed combination of netupitant and palonosetron and has been shown to be beneficial in patients receiving emetogenic chemotherapy, by preventing both the immediate and the delayed phases of nausea and vomiting. Palonosetron is a 5-hydroxytryptamine-3 (5-HT3) receptor antagonist and blocks the binding of serotonin and prevents early (within 24 h) and delayed (after 24 h) chemotherapy-induced nausea and vomiting (CINV). Netupitant blocks neurokinin-1 (NK-1) receptors in the nervous system and prevents delayed CINV (after 24 h). Patients undergoing chemotherapy receive one fixed combination capsule (300 mg netupitant and 0.5 mg palonosetron) about 1 h before the start of chemotherapeutic treatment.

Akynzeo was first authorised in the EU in 2015, and is indicated in adults for the:

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

Akynzeo is currently available for oral administration as hard capsules (300 mg netupitant/ 0.5 mg palonosetron) as well as for intravenous (IV) injection as powder for concentrate for solution for infusion and concentrate for solution for infusion (235 mg fosnetupitant/0.25 mg palonosetron) in single-dose vial.

With this extension application, the MAH has developed a new pharmaceutical form, 'Netupitant-Palonosetron Oral Suspension', which is a 10 mL oral suspension consisting of 300 mg netupitant and 0.5 mg palonosetron as a fixed combination in a sachet. The dosage strength of both active pharmaceutical ingredients (API)s is the same as Akynzeo hard capsules.

3.1. Aspects of development

The clinical development program for this line extension consisted of a single pharmacokinetic bioequivalence study (NEPA-23-01) to demonstrate bioequivalence between the proposed oral suspension formulation and the approved hard capsule formulation. This study investigated bioequivalence as a primary objective, and a comparison of safety as an additional objective.

No scientific advice or protocol assistance was received from the CHMP for this application.

3.2. Description of the product

The proposed 300 mg netupitant/0.5 mg palonosetron oral suspension in sachet has been developed as an alternative to the existing 300 mg netupitant/0.5 mg palonosetron hard capsule.

The indications for this product are identical to the indications for the hard capsule.

The posology for the suspension in sachet is identical to the hard capsule. The suspension in sachet is a liquid formulation compared to the solid dosage hard capsule, however, will still be administered as a single dose per sachet.

The proposed attributes for the suspension compared to the existing Akynzeo dosage forms (capsule, powder for concentrate for in for solution and injection, and concentrate for solution for injection) are:

- Taken by patients that have difficulty or cannot swallow capsules
- Stored at room temperature (≤25°C)
- Ready-to-use form and requires no further preparation

4. Quality aspects

Introduction

This Line Extension intends to introduce an oral suspension formulation to the already authorised Akynzeo pharmaceutical forms of 300 mg / 0.50 mg hard capsule, 235 mg / 0.25 mg powder for concentrate for solution for infusion and 235 mg / 0.25 mg concentrate for solution for infusion.

The finished product (FP) is presented as an oral suspension containing 300 mg netupitant and palonosetron hydrochloride equivalent to 0.5 mg of palonosetron as active substances.

Other ingredients are: Glycerol (E 422), Xanthan Gum, Citric Acid Anhydrous, Sodium Citrate Tribasic, Potassium Sorbate, Sorbitol Syrup (E 420) and Purified Water.

The oral suspension is available in 10 ml PET/ALU/PE (polyester/aluminium/polyethylene) laminate sachet and packed in a carton.

4.1. Active substance

No updates to this section are made as part of this line extension application.

4.2. Finished medicinal product

4.2.1. Description of the product and pharmaceutical development

Akynzeo 300 mg/0.5mg oral suspension is a white to off-white homogenous liquid, with palonosetron completely solubilised and netupitant suspended in the formulation, defined as suspension. The suspension is filled in a 10 ml PET/ALU/PE (polyester/aluminium/polyethylene) laminate sachet and packed in a carton. The qualitative composition of Akynzeo 300 mg/0.5mg oral suspension is presented in the SmPC section 6.1

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Pharmaceutical development

Quality by design elements including QTPP (Quality Target Product Profile), shown in Table 1,**Error! Reference source not found.** CQAs (Critical Quality Attributes) were considered in order to ensure that clinical and market needs are addressed by the oral suspension formulation.

Table 1. Quality Target Product Profile

QTPP Element	Target	Justification
Dosage Form and Route of Administration	Oral suspension formulation ready to be used	Clinical and market need
Dosage Design	Oral liquid dosage form to deliver the two active substances in a single administration	Clinical need
Dosage Strength	Fixed combination containing fixed dose of netupitant + palonosetron equal to Akynzeo Capsule (300mg-0.5mg)	Clinical need

Pharmacokinetics		Oral formulation bioequivalent to Akynzeo Capsule	Clinical need
Drug Product Quality Attributes	Physical attributes	To meet quality and compendial standards	Needed to ensure product quality, safety and efficacy throughout shelf-life.
	Identification		
	Assay		
	Uniformity of dosage		
	Purity		
	Dissolution		
	Elemental Impurities		
	Microbial limits		
Manufacturing Process		Robust and reproducible processes to meet the above requirements	Needed to consistently ensure product quality, safety and efficacy throughout shelf-life.
Container Closure System and Dosing System		Sufficient to assure product quality and integrity throughout shelf-life. Easy administration of the drug product. Complete recovery of the dose. Single or multiple sachets packaged in single container (secondary packaging)	Needed to ensure product quality, safety and efficacy throughout shelf-life. Pathology needs.
Stability		At least 36-month shelf-life at controlled room temperature (preferable)	Needed to ensure product quality, safety and efficacy throughout shelf-life.

No change to the quantitative composition was made in respect of netupitant and palonosetron active substances from clinical to commercial formulation. Formulation studies were performed to determine the most suitable suspending and wetting agents. Xanthan gum was selected as the optimal suspending agent and glycerin was the chosen wetting agent as less foam formation was observed. The inclusion of sorbitol was deemed sufficient in the absence of other sweetening agents. Excipient compatibility studies were performed and accepted. Stability of test formulations was examined at long term and accelerated conditions. The final proposed excipients are all subject to Ph. Eur. monographs and are commonly used in pharmaceutical products.

A Major Objection (MO) was raised questioning the need to include a preservative within the formulation, given that this the medicinal product is administered in a single-dose sachet and sorbitol syrup is known to have self-preservative activity.

In their response the applicant provided appropriate justification from the literature as well as data from formulation development studies carried out on batches with varying levels of preservative (potassium sorbate), and without preservative. These studies confirmed the necessity to include a preservative agent in the formulation.

Moreover tests were carried out to justify the preservative level over a 60-day period. The same tests showed that batches with no preservative fail the Ph. Eur. Antimicrobial Effectiveness Test (AET) requirement. In addition, stability results on clinical batch showed that at the proposed level is effective to maintain the microbial properties of the product up to 12 months. Overall, it is accepted that the amount used has been justified based on the above studies and there are no safety or efficacy concerns due to the use of this preservative or the level employed; the MO is considered resolved.

pH, to ensure palonosetron remains in solution, viscosity, to ensure netupitant remains in suspension, and netupitant dissolution were determined to be critical quality attributes in the formulation. Palonosetron is fully dissolved in the formulation and dissolution is deemed non-critical. A netupitant dissolution analytical method was presented. However, the dissolution method development was not described, and its suitability for the pharmaceutical form had not been justified. This resulted in a MO. Furthermore, data were also requested to confirm the discriminatory nature of the dissolution method for the oral suspension formulation.

In response to this MO, the applicant provided a development report on the dissolution method. Therein the applicant described the dissolution parameters assessed including paddle speed, dissolution media molarity, pH and SDS concentration. It was also clarified that the dissolution method development was conducted with a batch of the same formulation as the clinical batch.

Dissolution volume of 900 ml was selected along with a paddle speed of in buffer at SDS. These conditions have been suitably justified within the report as sink conditions are adequately met under these conditions.

Discriminatory power has been adequately demonstrated by carrying out a dissolution study on a high viscosity batch vs. a typical viscosity batch. Based on the response the MO was resolved.

Manufacturing process development was first performed on a small-scale batch, prior to process transfer to the commercial manufacturing site. Design of experiment (DoE) studies were performed to examine impact of the critical attributes and critical process steps, with changes made to the manufacturing process as a result of the results obtained. Where some limiting factors to the studies were identified, these are mitigated by controls within the FP specification. An overfill ensures the correct dosage is achieved and a deliverable volume test is included within the FP specification to ensure adequate dosing. While the applicant has applied QbD principles in the development of the manufacturing process, no design spaces were claimed for the manufacturing process of the finished product.

The FP is filled in PET/ALU/PE multilayer laminate sachet and packed in a carton box. Acceptable specifications including identification by IR were provided.

Compliance of the container closure system with legislation is stated, and no dedicated extractable study is considered necessary as per the EMA Guideline on Plastic Immediate Packaging Materials and since the PET/ALU/PE laminate material conforms to the requirements of Reg 1935/2004/EC for "materials in contact with food" and is in compliance with EU 10/2011 "Plastic materials in contact with foodstuffs" and EN 602:2004-07 "Aluminium & aluminium alloys in food contact". The choice of materials and physical aspects of the container closure are appropriate for the finished product form.

4.2.2. Manufacture of the product and process controls

Finished product manufacturer, packaging and batch release site are clearly stated in the dossier. Satisfactory evidence of GMP was provided for all sites involved in the manufacture, testing and batch release of the FP. The manufacturing process involves bulk solution preparation, with components added and mixed, prior to final mixing to form the suspension and filling into sachets. The manufacturing process is considered a non-standard process as a result of the low content of palonosetron active substance in the formulation.

A single batch size is proposed and the batch formula presented. The narrative description of the manufacturing process is generally well described, supported by a flowchart, in-process control tests and a list of equipment used.

Three critical process parameters during bulk manufacturing were identified within controls of mixing times, hold times and mixing speeds and are included within the manufacturing process description. In-process control tests are performed on the bulk suspension and on sachet filling and are acceptable.

The applicant has provided adequate process validation data for three batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The integrity of the packaging has been proved to be suitable. Seal test was performed as IPC during filling of registration batches and validation batches, and all the results are in compliance with the specification.

4.2.3. Product specification

The finished product specifications include appropriate tests for this kind of dosage form: appearance (visual), uniformity of dosage units (Ph. Eur.), seal test (dye ingress), dissolution (Ph. Eur.), viscosity (Ph. Eur.), deliverable volume, pH (Ph. Eur.), identification netupitant (HPLC, HPLC-DAD), identification palonosetron (HPLC, HPLC-DAD), assay netupitant (HPLC), assay palonosetron (HPLC), impurities netupitant (HPLC), impurities palonosetron (HPLC), identification potassium sorbate (HPLC), assay potassium sorbate (HPLC), microbiological enumeration test (Ph. Eur.).

The tests and the limits applied are in line with the Ph. Eur. dosage form chapter, EMA guidance on specifications and control tests on the finished product and ICH Q3B (R2) Impurities in New Drug Products.

The absence of a dissolution test for palonosetron is accepted, as this active substance is in solution within the formulation.

During the procedure a MO was raised about the dissolution specification limit. Specifically, it was requested that the dissolution limit in should be set based on the results obtained for the biobatch used in bioequivalence study NEPA-23-01. In addition, full biobatch dissolution data were requested in support of the proposed dissolution limit applied. It their response the applicant provided the requested data and tightened the netupitant dissolution specification limit as requested in line with the biobatch. The MO was thus resolved. Elemental impurities are appropriately controlled as per ICH Q3D. Batch analysis data from 3 batches was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory

The nitrosamine risk assessment presented initially was not satisfactory because it did not adequately address all of the potential risks of nitrosamine presence or nitrosamine formation within the formulation. A MO was raised, requesting to be demonstrated that any nitrosamines formed during the FP manufacturing process or throughout the proposed shelf-life can be controlled within the limits required by the latest version of Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products.

In response to the MO, an appropriate nitrosamine risk assessment has been provided as per the relevant guidance. Based on the results of the risk assessment, the applicant concluded that there is no risk of nitrosamines' formation during the manufacturing process of Akynzeo oral suspension or during the shelf life of the product. Therefore, CHMP concluded that no specific control measures are deemed necessary. This was accepted and resolved the MO.

The detail provided in relation to the analytical methods are acceptable. Acceptable method validation reports in line with ICH Q2(R2) are provided. Confirmation of compliance of microbial control tests with Ph. Eur. requirements is provided. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results for three registration batches and three PPQ (validation) batches were presented. All results comply with the specifications applied and confirm consistency of the manufacturing process.

4.2.4. Stability of the product

The applicant proposes a shelf life of 2 years with no special storage conditions.

Stability data is provided for three commercial scale batches under long term (25 ºC / 60% RH) and intermediate conditions (30 ºC / 75% RH), for18 months and under accelerated conditions (40 ºC / 75% RH) for6 months

according to the ICH guidelines were provided. The stability batches of are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, pH, viscosity, assay netupitant, assay palonosetron, impurities netupitant, impurities palonosetron, seal test and microbiological enumeration test. The analytical procedures used are stability indicating.

All batches met the specifications applied with no significant trending observed. A MO was raised, as in the initial stability package no dissolution testing was performed after the initial time point. Since netupitant dissolution is a critical quality attribute of the FP, additional data with this parameter included were requested in support of the FP shelf life.

The applicant responded by providing appropriate data to indicate that the FP will meet the dissolution specification up to the proposed shelf-life. The applicant has also provided data to demonstrate that the PSD is also consistent in the test batches over the shelf-life of the drug product with no agglomeration, aggregation or flocculation observed. Therefore, the MO was resolved.

Stress study has been performed in acidic, alkaline, oxidative, thermal, humidity and light stress conditions. The study results support of the stability-indicating nature of the methods. One impurity increased under oxidative stress while all other impurities were not affected by other stress conditions. Under light stress testing some degradation was observed. Finally, both netupitant and palonosetron can be considered stable upon exposure to light for 24 hours. While no formal photostability study was performed this is accepted as the packaging was shown to be light protective within 3.2.P.4.

The proposed shelf-life of 2 years without special storage conditions in the proposed container are justified by stability results and are acceptable.

4.2.5. Post-approval change management protocol(s)

Not applicable.

4.2.6. Adventitious agents

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

4.3. Discussion on chemical, pharmaceutical and biological aspects

No changes to the active substance section of the dossier are proposed with this Line Extension and this is acceptable. Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. During the procedure five Major Objections were raised related to the use and justification of the preservative in the formulation, the netupitant dissolution method development, the netupitant dissolution specification limit, the nitrosamine risk assessment, and the lack of dissolution testing as a stability parameter. The applicant provided additional justifications and data to support the choice of preservative, presented a satisfactory dissolution method development together with acceptable tighter dissolution specification limit, updated the nitrosamine risk assessment as requested and provided the missing information regarding the dissolution testing during stability. All MOs have been sufficiently addressed.

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.

4.4. Conclusions on 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.

4.5. Recommendation(s) for future quality development

Not applicable.

5. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

Netupitant/Palonosetron is already approved as an oral hard capsule and the oral suspension is intended as a substitution thus, no significant increase in environmental exposure is anticipated. The rationale for not providing an updated environmental risk assessment is considered acceptable.

6. Clinical aspects

6.1 Introduction

The Applicant has developed an oral suspension with the same fixed combination of 300 mg netupitant and 0.5 mg palonosetron as the hard capsule. A clinical trial (NEPA-23-01) has been conducted to demonstrate bioequivalence of the new oral suspension formulation to the approved hard capsule formulation. The trial was conducted according to an open-label, randomised, single centre, two-treatment, four-period, two-sequence replicative design. 74 healthy subjects were enrolled at one study centre to receive a single dose of 300 mg netupitant and 0.5 mg palonosetron during each period.

6.1.1. GCP aspects

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

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

6.1.2. Tabular overview of clinical trials

Table 2: Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Phase 1					
NEPA-23-01	Open-label, randomised, single centre, 2-treatment, 4-period, 2 sequence replicative design. Single dose, duration of approximately 18 weeks from screening to EoT	Test product as a single dose of 300 mg netupitant and 0.5 mg palonosetron oral suspension and Reference product as a single dose of 300 mg netupitant and 0.5 mg palonosetron oral hard capsule	Healthy male and female volunteers aged 18 to 55 years, 18.5 ≤ BMI ≤ 30.0 kg/m2 and BW > 50 kg at screening	Primary objective to demonstrate bioequivalence regarding the AUC0-t for netupitant and palonosetron after single oral dose administration of test and reference treatments.	74 subjects randomised and treated.

BMI: Body mass index, BW: Body weight, EoT: End of trial.

6.2. Clinical Pharmacology

6.2.1. Methods

An overview of the bioanalytical methods that were used to evaluate key pharmacological endpoints in clinical studies are presented Table 3 below. These methods and performance in the key pharmacology studies will be detailed in the following subsections.

Table 3. Summary of partially validated methods used in Study NEPA-23-01 – 23295/23296 submitted for this application.

Method ID	Sample Matrix	Testing Sites	Bioanalytical Method	Assay Description	Validation Status	Assay Validation Report	Clinical Studies
Netupitant, M1, M2, M3							
Ardena 23292	Human plasma (K2-EDTA)	Ardena Bioanalysis BV (Assen, Netherlands)	LC-MS/MS	Quantification of netupitant and metabolites (M1, M2, M3)	Partially Validated – Interim	23292 Partial Validation Interim Report	23295
Palonosetron							
Ardena 23290	Human plasma (K2-EDTA)	Ardena Bioanalysis BV (Assen, Netherlands)	LC-MS/MS	Quantification of palonosetron	Partially Validated	23290 Partial Validation of PALO	23296
Ardena 24344	Human plasma (K2-EDTA)	Ardena Bioanalysis BV (Assen, Netherlands)	LC-MS/MS	Quantification of palonosetron	Partially Validated	24344 Partial Validation of PALO Preparation	23296

Quantification of netupitant, M1, M2, M3 concentrations in human plasma (Study 23292

Method development, validation, and bioanalysis of netupitant concentrations in human plasma was conducted in support of the bioequivalence study, Study NEPA-23-01. The partial validation followed Ardena internal SOPs and validation was conducted in line with International Council for Harmonisation (ICH) Guideline M10 on bioanalytical method validation and study sample analysis.

A full validation for netupitant, M1, M2, and M3 (validation study 15056) was most recently submitted as part of EMEA/H/C/3728/X/018, the line extension application for Akynzeo 235 mg/ 0.25mg powder for concentrate for solution.

The partial validation parameters for this application were the matrix effect, response function of the calibration curve, dilution integrity, and stability in human K2-EDTA plasma.

Assay Principle

Plasma samples were analysed using a selective and sensitive LC–MS/MS assay with liquid–liquid extraction (LLE) of 50.0 µL human K_2-EDTA plasma. Netupitant and its metabolites M1, M2, and M3 were isolated by LLE and quantified on a triple quadrupole MS/MS (API/QTRAP 4000) system. Chromatographic separation was achieved isocratically on a C18column, and stable isotope-labelled internal standards (Netupitant-d_6, M1-d_6, M2-d_6, M3-d_6) were used for each analyte to ensure accuracy and reproducibility.

Validation summary

The interim partial method validation evaluated the quantitation range, dilutional integrity, stability (ongoing), and matrix effect.

The assay demonstrated linearity for netupitant and for M1, M2, and M3. A 10-point calibration curve with $1/x^2$ weighting showed acceptable accuracy (bias within ±15%) and precision (CV <15%) across all analytes. No significant matrix effects were observed across 9 plasma donors. One outlier for netupitant, one outlier for M1, and two outliers for M2 were deemed non-reproducible anomalies.

Accurate quantitation was maintained after diluting samples up to 5× above ULOQ. All diluted samples met accuracy criteria(±15%).
Netupitant and metabolites were stable for at least four freeze–thaw cycles and up to 18 hours on wet ice. Long-term frozen stability (≤−70 °C)is still under evaluation.

The LC–MS/MS method demonstrated acceptable matrix effect and stability in this partial validation using spiked plasma samples. The method is confirmed as suitable for quantifying netupitant, M1, M2, and M3 in human plasma, supporting reliable pharmacokinetic assessments in clinical studies.

Assay performance

Study NEPA-23-01

A total of 5847 plasma samples were analysed for concentrations of netupitant and its metabolites M1, M2, and M3 using a validated LC-MS/MS method. The study evaluated a bioequivalence trial comparing oral suspension and capsule formulations of netupitant/palonosetron in healthy volunteers. Assay performance was acceptable.

Quantification of palonosetron concentrations in human plasma

Partial validation Study 23290

Method development, validation, and bioanalysis of palonosetron concentrations in human plasma was conducted in support of the bioequivalence study, Study NEPA-23-01. The partial validation followed Ardena internal SOPs and validation was conducted in line with International Council for Harmonisation (ICH) Guideline M10 on bioanalytical method validation and study sample analysis.

A full validation for palonosetron (validation study 15150) was most recently submitted as part of EMEA/H/C/3728/X/018, the line extension application for Akynzeo 235 mg/ 0.25mg powder for concentrate for solution.

The partial validation parameters for this application were the matrix effect, response function of the calibration curve, and dilution integrity.

Assay principle

Plasma samples were analysed using a selective and sensitive LC–MS/MS assay. Palonosetron and the internal standard (palonosetron-d_3) were isolated from 100 µL of human K_2-EDTA plasma via protein precipitation followed by off-line solid phase extraction. Chromatographic separation was achieved using gradient elution on a C18column. The analytes were detected using a triple quadrupole MS/MS system (API 4000), with mass transitions of m/z 297→110 for palonosetron and m/z 300→111 for the internal standard.

Validation summary

No significant matrix effects were observed across five individual plasma lots and one pooled lot. A haemolysis-related deviation was observed in one matrix run but was resolved upon reanalysis. Both haemolysed and lipemic matrices met acceptance criteria following reanalysis.

Calibration standards met acceptance criteria for linearity, with coefficients of determination (r) ≥ 0.99 and back-calculated concentrations within ±15% (±20% at LLOQ).

Dilution integrity was demonstrated at 2× and 5× dilutions, with CVs and biases within ±15%, confirming assay reliability for samples above the ULOQ. QC samples at low, medium, and high concentrations showed precision and accuracy within acceptance limits (≤15% CV and bias).

Partial validation Study 24344

The partial validation followed Ardena internal SOPs and validation was conducted in line with International Council for Harmonisation (ICH) Guideline M10 on bioanalytical method validation and study sample analysis.

The partial validation evaluated selectivity, specificity, matrix effect (including haemolysed and lipemic plasma), calibration curve performance, precision and accuracy, dilution integrity, carryover, recovery, autosampler stability, re-injection stability, and maximum batch size.

Validation summary

Calibration standards met acceptance criteria, with linearity confirmed (r ≥ 0.999) and all points within ±15% (±20% at LLOQ). No significant matrix effects were observed across six plasma donors, including haemolysed and lipemic sources.

Precision and accuracy were demonstrated across all tested concentrations, with within- and between-run CVs and biases within 20% at LLOQ and ≤15% otherwise. Dilution integrity was confirmed for 2× and 5× dilutions, allowing accurate quantification up to. Processed sample stability was verified for, and re-injection was shown to be acceptable after 71 hours. Recovery was high and reproducible for both palonosetron and its internal standard. No carryover was observed for the analyte.

Assay performance

Study NEPA-23-01

A total of 5847 plasma samples were analysed for concentrations of palonosetron using a validated LC-MS/MS method. The study evaluated a bioequivalence trial comparing oral suspension and capsule formulations of netupitant/palonosetron in healthy volunteers. Assay performance for palonosetron was acceptable.

6.2.2. Pharmacokinetics

6.2.2.1. Introduction

For this line extension application, the MAH has submitted a single pharmacokinetics study (Study NEPA-23-01) to demonstrate bioequivalence between the test product in this application, 300 mg netupitant/0.5 mg palonosetron oral suspension, and the already approved reference product, 300 mg netupitant/0.5 mg palonosetron hard capsule, for which a marketing authorisation was issued on 27 May 2015.

6.2.2.2. Evaluation and qualification of models

PK parameters were derived using non-compartmental methods.

No population PK or physiology-based PK models were used to support this application.

6.2.2.3. Bioequivalence

Study NEPA-23-01

Study Design

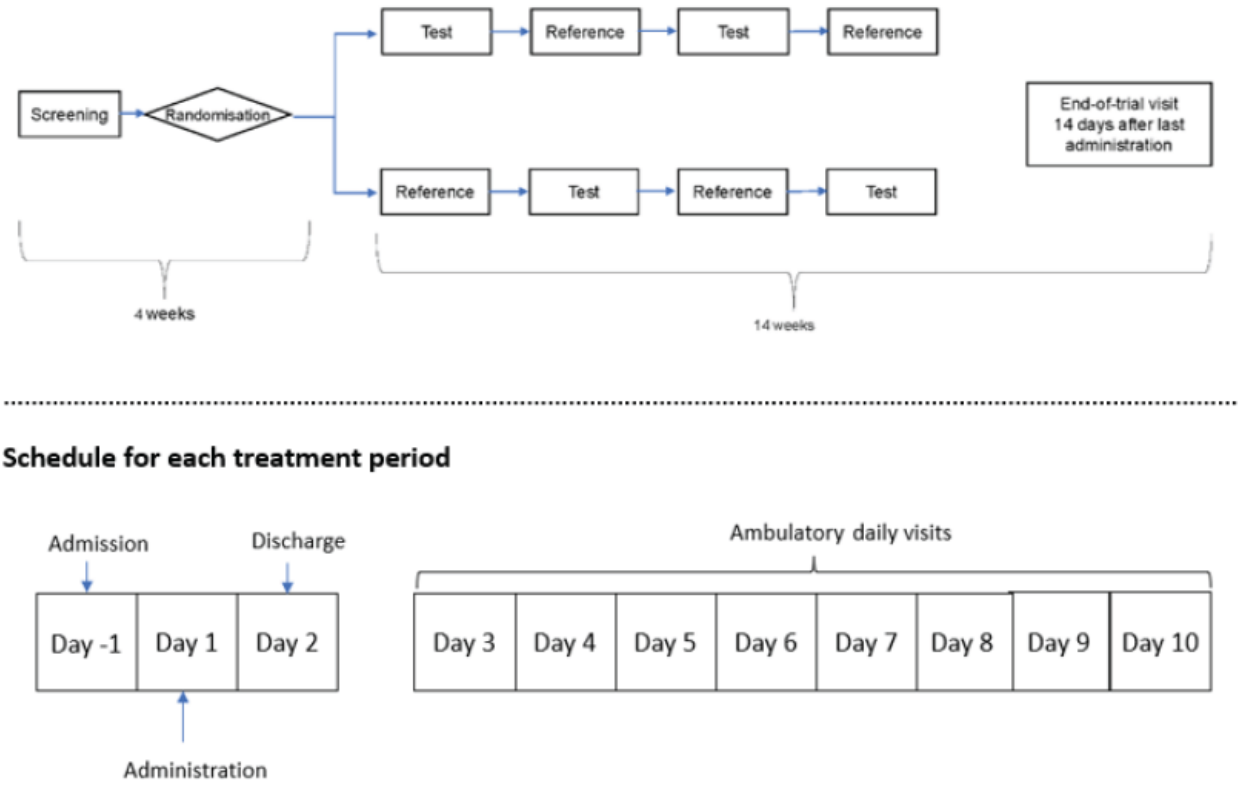
This was a Phase 1, single dose, open-label, randomised, 2-treatment, 4-period, 2-sequence replicative design, single centre study in healthy adult subjects (n = 74). This was a pharmacokinetic bioequivalence study designed to evaluate bioequivalence between an oral suspension 300 mg netupitant/ 0.5 mg palonosetron (Test) and the marketed hard capsule containing 300 mg netupitant/ 0.5 mg palonosetron (Reference).

Subjects received both the test and reference product over 4-periods according to 1 of 2 treatment sequences:

- Sequence A: Test-Reference-Test-Reference
- Sequence B: Reference-Test-Reference-Test

The study schematic and schedule for each treatment period is outlined in **Error! Reference source not found.**below.

Figure 1. Schematic for NEPA-23-01



Study population

A total sample size of 66 evaluable subjects was needed to achieve 90% power to conclude bioequivalence for an assumed intra-individual geoCV of 33% if the Test/Reference ratio was not more than 10% different from the ratio of 100% (which reflects no difference in exposure). To account for uncertainty in the estimated geoCV and dropouts, a total of 74 subjects was included in this trial.

74 subjects were randomised in a 1:1 ratio to the 2 treatment sequences according to a randomisation list. Block randomisation without stratification factors was used. 7 subjects did not receive the full 4 planned doses while 67 subjects completed the entire course of the study and received 2 single doses each of the Test and Reference Treatment.

Eligibility criteria

In order to be considered eligible for the study all inclusion criteria must be met, and no exclusion criteria met. Some of the key eligibility criteria include:

1. Male or female healthy volunteer, 18-55 years old, inclusive, at screening.
2. 18.5 ≤ BMI ≤ 30.0 kg/m2 and body weight (BW) > 50 kg at screening.
3. Negative pregnancy test (female subjects of childbearing potential only) at screening (in serum) and Day -1 (in urine) Period 1.
4. Female subjects of childbearing potential and with active sexual life had to be practicing a highly effective method of contraception for at least 2 months before the screening.
5. Not have any condition which could have interfered with the absorption of the IMP.
6. No intake of any concomitant medications (including herbal remedies) within 14 days before Day -1 of Period 1 or scheduled to receive such products during the study.
7. No intake of any known inducers or inhibitors (drugs, grapefruit juice) of CYP3A4.

Treatments

All subjects received the same treatments. Each subject was to receive 2 single dose administrations of the Test and 2 single dose administrations of the Reference Treatment either in sequence T-R-T-R or R-T-R-T, with at least 28 days washout between consecutive administrations.

The identity of the investigation products is detailed in Table 4 below.

Table 4. Study interventions

Intervention Label	Test	Reference
Intervention Name	Netupitant / palonosetron oral suspension	Akynzeo 300 mg/0.5 mg hard capsules
Intervention Description	Oral suspension of netupitant and palonosetron	Hard capsule of netupitant and palonosetron
Type	Drug	Drug
Dose Formulation	Oral suspension	Hard capsule
Unit Dose Strength(s)	300 mg netupitant / 0.5 mg palonosetron in 10 mL suspension	300 mg netupitant / 0.5 mg palonosetron hard capsule
Dosage Level(s)	Single dose of 300 mg netupitant / 0.5 mg palonosetron	Single dose of 300 mg netupitant/ 0.5 mg palonosetron
Route of Administration	Oral	Oral
Storage Conditions	Protected from light at 15°C-25°C	Below 30°C
Use	Experimental	Experimental
IMP and NIMP/AxMP	IMP	IMP
Sourcing	Doppel Farmaceutici S.r.l. Via Volturno 48, Rozzano, 20089 – Italy	Helsinn Birex Pharmaceuticals Ltd. Damastown, Mulhuddart, Dublin 15 – Ireland
Packaging and Labelling	10 mL amber bottles	1 capsule in blister per carton
Current/ Former Name(s) or Alias(es)	Not applicable	Akynzeo
Batch Number	K240075	K240074
Expiry Date	03/2025	03/2027

Objectives

The primary objective of this study was to demonstrate bioequivalence regarding AUC0-t for netupitant and palonosetron after single oral dose administration of Test (T) and Reference (R). The secondary objective of this study was to support bioequivalence of netupitant and palonosetron regarding Cmax, tmax, and AUC0-∞.

The PK parameters for the metabolites of netupitant, M1, M2, and M3 were also evaluated.

An additional objective of this study was to collect safety and tolerability data of the Test and Reference after single dose administrations.

Outcome/Endpoints

The values for the pharmacokinetic parameters of netupitant (and metabolites M1, M2, M3) and palonosetron were estimated using non-compartmental methods. The pharmacokinetic endpoints include:

- the area under the serum concentration-time curve (AUC) from time 0 to time of the last measurable concentration (AUC0-t)
- maximum observed serum concentration (Cmax)
- the AUC from time 0 to infinity (AUC0-inf)
- time to Cmax (Tmax)

- the apparent terminal phase elimination rate constant (λz)
- the terminal phase elimination half-life (t1/2)
- Percentage of AUC up to final time-point (%AUC0-t) and the percentage of AUC extrapolated to infinity (%AUCt-inf)

The following safety evaluations were performed during the study: adverse event (AE) monitoring, physical examination, clinical laboratory tests and electrocardiogram (ECG) assessments.

Sampling time-points

There were 4 treatment periods with 28-day washout phase between each period. Study participants received the test of reference product at 0 h on Day 1. Blood samples for PK analysis were collected predose, and at 1 h, 2 h, 3 h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h, 8 h, 11 h, 12 h, 24 h, 48 h, 72 h, 96 h, 120 h, 144 h, 168 h, 192 h, and 216 h.

Pharmacokinetic data analysis

Calculation of the PK parameters were performed by means of a non-compartmental model using Phoenix WinNonlin. Calculation of the PK parameters were based on actual blood sampling times [h] relative to the corresponding administration time. Negative predose times were set to zero.

The primary PK parameters were analysed using an Analysis of Variance (ANOVA) on the logarithmic scale according to the recommendation of the EMA. The ANOVA model included the sequence, period, and treatment effect.

Bioequivalence between the Test and Reference drug was concluded if the two-sided 90% CIs for the ratio of the geometric means (Test/Reference) for the primary endpoints AUC0-t of netupitant and palonosetron are contained entirely within the range of [80.00%, 125.00%]. The PK variables to analyse as secondary endpoint were Cmax, tmax, AUC0-inf of netupitant and palonosetron and the same ANOVA model was performed for Cmax and AUC0-inf.

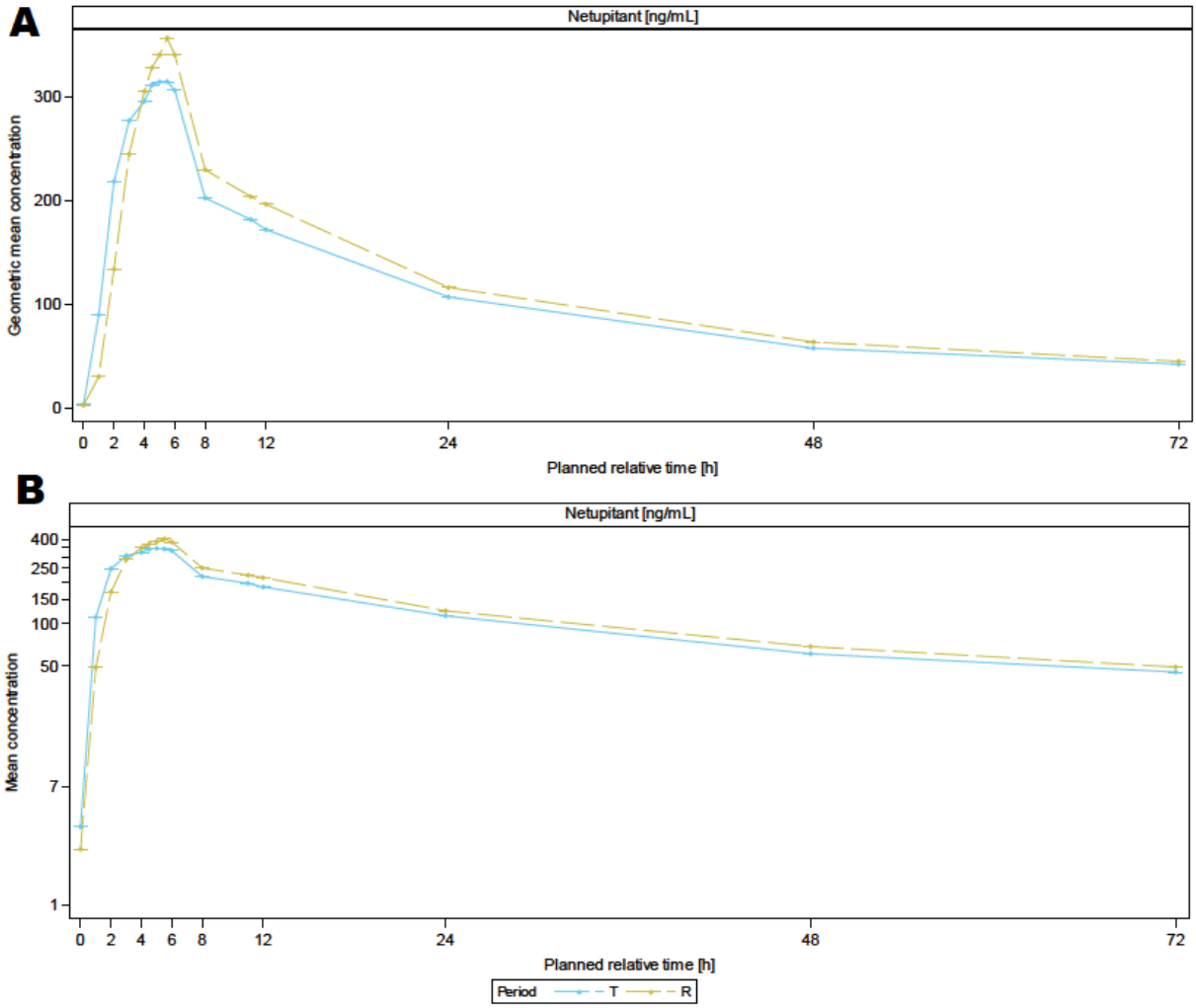
The PK analysis was performed on the pharmacokinetic set (PKS). Two subjects were excluded from the PKS, as they only had one valid treatment period (T1). Therefore, the PKS included 72 subjects. Single samples or periods were excluded from the analysis in line with criteria outlined in the analysis populations criteria.

Pharmacokinetic results

Plasma concentration-time profiles

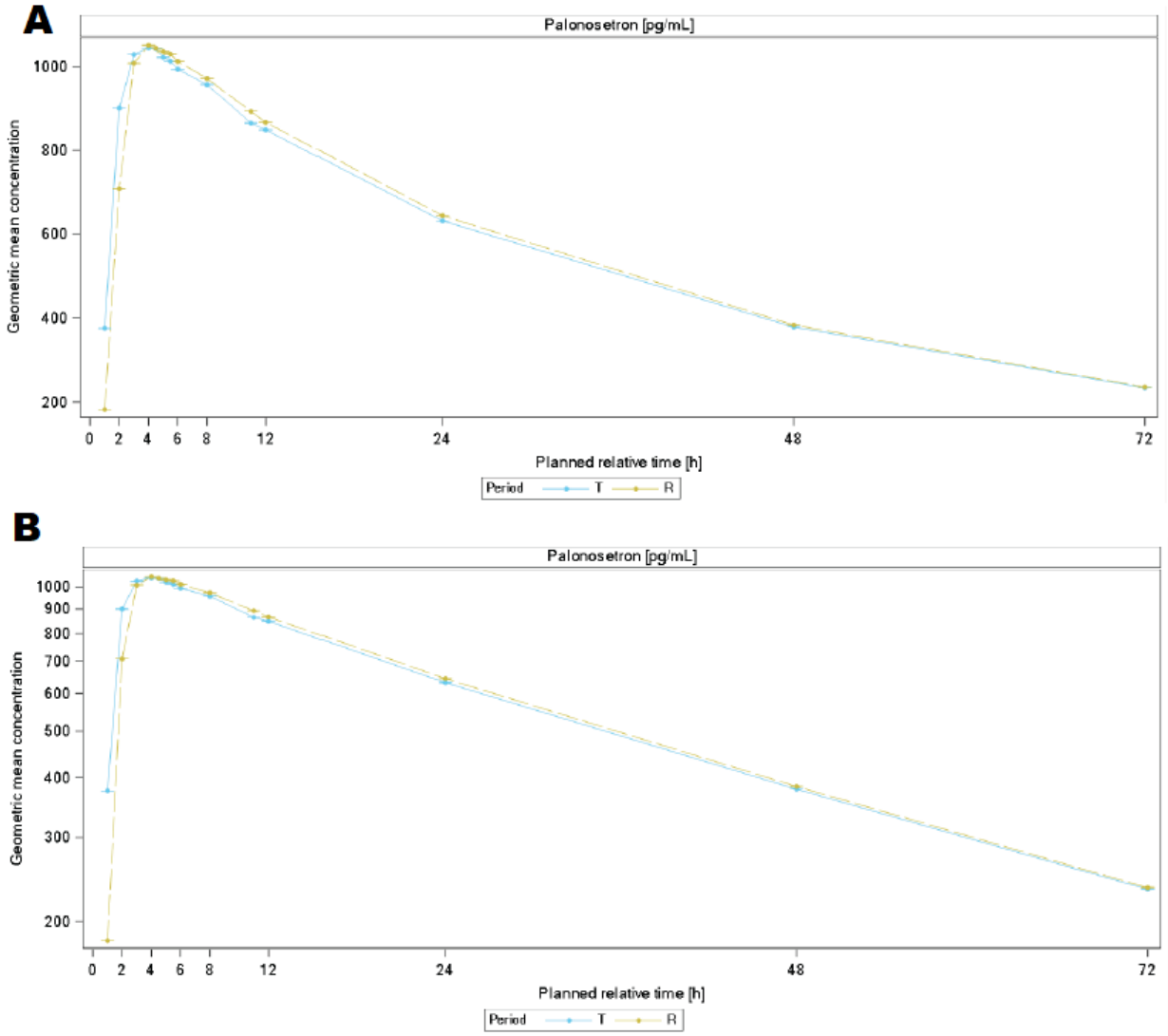
Netupitant profiles up to 72 h after administration are shown in Figure 2-A (linear scale) and Figure 2-B (logarithmic scale) for Test and Reference Treatment. After administration of the Test Treatment (T), netupitant concentrations were slightly lower than after the Reference Treatment (R) during the first 24 h after administration, thereafter, concentrations were similar.

Figure 2. (A) Geometric mean plasma concentration-time profile of netupitant from 0-72 h by treatment (T, R) on linear scale, (B) Geometric mean plasma concentration-time profile of netupitant from 0 to 72 h by treatment (T, R) on logarithmic scale



Palonosetron profiles up to 72 h after administration are shown in Figure Figure 3-A (linear scale) and Figure 3-B (logarithmic scale) for Test and Reference Treatment. Geometric mean concentration profiles of palonosetron showed no differences between Test (T) and Reference Treatment (R).

Figure 3. (A) Geometric mean plasma concentration-time profile of palonosetron from 0-72 h by treatment (T, R) on linear scale, (B) Geometric mean plasma concentration-time profile of palonosetron from 0 to 72 h by treatment (T, R) on logarithmic scale



PK parameters

The geometric mean values of the primary PK endpoint AUC0-t of netupitant were similar in both treatments (Table 5). Geometric mean values were 10879.491 h*ng/mL (T) and 11737.057 h*ng/mL (R). The variability of AUC0-t was moderate, with geoCVs of 35% (T) to 39% (R).

The geometric mean values of the primary PK endpoint AUC0-t of palonosetron were similar in both treatments (Table 5). Geometric mean values were 48936.593 h*pg/mL (T) to 49229.671 h*pg/mL (R). The variability of AUC0-t was low, with geoCVs of 30% (T) and 29% (R).

Table 5. Primary pharmacokinetic parameter by treatment.

Pharmacokinetic parameter [unit]	Statistics	T	R
Netupitant			
AUC_{0-t} [h*ng/mL]	N	139	138
	n	139	137
	GeoMean	10879.491	11737.057
	GeoCV [%]	35.356	38.745
Palonosetron			
AUC_{0-t} [h*pg/mL]	N	139	137
	n	139	136
	GeoMean	48936.593	49229.671
	GeoCV [%]	29.562	28.738

AUC_{0-t} = AUC from time 0 to time of last measurable concentration, calculated up by linear trapezoidal rule, down by logarithmic trapezoidal rule, GeoMean = geometric mean, GeoCV = geometric coefficient of variation, n = number of observations, N= total number of samples

The geometric mean values of the secondary PK endpoints AUC0-∞, Cmax, and median tmax of netupitant were similar for both treatments (Table 6). Variability was moderate, with geoCV of 38% (T) and 43% (R) for AUC0-inf and of 44% (T) and 55% (R) for Cmax. Median tmax of netupitant was 5 h (T) and 5.5 h (R).

The geometric mean values of the secondary PK endpoints AUC0-∞, Cmax, and median tmax of palonosetron were similar for both treatments (Table 6). Variability was low, with geoCV of 29% (T) and 28% (R) for AUC0-∞ and of 21% (T) and 22% (R) for Cmax. Median tmax of palonosetron was 4.0 h for both treatments.

Table 6. Secondary pharmacokinetic parameters by treatment.

Pharmacokinetic parameter [unit]	Statistics	T	R
Netupitant			
$AUC_{0-\infty}$ [h*ng/mL]	N	139	138
	n	139	137
	GeoMean	12327.116	13340.271
	GeoCV [%]	38.346	42.902
C_{max} [ng/mL]	N	139	138
	n	139	137
	GeoMean	360.536	398.824
	GeoCV [%]	44.269	54.810
t_{max} [h]	N	139	138
	n	139	137
	Median	5.000	5.500
	Min - Max	2.00 - 12.00	3.00 – 47.97
Palonosetron			
$AUC_{0-\infty}$ [h*pg/mL]	N	139	137
	n	139	136
	GeoMean	52616.875	53158.512
	GeoCV [%]	28.808	27.784
C_{max} [pg/mL]	N	139	137
	n	139	136
	GeoMean	1143.703	1152.614
	GeoCV [%]	20.776	21.493
t_{max} [h]	N	139	137
	n	139	136
	Median	4.000	4.000
	Min - Max	1.00 – 12.00	1.00 – 12.02

$AUC_{0-\infty}$ = area under the concentration vs. time curve from zero to infinity after single dose, C_{max} = maximum observed drug concentration, directly taken from analytical data, GeoMean = geometric mean, GeoCV = geometric coefficient of variation, n = number of observations, N = total number of samples, t_{max} = time of observed maximum drug concentration

Both for netupitant and for palonosetron, the extrapolated part of AUC0-inf was in average small. For netupitant, the geometric mean value of AUC0-t was 88% for both treatments and the geometric mean of the extrapolated part of AUC0-inf was about 10%. For palonosetron, the geometric mean value of AUC0-t was 93% for both treatments and the geometric mean of the extrapolated part of AUC0-inf was about 10%. Geometric mean t1/2 of netupitant was 67 h (T) and 65 h (R) and for palonosetron it was 38 h (T) and 39 h (R).

Statistical analysis

Bioavailability of netupitant was slightly lower following administration of the test formulation (oral suspension) compared to the reference formulation (capsule), as the 90% CI was entirely below 100%, and the ratio of LS means T/R was 93%. Bioavailability of palonosetron showed no difference between the 2 formulations, as the 90% CI contained the 100% and the ratio of LS means T/R was 99%. Intra-subject variability of AUC0-t was low, with intra-subject geoCV of 0.2 for netupitant, and 0.1 for palonosetron (Table 7).

Table 7. Statistical comparison of primary PK parameters using ANOVA.

Substance	Pharmacokinetic parameter	Ratio (Test/Ref.) of geo. LS means [%]	90% CI of Ratio (Test/Ref.) [%]	Intra-subject geo. CV
Netupitant	AUC_{0-t} [h*ng/mL]	92.39	88.73, 96.19	T: 0.20 / R: 0.20
Palonosetron	AUC_{0-t} [h*pg/mL]	99.33	97.42, 101.28	T: 0.10 / R: 0.10

AUC_{0-t} = area under the concentration vs. time curve from time 0 to time of last measurable concentration, CI = confidence interval, geo. CV = geometric coefficient of variation; LS = Least Squares; R = Reference Treatment; T = Test Treatment.

With respect to secondary PK parameters, a slightly lower bioavailability was seen for netupitant for the oral suspension, and no difference between the formulations in bioavailability of palonosetron. Intra-subject variability of Cmax and AUC0-∞ was low both for netupitant and for palonosetron, with intra-subject geoCV of 0.3 or smaller (Table 8).

Table 8. Statistical comparison of the secondary PK parameters using ANOVA.

Substance	Pharmacokinetic parameter	Ratio (Test/Ref.) of geo. LS means [%]	90% CI of Ratio (Test/Ref.) [%]	Intra-subject geo. CV
Netupitant	C_{max} [ng/mL]	90.02	84.86, 95.50	T: 0.30 / R: 0.30
	$AUC_{0-\infty}$ [h*ng/mL]	92.03	88.03, 96.22	T: 0.23 / R: 0.23
Palonosetron	C_{max} [pg/mL]	99.06	97.05, 101.12	T: 0.10 / R: 0.10
	$AUC_{0-\infty}$ [h*pg/mL]	98.93	97.03, 100.86	T: 0.10 / R: 0.10

$AUC_{0-\infty}$ = area under the concentration vs. time curve from zero to infinity after single dose, C_{max} = maximum observed drug concentration, directly taken from analytical data, CI = confidence interval, geo. CV = geometric coefficient of variation; LS = Least Squares; R = Reference Treatment; T = Test Treatment.

Safety summary

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Display of adverse events

An overview of AEs including treatment-emergent adverse events (TEAEs), SAEs, AEs leading to study withdrawal is given in Table 9.

Overall, 61 of the 74 subjects (82.4%) reported 202 TEAEs; 44 subjects (59.5%) reported 92 TEAEs after the Test Treatment, and 48 subjects (64.9%) reported 111 TEAEs after the Reference Treatment. (Note: 1 TEAE was allocated to both treatments, as date of onset was missing.)

52 subjects (70.3%) reported 158 TEAEs of mild intensity, and 25 subjects (33.8%) reported 44 TEAEs of moderate intensity. None of the subjects experienced TEAEs of severe intensity.

Table 9. Overview of treatment-emergent adverse events.

Parameter	Category	Test (N=74) n (%) events	Reference (N=74) n (%) events	Total (N=74) n (%) events
Any TEAE		44 (59.5%) 92	48 (64.9%) 111	61 (82.4%) 202
Any serious TEAE	No	44 (59.5%) 92	48 (64.9%) 111	61 (82.4%) 202
	Yes	0	0	0
Any severe TEAE	No	44 (59.5%) 92	48 (64.9%) 111	61 (82.4%) 202
	Yes	0	0	0
Any drug-related TEAEs*	No	25 (33.8%) 36	27 (36.5%) 40	43 (58.1%) 76
	Yes	31 (41.9%) 56	37 (50.0%) 71	45 (60.8%) 126
Any TEAE leading to study discontinuation	No	44 (59.5%) 92	48 (64.9%) 111	61 (82.4%) 202
	Yes	0	0	0
Any TEAE leading to treatment discontinuation	No	44 (59.5%) 92	48 (64.9%) 111	61 (82.4%) 202
	Yes	0	0	0
Intensity of TEAEs	Mild	34 (45.9%) 72	40 (54.1%) 87	52 (70.3%) 158
	Moderate	15 (20.3%) 20	18 (24.3%) 24	25 (33.8%) 44
	Severe	0	0	0
Intensity of drug-related TEAEs*	Mild	27 (36.5%) 46	32 (43.2%) 58	42 (56.8%) 103
	Moderate	7 (9.5%) 10	10 (13.5%) 13	13 (17.6%) 23
	Severe	0	0	0
Relationship to study treatment	Not Related	23 (31.1%) 30	20 (27.0%) 25	37 (50.0%) 55
	Unlikely Related	4 (5.4%) 6	11 (14.9%) 15	14 (18.9%) 21
	Probably Related	10 (13.5%) 13	11 (14.9%) 14	19 (25.7%) 27
	Possibly Related	13 (17.6%) 20	17 (23.0%) 27	23 (31.1%) 46
	Definitely Related	16 (21.6%) 22	20 (27.0%) 30	24 (32.4%) 52
	Unassessable	1 (1.4%) 1	0 (0.0%) 0	1 (1.4%) 1

events = number of TEAEs, N = number of subjects who received treatment formulation, n (%) = number (frequency) of subjects with at least one TEAE, TEAE = treatment-emergent adverse event

* Drug-related AEs are those assessed by the Investigator as 'Definitely related', 'Probably related', 'Possibly related', or 'Unassessable'.

45 subjects (60.8%) reported 126 TEAEs assessed by the Investigator as 'definitely', 'probably', or 'possibly' related to the IMP or relationship was 'unassessable'. Of these, 42 subjects (56.8%) reported 103 TEAEs of mild intensity, and 13 subjects (17.6%) reported 23 TEAEs of moderate intensity. The most frequently affected SOCs with drug-related TEAEs were Gastrointestinal disorders, Nervous system disorders, and General disorders and administration site conditions (Table 10Table 10).

Table 10. Drug-related treatment-emergent adverse events.

System Organ Class	Preferred Term	Test N=74 n (%) Events	Reference N=74 n (%) Events	Total N=74 n (%) Events
Any SOC	All	31 (41.9%) 56	37 (50.0%) 71	45 (60.8%) 126
Ear and labyrinth disorders	Any	-	1 (1.4%) 1	1 (1.4%) 1
	Ear discomfort	-	1 (1.4%) 1	1 (1.4%) 1
Gastrointestinal disorders	Any	18 (24.3%) 26	24 (32.4%) 32	29 (39.2%) 58
	Abdominal discomfort	1 (1.4%) 2	-	1 (1.4%) 2
	Abdominal distension	1 (1.4%) 1	-	1 (1.4%) 1
	Abdominal pain	3 (4.1%) 3	2 (2.7%) 2	4 (5.4%) 5
	Abdominal pain lower	1 (1.4%) 1	1 (1.4%) 1	2 (2.7%) 2
	Abdominal pain upper	4 (5.4%) 4	3 (4.1%) 3	5 (6.8%) 7
	Constipation	9 (12.2%) 9	17 (23.0%) 20	19 (25.7%) 29
	Diarrhoea	2 (2.7%) 2	1 (1.4%) 1	2 (2.7%) 3
	Faeces hard	2 (2.7%) 2	1 (1.4%) 1	3 (4.1%) 3
	Flatulence	1 (1.4%) 1	-	1 (1.4%) 1
	Nausea	1 (1.4%) 1	3 (4.1%) 3	4 (5.4%) 4
	Paraesthesia oral	-	1 (1.4%) 1	1 (1.4%) 1
General disorders and administration site conditions	Any	7 (9.5%) 7	9 (12.2%) 13	13 (17.6%) 20
	Fatigue	7 (9.5%) 7	9 (12.2%) 13	13 (17.6%) 20
Metabolism and nutrition disorders	Any	1 (1.4%) 1	-	1 (1.4%) 1
	Decreased appetite	1 (1.4%) 1	-	1 (1.4%) 1
Musculoskeletal and connective tissue disorders	Any	-	2 (2.7%) 2	2 (2.7%) 2
	Myalgia	-	1 (1.4%) 1	1 (1.4%) 1
	Pain in extremity	-	1 (1.4%) 1	1 (1.4%) 1
Nervous system disorders	Any	13 (17.6%) 15	16 (21.6%) 18	23 (31.1%) 33
	Dizziness	1 (1.4%) 1	2 (2.7%) 2	3 (4.1%) 3
	Headache	10 (13.5%) 12	13 (17.6%) 15	18 (24.3%) 27
	Intercostal neuralgia	-	1 (1.4%) 1	1 (1.4%) 1
	Orthostatic intolerance	1 (1.4%) 1	-	1 (1.4%) 1
	Taste disorder	1 (1.4%) 1	-	1 (1.4%) 1
Renal and urinary disorders	Any	2 (2.7%) 2	1 (1.4%) 1	2 (2.7%) 3
	Micturition urgency	-	1 (1.4%) 1	1 (1.4%) 1
	Urethritis noninfective	1 (1.4%) 1	-	1 (1.4%) 1
	Urinary incontinence	1 (1.4%) 1	-	1 (1.4%) 1
Respiratory, thoracic and mediastinal disorders	Any	1 (1.4%) 1	-	1 (1.4%) 1
	Nasal congestion	1 (1.4%) 1	-	1 (1.4%) 1
Skin and subcutaneous tissue disorders	Any	3 (4.1%) 3	3 (4.1%) 3	5 (6.8%) 5
	Acne	1 (1.4%) 1	1 (1.4%) 1	1 (1.4%) 1
	Alopecia	1 (1.4%) 1	-	1 (1.4%) 1
	Hyperhidrosis	1 (1.4%) 1	1 (1.4%) 1	2 (2.7%) 2
	Papule	-	1 (1.4%) 1	1 (1.4%) 1
Vascular disorders	Any	1 (1.4%) 1	1 (1.4%) 1	2 (2.7%) 2
	Hot flush	1 (1.4%) 1	1 (1.4%) 1	2 (2.7%) 2

events = number of TEAEs, N = number of subjects who received treatment formulation, n (%) = number (frequency) of subjects with at least one TEAE, SOC = System Organ Class, TEAE = treatment-emergent adverse event

Adverse events are coded according to MedDRA Version 27.0.

A TEAE was considered to be related to study treatment if it was reported as 'Definitely related', 'Probably related', 'Possibly related', or 'Unassessable'.

Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths, no other serious and no other significant events were reported. No subject discontinued the study due to an AE.

Laboratory values over time

Safety laboratory parameters (haematology, clinical chemistry, coagulation, urinalysis), measured at screening, on Day -1 of each period, and at the EoT visit, showed no relevant changes over time.

Vital signs

Some abnormal values in vital signs measurements were observed after administration of the Test and Reference Treatment. One elevated body temperature (38.1°C) was assessed as clinically significant and was related to the subject's COVID-19 infection, which was not considered related. All other abnormal vital signs were considered clinically insignificant.

ECG

In 39 subjects, abnormal findings in the ECG measurements were observed after administration of the Test or Reference Treatment (1st degree atrioventricular (AV) block, nonspecific intraventricular conduction delay, bradycardia, QTc prolongation, QTcB prolongation, prolonged QT, sinus arrhythmia, sinus bradycardia, junctional premature complex). None of them was assessed as clinically significant.

6.2.3. Pharmacodynamics

6.2.3.1. Mechanism of action

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

6.2.3.2. Primary and secondary pharmacology

No new studies evaluating pharmacodynamics were performed for this application.

6.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

PK/PD was not evaluated as part as part of this application.

6.2.5. Overall discussion and conclusions on clinical pharmacology

6.2.5.1. Discussion

Bioanalytical methods

Quantification of netupitant and metabolites M1, M2, M3 concentrations in human plasma

Validation

Partial validation was developed in accordance with ICH M10 on bioanalytical method validation and study sample analysis, coming into effect in January 2023 for EMA applications. Preceding full validation (15056) was assessed previously as part of EMEA/H/C/3728/X/018, the line extension application for Akynzeo 235 mg/ 0.25mg powder for concentrate for solution.

The LC-MS/MS used to quantify netupitant and metabolites M1-M3 in human K2-EDTA plasma has been adequately described. The assay was appropriately validated with respect to quantitation range, dilutional linearity, matrix effect, freeze/thaw stability and short-term stability.

The established calibration curve and limits of quantification are considered acceptable. Dilutional linearity is considered demonstrated. Dilution integrity was adequately demonstrated. OQC (2xQC-High) showed |bias| = 19.1% for AB001 run while |bias| for OQC2 (5xOQC-High) was within limits (13.2%). The MAH attributed deviation to a dilution error for OQC in AB001.

M2 freeze-thaw and short-term stability was validated in the updated bioanalytical report 23292.

The partial validation is overall considered acceptable and is appropriately validated in line with the ICH M10 guideline.

Assay performance

Assay performance for netupitant and its metabolites in study NEPA-23-01 is considered acceptable and in line with the requirements set in the ICH M10 guideline. Calibration curves are described as in the validation and meet the acceptance criteria. Sufficient QCs were run and meet the acceptance criteria. In each study approximately 10% of samples were selected for incurred sample reanalysis (ISR). This number of samples is considered sufficient (10% for 1000 samples, and 5% of samples >1000) and the incurred sample reanalysis showed reproducibility (>2/3 within 20% of original measurement) of the method.

Reanalysed samples are identified in the Bioanalytical Report and the initial value, the reason for reanalysis, the values obtained in the reanalyses, the final accepted value and a justification for the acceptance have been provided in each case.

Quantification of palonosetron concentrations in human plasma

Validation

Two partial validations were conducted in accordance with ICH M10 Guideline on Bioanalytical Method Validation to support clinical studies involving palonosetron quantification in human K_2-EDTA plasma. The first partial validation (23290) retained the previously validated method but reassessed key parameters. The second (24344) introduced a modified sample preparation workflow, replacing manual SPE with a 96-well plate format. Both validations were performed under GLP-compliant conditions using Ardena SOPs and documented study plans. Preceding full validation (15059) was assessed previously as part of EMEA/H/C/3728/X/018, the line extension application for Akynzeo 235 mg/ 0.25mg powder for concentrate for solution.

The LC-MS/MS method is considered adequately described. The assay was partially validated for quantitation range, calibration curve performance, selectivity, specificity, matrix effects (including lipemic and haemolysed plasma), dilution integrity, precision and accuracy, processed sample stability, re-injection stability, recovery, carryover, and batch size.

Calibration curves (50.0–2000 pg/mL) consistently met acceptance criteria, with correlation coefficients ≥0.99 and back-calculated standards within ±15% (±20% at LLOQ). Matrix effects were evaluated across multiple plasma lots, including haemolysed and lipemic matrices, with no significant interference observed. Selectivity and specificity were confirmed, and no mutual interference between analyte and IS was detected.

Precision and accuracy were demonstrated both within and between runs, meeting ICH M10 thresholds at all QC levels. Dilution integrity was shown up to 5x (8,000 pg/mL) with acceptable bias and CVs. Processed sample stability and re-injection stability were confirmed up to 71 hours at +10 °C. Recovery was reproducible (93.6–96.5%). No carryover was observed, and batch size of 192 injections was validated.

Assay performance

Assay performance for palonosetron in study NEPA-23-01 is considered acceptable and in line with the requirements set in the ICH M10 guideline. The calibration range was suitable for the expected concentration range in study samples, and the lower limit of quantification (LLOQ) was demonstrated to be adequate. Calibration curves were constructed using a $1/x^2$ weighted linear regression model, and back-calculated concentrations for calibration standards were within ±15% (±20% at LLOQ), confirming acceptable linearity and accuracy. Intra- and inter-run precision and accuracy were within the acceptance criteria at all QC levels (low, medium, high, and dilution QCs), with %CV and %Bias values consistently below 15%.

ISR was performed on a representative subset of study samples. The percentage of samples with reanalysis results within ±20% of the original value exceeded 90%, demonstrating acceptable assay reproducibility in real study conditions.

A total of 39 analytical runs were accepted for palonosetron. Deviations were limited and appropriately documented. Rejected runs were due to procedural or instrument-related issues and were not indicative of systemic problems. Reanalysis was performed where necessary, and results from valid runs were used. No critical deviations affecting data integrity were identified.

Pharmacokinetics

Study NEPA-23-01

Study design

The overall study design and methodology for Study NEPA-23-01 is overall considered acceptable for the purpose of the study, to demonstrate bioequivalence between the oral suspension 300 mg netupitant/ 0.5 mg palonosetron (Test) and the marketed hard capsule containing 300 mg netupitant/ 0.5 mg palonosetron (Reference).

The replicate 4-period, 2-sequence design is considered acceptable given the justification of relatively high intra-individual variability seen for netupitant in previous studies. The sample size was sufficiently justified and is in line with EMA bioequivalence guidance. Eligibility criteria were considered acceptable for the study.

The sampling time-points for the study demonstrate sufficient sampling around the Tmax for both actives (~5 h). The sampling duration of 216 h for each period gives sufficient gives coverage for the PK profile of palonosetron (t1/2: 40 h, >5 half-lives). The sampling duration only covers 2-3 half-lives for netupitant (t1/2: 80 h), however given the mean %AUCt-inf is <20% for netupitant, this is considered acceptable.

The described primary objective to demonstrate bioequivalence regarding AUC0-t is agreed, however demonstrating bioequivalence with regards to the Cmax should also be considered a primary objective/outcome for a bioequivalence study. Analysis of Cmax was included and presented as a secondary objective/outcome so the objectives of the study are still considered acceptable overall. The described PK data analysis is acceptable and the criteria to conclude bioequivalence between the test and reference product is in line with the bioequivalence guidance.

An overview details of the test and reference products have been provided as **Error! Reference source not found.**. The MAH has provided sufficient justification, with reference to Section 3.2.P.2.3 of the eCTD, that that the test product used in this study is representative of the product to be marketed based on the criteria set in the bioequivalence guidance (Section 4.1.2, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

Pharmacokinetics results

Following oral administration of 300 mg netupitant/ 0.5 mg palonosetron as an oral suspension (test) or hard capsule (reference) the geometric mean plasma concentration-time profiles for palonosetron were overall similar. For netupitant, there was a notable difference between the test and reference concentration-time profiles, with the test demonstrating slightly more rapid absorption up to 5 hours with a lower Cmax, and lower concentrations up to 24 hours.

There were no notable differences between the PK parameters for the test and reference for palonosetron. There were minimal differences in the AUC0-t, AUC0-inf, and Cmax, and the median Tmax was similar for both treatments. The extrapolated part of AUC0-inf was <20% overall which indicates the terminal elimination phase was well characterised.

The differences between the PK parameters for the test and reference formulations for netupitant were overall similar. The AUC0-t and AUC0-inf showed greater differences than palonosetron but were overall similar. There is a notable difference in the value for Cmax, and the median Tmax for the test (5 h) is slightly lower than the reference (5.5 h) which is reflective of what was seen in the concentration time-profiles. The extrapolated part of AUC0-inf was <20% overall, which indicates that the terminal elimination phase was well covered, despite 5 half-lives not being covered by the sampling period for netupitant.

Although not presented in this report, the metabolites for netupitant, M1, M2, and M3 demonstrated similar trends in PK as netupitant itself. Considering the differences in metabolite PK were in line with what was seen for netupitant between the test and reference products, it can be accepted that the different formulation had no notable effect on netupitant metabolism.

The statistical analysis to demonstrate bioequivalence between the test (oral suspension) and reference (hard capsule) formulations compared AUC0-t as the primary PK parameter, and Cmax and AUC0-inf as secondary parameters. For palonosetron, the point estimates (90% CIs) for the ratio of geometric means were 99.33 (97.42 – 101.28) for AUC0-t, 98.93 (97.03 – 100.86) for AUC0-inf, and 99.06 (97.05 – 101.12) for Cmax. The point estimates for the palonosetron comparison are close to 1, the 90% CIs contain unity, and are contained entirely within the bioequivalence guideline criteria of 0.8 – 1.25. For netupitant , the point estimates (90% CIs) for the ratio of geometric means were 92.39 (88.73 – 96.19) for AUC0-t, 92.03 (88.03 – 96.22) for AUC0-inf, and 90.02 (84.86 – 95.50) for Cmax. The point estimates for the netupitant comparison are below 1 and the 90% CIs do not contain unity. However, as the 90% CIs are entirely contained within the bioequivalence guideline criteria of 0.8 – 1.25 this is still considered acceptable.

Given the bioequivalence criteria were met for the comparisons for both netupitant and palonosetron it can be concluded that bioequivalence has been demonstrated between the 300 mg netupitant/ 0.5 mg

palonosetron as an oral suspension and 300 mg netupitant/ 0.5 mg palonosetron hard capsule formulations.

Safety Summary

Following a dosing with the 300 mg netupitant/0.5 mg palonosetron as either an oral suspension(test) or hard capsule (reference) the products tested were generally well tolerated by the subjects.

There was a relatively high incidence of any TEAE (test: 59.5%, reference: 64.9%) and a high incidence in drug-related TEAEs (test: 41.9%, reference: 50%) following study drug administrations. There were no deaths, or other serious TEAEs. There were no TEAEs of severe intensity, with the majority being mild (158) in intensity and fewer of moderate (44) intensity. There were no clinically significant changes to laboratory values, vital signs, or ECG that could be related to the drug treatment.

Given the relatively small size of the study, it is difficult to draw any meaningful conclusions from the safety data, however the incidence of TEAEs was similar between the test and reference treatments and is in line with what was previously reported for Akynzeo. There do not appear to be any substantial differences in safety between the oral suspension and oral capsule formulations for 300 mg netupitant/0.5 mg palonosetron.

No new studies evaluating pharmacodynamics or PK/PD were performed for this application which is considered acceptable.

6.2.5.2. Conclusions

Bioequivalence has been demonstrated between the 300 mg netupitant/ 0.5 mg palonosetron as an oral suspension and 300 mg netupitant/ 0.5 mg palonosetron hard capsule formulations in Study NEPA-23-01. The benefit-risk balance for the 300 mg netupitant/ 0.5 mg palonosetron as an oral suspension formulation is considered positive from a clinical perspective.

6.3. Clinical efficacy

No new clinical efficacy data were submitted as part of this extension application which was considered acceptable by CHMP.

6.4. Clinical safety

Clinical safety data were collected as a secondary objective of Study NEPA-23-01 and have been summarised in Section 6.2.2.3. of this report. There were no significant safety concerns arising as a result of Study NEPA-23-01.

7. Risk management plan

The currently authorised version of RMP for AKYNZEO is version 3.0, DLP 10 October 2019, approved on 16 September 2021 under procedure EMEA/H/C/003728/X/0031. The MAH submitted a proposed updated version number 3.2, DLP 10 October 2024, part of the line-extension application for a new pharmaceutical form of Akynzeo, i.e., Akynzeo 300 mg/0.5 mg oral suspension.

Administrative details on the new formulation in Part I "Product Overview" should be aligned with the CHMP's conclusion on the line extension application, as well as in any impacted RMP section. A consolidated version of the RMP (version 4.0 09 Dec 2025) was submitted for adoption.

7.1. Safety specification

7.1.1. Proposed safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

This section has been updated with the inclusion of a table showing Relative emetogenic potential of chemotherapy in adults – Intravenous and Oral, in accordance with the classification of the *2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting.* (Herrstedt J. et al. 2024).

Moreover, the MAH included the updated recommendations on the prevention of Acute And Delayed Nausea And Vomiting Induced By Highly Emetogenic Chemotherapy (HEC) and Moderately Emetogenic Chemotherapy (MEC), in accordance with the same guideline of Herrstedt J. et al. 2024.

Epidemiology of the disease was also updated with the recent cancer statistics.

References

Herrstedt J, Clark-Snow R, Ruhlmann CH, Molassiotis A, Olver I, Rapoport BL, Aapro M, Dennis K, Hesketh PJ, Navari RM, Schwartzberg L, Affronti ML, Garcia-Del-Barrio MA, Chan A, Celio L, Chow R, Fleury M, Gralla RJ, Giusti R, Jahn F, Iihara H, Maranzano E, Radhakrishnan V, Saito M, Sayegh P, Bosnjak S, Zhang L, Lee J, Ostwal V, Smit T, Zilic A, Jordan K, Scotté F; participants of the MASCC/ESMO Consensus Conference 2022. Electronic address: clinicalguidelines@esmo.org. 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting. ESMO Open. 2024 Feb;9(2):102195. doi: 10.1016/j.esmoop.2023.102195. Epub 2024 Jan 11. PMID: 38458657; PMCID: PMC10937211.

Part II: Module SII - Non-clinical part of the safety specification

In this section it is stated that phospholipidosis (due to netupitant), convulsive events, liver transaminases increase were removed from the list of safety concerns in the RMP 2.7

Part II: Module SIII - Clinical trial exposure

This section was updated based on the latest PSUR (3-year PSUR No.16 with the data lock point on 10 October 2024, submitted to the EMA on 17 December 2024; PSUSA/00010393/202410, EMA reference EMA/PSUR/0000248514) and data regarding the new oral suspension formulation. The MAH plans to further update this section after PRAC outcome on the PSUSA procedure.

Reference to the Akynzeo IV concentrate for solution for infusion, approved in the EU on 12 November 2021 (EU/1/15/1001/004), was introduced. The clinical development programme of the IV FDC was updated with reference to further performed 3 Phase I studies.

The clinical trial NEPA-23-01 has been conducted in 74 healthy volunteers to demonstrate bioequivalence of the new oral suspension formulation to the approved hard capsule formulation. The trial was conducted according to an open-label, randomised, single centre, two-treatment, four-period, two-sequence replicative design. Safety data from this trial were introduced in this section.

The tables of patient exposure in the clinical trials have been updated until the DLP of this RMP version.

The table of exposure by study in Phase I healthy volunteer studies has been updated as follows:

Table 11 Exposure by study in Phase I healthy volunteer studies

Treatment	**Study**	**Number of subjects**
netupitant/palonosetron	NETU-08-12	8
	NETU-09-07	49
	NETU-10-08	24
	NETU-10-12	36
	NETU-10-11	35
	NETU-09-11	28
	NETU-11-02	88
	NETU-11-23	24
	NEPA-14-02	18
	NEPA-14-39	24
	NEPA-18-39*	44
	NEPA-19-13	8
	NEPA-23-01	74
	PNET-22-08	10
	PNET-12-23	134
TOTAL		**604**

**NEPA-18-39 is a 2x2 cross-over study of NEPA IV and NEPA Oral, with 44 randomized subjects*

The updated number of patients and the overall cancer patient exposure for netupitant/palonosetron have been displayed in the table below:

Table 12 Exposure by Phase I, II and III studies in adult cancer patients – netupitant/palonosetron

Study	**Dose (mg)**	**Number of exposed subjects**	**Number of exposures***
NETUPITANT/PALONOSETRON (oral)			
NETU-08-18	300 / 0.5	725	2,983
NETU-10-09	300 / 0.5	40	40
NETU-10-29	300 / 0.5	308	1,446
NETU-12-07	300 / 0.5	413	413
NEPA-15-18	300 / 0.5	201	645
NEPA-17-05	300 / 0.5	203[(a)]	660
	Sub-Total	**1,890**	**6,187**
FOSNETUPITANT/PALONOSETRON			
NEPA-15-18 (IV)	235 / 0.25	203	667
NEPA-17-05 (IV)	235 / 0.25	200	641
NEPA-15-19	235 / 0.25	36	36
	Sub-total	**439**	**1344**
NETUPITANT/PALONOSETRON (oral)**			
NETU-07-07	100 / 0.5	135	135
	200 / 0.5	138	138

	300 / 0.5	136	136
	Sub-Total	**409**	**409**
TOTAL		**2,737[(a)]**	**7,940**

**No limit in the number of repeated consecutive cycles for each patient in studies NETU-08-18 and NETU-10-29. In study NEPA-15-18 patients were treated up to 4 repeated consecutive cycles. Therefore multiple exposures to netupitant/palonosetron considered.*
***Extemporaneous combination*
[#] Fosnetupitant 235 mg as free base
(a) A patient received active IV NEPA FDC in cycles 1,3,4 and active ORAL NEPA FDC in Cycle 2 and therefore it is counted in both treatment groups but only once in the totals.

The updated figures are related to studies NEPA-17-05 (oral), NEPA-15-18 (IV), NEPA-17-05 (IV) and NEPA-15-19. The tables of Exposure by treatment, age, ethnic or racial origin, gender in adult cancer patients have been aligned accordingly.

The number of patients and the overall cancer patient exposure for comparators have not been changed.

Part II: Module SIV - Populations not studied in clinical trials

Information on the planned paediatric study NEPA-22-01 has been introduced.

Part II: Module SV - Post-authorisation experience

Exposure figures from the post marketing setting have been updated until the DLP of this version of the RMP. The number of patients exposed to all the formulations of Akynzeo is 2,310,140 (2,186,944 patients exposed to oral form, 28,963 patients exposed to Akynzeo powder for concentrate for solution for infusion and 94,233 patients exposed to Akynzeo concentrate for solution for infusion.

An update regarding off label use was also included in this section. The MAH referred to have collected 100 off label cases in the safety database, most of them were non-serious cases and no associated adverse reactions. Most of these cases derive from the USA, are solicited from a paediatric study plan, and the off label use is mainly coded because the indication of Akynzeo is often erroneously reported as the underlying cancer diagnosis rather than CINV. The same cases were evaluated in the recently finalised procedure PSUSA/00010393/202410 for Akynzeo, and the PRAC concluded that the increase in the off label use cases does not represent a safety concern at this stage.

Part II: Module SVII - Summary of the safety concerns Identified and potential risks

Updated figures on medication errors, on off-label use, on use in pregnant and lactating women, on use in paediatric population, mostly derived from the study NEPA-15-31, have been introduced. The DLP of the update is 10 October 2024, i.e. the PSUR 16 DLP.

Part II: Module SVIII - Summary of the safety concerns

The Summary of the Safety Concerns remains unchanged.

Table 13: Summary of safety concerns in the proposed RMP

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

7.1.2. Discussion on proposed safety specification

The currently authorised version of RMP for AKYNZEO is version 3.0, DLP 10 October 2019, approved on 16 September 2021 under procedure EMEA/H/C/003728/X/0031. The MAH submitted two proposed updated version numbers 3.1 and 3.2, DLP 10 October 2024, as part of the line-extension application for a new pharmaceutical form of Akynzeo, the 300 mg/0.5 mg oral suspension.

The main changes implemented in version 3.1 (first version submitted with this procedure) are included in Part II, safety specifications. The MAH did not propose any update to the summary of the safety concerns, and this is endorsed, since no impact on the important risks or missing information is expected by the introduction of oral suspension. The proposed changes to the RMP are mainly related to :

- updates according to the 2023 MASCC and ESMO guideline for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting. (Herrstedt J. et al. 2024). The emetogenic potential of chemotherapy agents (intravenous and oral) in adults was reported, as well as the guidelines for prevention of acute and delayed nausea and vomiting of different severities induced by chemotherapy;
- updated information about clinical development program. Three more Phase I studies were conducted for IV FDC in healthy volunteers, one PK and safety studies in healthy volunteers, PNET-22-08, with fosnetupitant administration, one PK and safety study in healthy volunteers, NEPA-19-13, with IV NEPA FDC administered as IV bolus versus 30-minute IV infusion, one bioequivalence study in healthy subjects, NEPA-18-39, with IV NEPA FDC and oral NEPA. Moreover, NEPA-23-01 Phase I bioequivalence study of the new oral suspension formulation versus the approved hard capsule formulation was conducted in in healthy volunteers, and consequently mentioned in the RMP.
- Information on the pivotal trial NEPA-17-05 performed in cancer patients administered with IV NEPA FDC was also included. Figures of the exposure of healthy volunteers and of cancer patients to administered with the study drugs were updated, until the DLP.

The submitted 3.2 version of the RMP contains several updates not related to this procedure, such as (main changes): epidemiology of the disease updated with the recent cancer statistics (Part II Mod SI), information on the planned paediatric study NEPA-22-01 (part II Mod SIV), updated figures on medication errors, on off-label use, on use in pregnant and lactating women, on use in paediatric population, mostly derived from the study NEPA-15-31 (Part II Mod SVII). An up-versioned RMP v. 4.0 (09 Dec 2025) was submitted and adopted.

No other major changes were introduced. The safety specifications are acceptable.

7.2. Pharmacovigilance plan

7.2.1. Proposed pharmacovigilance plan.

Not applicable

7.2.2. Discussion on the Pharmacovigilance Plan

7.2.2.1. Routine pharmacovigilance activities

No amendments for routine pharmacovigilance activities have been proposed. Routine pharmacovigilance activities are sufficient to monitor safety.

7.2.2.2. Additional pharmacovigilance activities

No additional pharmacovigilance activities are in place for Akynzeo, and no update on this has been proposed by the MAH. This is acceptable, routine pharmacovigilance activities are sufficient to monitor safety.

7.3. Plans for post-authorisation efficacy studies

Not applicable.

7.4. Risk minimisation measures

7.4.1. Proposed risk minimisation measures

No changes of the routine risk minimisation activities were proposed.

The MAH did not propose any changes of the additional risk minimisation measures.

7.4.2. Discussion on the risk minimisation measures

7.4.2.1. Routine risk minimisation measures

Routine Risk Minimisation Measures are sufficient

7.4.2.2. Additional risk minimisation measures

Not applicable

7.4.2.3. Patients engagement on the risk minimisation activities

Not applicable

7.5. RMP Summary and RMP Annexes overall conclusion

The RMP summary is acceptable. The RMP Annexes have not been modified.

7.6. PRAC Outcome at D166

PRAC endorsed the PRAC Rapporteur's assessment of the RMP and its conclusions, without further additions.

7.7. Overall conclusion on the Risk Management Plan

The PRAC consider that the updated risk management plan version 3.2 is acceptable. A consolidated version of the RMP (version 4.0 of 09 Dec 2025) was submitted and adopted.

8. Pharmacovigilance

Pharmacovigilance system

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

8.1. 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.

9. Product information

9.1. Summary of Product Characteristics (SmPC)

A new SmPC for the proposed 300 mg netupitant/0.5 mg palonosetron suspension sachet formulation has been detailed. There are no substantial changes between the proposed SmPC for oral suspension in sachet and the already approved hard capsule formulations (EMEA/H/C/003728/0000).

The only changes to the SmPC relate to the oral suspension specific differences in formulation, excipients and to the method for administration to squeeze the entire contents of the sachet into the mouth.

9.2. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet was submitted by the MAH and has been found acceptable for the following reasons: The proposed package leaflet for Akynzeo oral suspension is based on the current approved package leaflet for Akynzeo hard capsules. Proposed changes to the 'pharmaceutical form', 'how to take it', 'excipients (and warnings with excipients)', 'what the product looks like' and the 'contents of the pack' sections of the package leaflet are minimal and clearly presented. It is agreed that these changes, as well as the lifecycle changes made to the package leaflet for the hard capsule, are not substantial enough to necessitate additional testing or the preparation of a bridging report in relation to the proposed leaflet for the new oral suspension.

10. Benefit-risk assessment

Therapeutic context

10.1.1. Disease or condition, therapeutic indication

Akynzeo is currently licensed in adults as an oral capsule, powder for concentrate for solution for infusion, and concentrate for solution for infusion for the prevention of acute and delayed vomiting associated with both a) moderately emetogenic cancer chemotherapy and b) highly emetogenic cisplatin-based cancer chemotherapy. The current application is a line extension for an oral suspension formulation with the same indications.

Chemotherapy induced nausea and vomiting (CINV) is a common adverse drug reaction and one of the most feared reactions by patients. If severe enough, it 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.

10.1.2. Available therapies

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

While Akynzeo is already approved in an oral dosage form, and as solutions for infusion, the option of a single dose presentation of an oral suspension would be considered beneficial for patients for whom swallowing a hard capsule is difficult. This dosage form also has benefits as a ready-to-use form requiring no additional preparation for these patients compared to the formulations for infusion.

10.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 6.1.2. of this document.

Bioequivalence of the suspension formulation with the hard capsule was investigated in Study NEPA-23-01. Study NEP-23-01 was conducted according to an open-label, randomised, single centre, two-treatment, four-period, two-sequence replicative design. 74 healthy subjects were enrolled at one study centre to receive a single dose of 300 mg netupitant and 0.5 mg palonosetron during each period.

10.3. Favourable effects

Study NEPA-23-01 demonstrated bioequivalence of the oral suspension formulation with the oral hard capsule formulations for the AUC0-t and Cmax for both netupitant and palonosetron. For netupitant, the point estimate and 90% CIs for the ratio of the test and reference products were 92.39 % (88.73 – 96.19%) for AUC0-t and 90.02% (84.86 – 95.50%) for Cmax. For palonosetron, the point estimate rand 90% CIs were 99.33% (97.42 – 101.28%) for AUC0-t and 99.06% (97.05 – 101.12%) for Cmax. These are in line with the bioequivalence criteria (90% confidence interval for the ratio of the test and

reference products should be contained within the acceptance interval of 80.00 - 125.00%) set in the Guideline on the investigation for bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

Study NEPA-23-01 did not provide any signal to suggest that the safety profile between the two oral formulations is not comparable.

10.3.1. Uncertainties and limitations about favourable effects

Bioequivalence criteria have been met in Study NEPA-23-01 acceptably. There are no uncertainties or limitations to this favourable effect.

10.4. Unfavourable effects

No new unfavourable effects of netupitant/palonosetron were identified in the Study NEPA-23-01.

10.4.1. Uncertainties and limitations about unfavourable effects

Given the relatively small size of study NEPA-23-01, it is difficult to draw any meaningful conclusions from the safety data; however, the incidence of TEAEs was similar between the test and reference treatments and is in line with what was previously reported for this fixed combination product.

It is not considered that the proposed oral suspension formulation is associated with any additional uncertainties about unfavourable effects relative to the known safety profile of netupitant/palonosetron.

10.5. Effects Table

N/A

10.6. Benefit-risk assessment and discussion

10.6.1. Importance of favourable and unfavourable effects

From a clinical perspective, bioequivalence of 300 mg netupitant/ 0.5 mg palonosetron as an oral suspension and 300 mg netupitant/ 0.5 mg palonosetron hard capsule formulations has been demonstrated in Study NEPA-23-01. The option of a single dose presentation of an oral suspension is considered beneficial for patients for whom swallowing a hard capsule is difficult. This dosage form also has benefits as a ready-to-use form requiring no additional preparation for these patients compared to the formulations for infusion.

No new unfavourable effects of netupitant/palonosetron were identified. There are no remaining clinical concerns impacting a positive benefit-risk balance.

10.6.2. Balance of benefits and risks

The benefit-risk balance is positive.

10.7. Benefit-risk conclusions

The benefit-risk balance for the proposed oral suspension formulation is **positive.**