22 October 2015
EMA/787667/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

EMEND

International non-proprietary name: aprepitant

Procedure No. EMEA/H/C/000527/X/0049/G

Note

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

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List of abbreviations

AS	Active substance= Active Pharmaceutical Ingredient
API	Active Pharmaceutical Ingredient= Active substance
CHMP	Committee for Medicinal Products for Human use
CFU	Colony Forming Units
CQA	Critical Quality Attribute
DAD	Diode Array Detector
EC	European Commission
EP	European Pharmacopoeia
FMEA	Failure mode effects analysis
GMP	Good Manufacturing Practice
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
LLDPE	Linear Low density polyethylene
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
NMT	Not More Than
PAR	Proven Acceptable Range
PET	Polyester
Ph. Eur.	European Pharmacopoeia
PSD	Particle Size Distribution
QWP	Quality Working Party
RH	Relative Humidity
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The Marketing Authorisation Holder, Merck Sharp & Dohme Limited, (MAH) submitted to the European Medicines Agency (EMA) on 7 November 2002 an application for a grouping of variations in accordance with Article 7(2) of Commission Regulation (EC) No 1234/2008, consisting of an extension of the marketing authorisation, a Type II C.1.6a variation and a Type II C.I.4 variation for EMEND.

The MAH applied for an extension of the marketing authorisation consisting of the addition of a new pharmaceutical form (powder for oral suspension) to support the extension of the target population covered by the authorised therapeutic indication for EMEND to treat paediatric patients aged 6 months to 11 years with chemotherapy-induced nausea and vomiting (CINV), grouped with a variation to extend the indication for CINV to paediatric patients aged 12 to 17years for 80mg and 125mg hard capsules, and a variation to reflect the paediatric results for prevention of post-operative nausea and vomiting (PONV) for 40mg hard capsules.

The applicant applied for the following indication for 125mg powder for oral suspension:

- *Prevention of nausea and vomiting associated with highly and moderately emetogenic chemotherapy in children, toddlers and infants from the age of 6 months to less than 12 years.*

  EMEND powder for oral suspension is given as part of combination therapy (see section 4.2).

For the approved 80mg and 125mg hard capsules, the applicant requested the following variation:

- *Update of section 4.1 of the Summary of Product Characteristics (SmPC) to extend the indication for chemotherapy-induced nausea and vomiting (CINV) in adults to paediatric patients (12 to 17years) for 80mg and 125mg hard capsules. The MAH updated section 4.2 of the SmPC with dose recommendation for the use 80mg and 125mg capsule strengths in the paediatric population.*

  Sections 4.5, 4.8 and 5.1of the SmPC were also updated to include relevant information about a randomized, double-blind, active comparator-controlled clinical study that included 302 children and adolescents (aged 6 months to 17years) receiving moderately or highly emetogenic chemotherapy, in which aprepitant was compared to a control regimen for the prevention of CINV. Section 5.3 of the SmPC was updated to reflect the non-clinical investigations performed for the paediatric development program.

  As a consequence, SmPC section 4.2 of 165mg hard capsules was updated to reflect that other pharmaceutical forms/strengths may be more appropriate for administration to this population as in accordance with the current SmPC guideline. SmPC section 5.3 of the 165mg hard capsules was also updated to reflect the conclusions of the juvenile toxicity studies.

The applicant applied for the following indication for 80mg and 125mg hard capsules:

- *Prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adolescents from the age of 12 through 17 years.*

For the approved 40mg hard capsules, the applicant requested the following variation:

- *Update of sections 4.2, 5.1 and 5.2 of the SmPC for 40mg hard capsules with regards to Study protocol 148 investigating a 40mg powder for oral suspension in paediatric patients 6 months to 17 years for the prevention of post-operative nausea and vomiting (PONV).*

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I (point 2 c and d) thereof – Extension of marketing authorisation

Article 10 of Commission Regulation (EC) No 1234/2008 – "Prior Approval" procedure for major variation of type II

Article 7(2) of Commission Regulation (EC) No 1234/2008- Grouping of variations

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

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0008/2014 on the agreement of a paediatric investigation plan (PIP).

The scope of this EMA Decision is without prejudice to the regulatory status of fosaprepitant and to the applicability of the rules of data protection to Emend and Ivemend.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Pieter de Graeff

- The application was received by the EMA on 3 December 2014.
- The procedure started on 24 December 2014.
- The Rapporteur's Assessment Report was circulated to all CHMP members 13 March 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 March 2014.
- PRAC RMP advice and assessment overview adopted by PRAC on 10 April 2015.
- During the meeting on 23 April 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 July 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 August 2015.

- During the CHMP meeting on 24 September 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 6 October 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 16 October 2015.
- During the meeting on 22 October 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for the group of variations.

2. Scientific discussion

2.1. Introduction

Problem statement

Chemotherapy induced nausea and vomiting (CINV) continues to be one of the most undesirable side effects in subjects receiving chemotherapy. In addition to lowering the quality of life for subjects, CINV can potentially delay or reduce the dosage of planned chemotherapy regimens for subsequent cycles and may result in a reduction in the number of planned cycles.

In adults, aprepitant administered concomitantly with a 5-HT3 antagonist and a corticosteroid regimen is considered the standard of care and recommended by the Multinational Association of Supportive Cancer Care (MASCC)/ European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) for the prevention of nausea and vomiting associated with HEC and selected MEC regimens

For children undergoing chemotherapy, current MASCC/ESMO, and ASCO guidelines recommend the use of a 5-HT3 antagonist, such as ondansetron, and a corticosteroid to alleviate nausea and vomiting associated with emetogenic chemotherapy. However, despite the widespread use of these agents, nausea and vomiting continue to occur and remain a major source of distress for children undergoing emetogenic chemotherapy. Thus, there is an ongoing need to evaluate antiemetic agents, such as aprepitant, in alleviating CINV in children receiving emetogenic chemotherapy.

About the product

EMEND (aprepitant, MK-0869) is a substance P (NK1 receptor) antagonist, which in combination with other antiemetic agents, is indicated for prevention of acute and delayed nausea and vomiting in adults. EMEND is previously available as 40 mg hard capsules, currently indicated for prevention of post-operative nausea and vomiting (PONV) in adults, and as 80 mg, 125 mg and 165 mg hard capsules currently indicated for prevention of chemotherapy-induced nausea and vomiting (CINV) in adults.

The approved adult dosage is:

EMEND 40 mg capsules (PONV): *A single 40 mg dose within 3 hours prior to induction of anaesthesia*
EMEND 80 mg and 125 mg capsules (CINV): *EMEND is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. The recommended dose is 125 mg orally once daily one hour before start of chemotherapy on Day 1 and 80 mg orally once daily on Days 2 and 3 in the morning*.

EMEND 165 mg capsules (CINV): *A single 165 mg dose is given on Day 1 only, approximately one hour before the start of chemotherapy, as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist*

EMEND is not previously approved for paediatric patients (< 18 years).

Type of Application and aspects of development

This extension application is grouped together with two type II variations affecting different EMEND SmPCs as shown in the tables below.

Table 1. Overview of the procedure with affected SmPCs and studies involved

Type of procedure	Indication (disease)	Description	Ages concerned	SmPCs and main sections affected*	Studies involved
Extension	**CINV**	New pharmaceutical form and new paediatric indication	6 months to 11 years	New SmPC: 125 mg powder for oral suspension (all sections)	Pivotal: P208 Supportive: P134, P097 Juvenile toxicity studies: 09-7200, 08-7605, 10-9013, 10-9017
Variation type II - Indication C.I.6.a	**CINV**	New paediatric indication	12 to 17 years	SmPCs: 80 mg; 125 mg; and 125+ 80 mg hard capsules. Sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 5.3	Pivotal: P208 Supportive: P134, P097 Juvenile toxicity studies: 09-7200, 08-7605, 10-9013, 10-9017
				SmPC: 165 mg hard capsules. Sections 4.2 and 5.3	
Variation type II - Others C.I.4	**PONV**	SmPC update with paediatric information	6 months to 17 year	SmPC: 40mg hard capsules. Sections 5.1, 5.2 and 5.3	P148 Juvenile toxicity studies: 09-7200, 08-7605, 10-9013, 10-9017

CINV: chemotherapy-induced nausea and vomiting.

PONV: post-operative nausea and vomiting

* In addition, minor changes with additions or substitutions of single words were made in other sections.

Line extension

This grouped variation application includes an extension application for a new paediatric formulation, a 125 mg Powder for oral suspension, intended for *prevention of CINV in children 6 months – 11 years of age*.

The reconstituted oral suspension has an aprepitant concentration of 25 mg/ml.

The proposed dose of the oral suspension for children 6 months to 11 years of age is:

EMEND is given for 3 days as part of a regimen that includes a 5-HT3 antagonist. The recommended dose of EMEND powder for oral suspension is based on weight, as specified in a dose nomogram in section 4.2 of the SPC. EMEND is administered orally 1 hour prior to chemotherapy on Days 1, 2 and 3. If no chemotherapy is given on Days 2 and 3, EMEND should be administered in the morning. See the Summary of Product Characteristics (SmPC) for the selected 5-HT3 antagonist for appropriate dosing information. If a corticosteroid, such as dexamethasone, is co-administered with EMEND, the dose of the corticosteroid should be administered at 50% of the usual dose (see section 5.1).

The paediatric indication for the new oral suspension is supported primarily by Study 208.

Extension of indication for the 80 mg and 125 mg capsules

This grouped variation also includes an extension of the indication for the previously approved 80 mg and 125 mg capsules to include *Prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adolescents from the age of 12 through 17 years*.

The proposed dose to adolescents is:

EMEND is given for 3 days as part of a regimen that includes a 5-HT3 antagonist. The recommended dose of capsules of EMEND is 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3. EMEND is administered orally 1 hour prior to chemotherapy on Days 1, 2 and 3. If no chemotherapy is given on Days 2 and 3, EMEND should be administered in the morning. See the Summary of Product Characteristics (SmPC) for the selected 5-HT3 antagonist for appropriate dosing information. If a corticosteroid, such as dexamethasone, is co-administered with EMEND, the dose of the corticosteroid should be administered at 50% of the usual dose (see section 5.1).

The extension of indication is supported primarily by Study 208.

Other variation

This grouped variation also includes update of the SmPCs for the approved EMEND capsules as follows:

80 and 125 mg capsules: Include new paediatric information in sections 4.8, 5.1 and 5.2. These changes are based primarily on CINV paediatric studies 208 (pivotal efficacy/safety study), 134 and 097.

40 mg capsule: Update SmPC section 5.1 and 5.2 with results from study 148 for paediatric patients 6 months to 17 years in PONV. These data are not sufficient to support safe and effective use for the prevention of PONV across paediatric population. Therefore, the MAH does not intend to seek an indication in this application.

All capsules (40 mg, 80mg, 125 mg and 165 mg): SmPC section 5.3 update in order to reflect the conclusions of the two new juvenile toxicity studies for all capsule strengths

165 mg hard capsule: Update section 4.2 with a standard sentence as per current SmPC guideline.

In addition, minor editorial changes have been made to clarify when data have been obtained in adults and in children, respectively.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder for oral suspension containing 125 mg of aprepitant as active substance.

Other ingredients are: hydroxypropylcellulose (E 463), sodium laurilsulfate (E 487), sucrose, lactose (anhydrous), red iron oxide (E 172) and sodium stearyl fumarate (E 485), as described in section 6.1 of the SmPC.

The product is available in PET/aluminium/LLDPE sachets. The product is provided with one 5 ml polypropylene oral dispenser with silicone o-ring and one polypropylene mixing cup, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

No new information has been presented with regard to the active substance aprepitant and therefore no further assessment has been performed within this line extension application. The proposed daily dose (125 mg) is the same as the maximum daily dose for the capsules, so no additional requirements for impurities in the active substance specification are needed. The proposed specification of the active substance in relation to the new pharmaceutical form is the same as for the capsules. As the first step of the manufacturing process of the powder for oral suspension is the same as for the capsules, the current specification of the active substance is considered acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The objective of the pharmaceutical development was to develop a dosage form capable of providing dosing flexibility and convenient administration for use in paediatric patients as an alternative to the existing capsule formulation. Acceptable taste was also important considering the intended age group of 6 months to 12 years of age.
A powder for oral suspension has been developed which utilizes the same aprepitant colloidal dispersion intermediate which is used in the manufacture of the capsule formulations.
EMEND powder for oral suspension 125 mg is supplied as a sachet containing the lubricated blend for reconstitution in water. The sachet contains 125.0 mg of aprepitant in 748.7 mg (theoretical weight) of powder.
Due to the low aqueous solubility of the active substance, the product development focused on decreasing the active substance particle size to nanoscale in order to enhance the bioavailability of the active substance. Thus, the product manufacture was based on the current formulation intermediate (aprepitant colloidal dispersion) and a powder for oral suspension formulation was developed for paediatric patients which allows for weight based dosing flexibility to properly address this age range.
The powder for oral suspension formulation consists of the aprepitant colloidal dispersion coated onto

the lactose substrate. The substrate for the capsules is microcrystalline cellulose; however, in order to achieve an acceptable taste, several soluble substrates were investigated. The choice of anhydrous lactose was justified.
The coating process focused on fluid bed coating to maintain similarity to the commercial process applied for the capsules. The goal of the fluid bed coating process and formulation development was to ensure a robust coating process that gave a soluble coated particle. Developmental batches were characterised for assay, PSD, and nanoparticle re-dispersion.
The excipients were selected based on the following considerations: provide satisfactory suspension performance, provide appropriate process robustness for the formulation, and ensure acceptable palatability/appearance of the formulation during dosing.
The excipients of the formulation are completely soluble in water, resulting in a nanosuspension with acceptable mouth feel. In addition, the insoluble nature of aprepitant and the addition of sucrose (redispersant/binder) and lactose (substrate) to the formulation results in a formulation with acceptable taste. The proposed formulation for the powder for oral suspension allows for convenient and simple dose adjustment via an oral syringe.
The formulation contains 16.7% sucrose and 62.6% lactose corresponding to a daily dose of 0.125 g sucrose and 0.47 g lactose per day for a 30 kg child. This is considered acceptable for a medicinal product which is administered for three days in connection with chemotherapy treatment. Regarding the other excipients no specific risks related to the paediatric population are foreseen.
The homogeneity of the suspension and PSD of the active substance after reconstitution and the risk of segregation of the aprepitant particles in-use have been evaluated. It was concluded that the suspension is homogeneous after reconstitution and remains homogeneous up to 8 hours of storage. No segregation was observed.

Some slight differences in the formulations used in clinical studies have been presented. However the bioavailability of aprepitant is driven by the PSD of aprepitant and thus the exposure of the powder for oral suspension is expected to be equivalent to EMEND capsules. The control of PSD is included as an in-process control (IPC) tested near the end of media milling and as lubricated blend release specification.
Clinical batches were initially manufactured at a smaller scale. Process development activities were conducted at different scales. A summary and comparison of the equipment and scale used during development and for the proposed commercial manufacturing process has been presented and is deemed satisfactory.
A risk-based approach was taken for the development of the manufacturing process to consistently provide a final product of acceptable quality and stability for patient safety and efficacy. The finished product has been designed to meet the critical quality attributes (CQAs) of identity, appearance, API content uniformity and assay, degradants/impurities, aprepitant PSD, and sachet hold-up and dosing.
An overview of the manufacturing process development program was presented. The initial FMEA risk assessment indicated that content uniformity and assay are the CQA with the highest potential risk, and helped to identify the process steps requiring further understanding and characterisation.
Development studies indicated that lubricated blend particle size distribution (PSD) may directly impact segregation risk and content uniformity. To minimise these risks, fluid bed coating focused on minimising spray drying and granulation. Through development activities, additional process understanding and controls were implemented that either eliminated or mitigated the risks identified in the initial risk assessment.
After the completion of the development campaign, process characterization studies were transferred to the proposed commercial site. An updated risk assessment was completed which focused on the potential product impacts created by the change in equipment and scale at the commercial site. A series of development batches were run at the proposed commercial site.

Finally a development campaign was executed at the commercial site on the commercial fluid bed column and scale. These batches focused on the potential impact created by the change in fluid bed scale. A summary and comparison of the equipment and scale used during manufacturing process development was presented.
Due to an expected low assay from the fluid bed coating process it has been justified that the target sachet fill weight will be adjusted for each batch based on the actual assay of the lubricated blend.
A bulk hold time study was initiated for the final blend using small scale containers to represent commercial bulk drums and based on the results the proposed bulk hold time of 12 months in HDPE bulk drums is considered acceptable.

The container closure system is a heat sealed foil laminate sachet. An extractable assessment of the sachet laminate confirmed no safety concerns with regards to volatile leachables after sealing.
The finished product commercial configuration further comprises the following components necessary to prepare and administer doses: a mixing cup and a graduated 5 ml oral dispenser (syringe). The mixing cup is made of polypropylene which meets regulatory and compendial requirements, and has an attached tight-fitting hinged lid that is snapped into place to seal the mixing cup. Since the mixing cup does not meet the definition of a medical device under Article I of Directive 93/42/EEC and does not have a specific medical purpose, it would not be regulated as a medical device and does not require a CE Mark. The material meets food contact EC Regulation 10/2011/EC and 1935/2004. Compatibility studies and in-use testing have demonstrated acceptable compatibility with the formulation.

The oral dispenser is a Class I medical device (as defined in EC Directive 93/42/EEC) with measuring function, marked with CE Mark. The graduation marks printed on the dispenser correspond to all doses in the dosing table in section 4.2 of the SmPC. The dispenser's components are the barrel, plunger rod, and O-ring. The barrel is composed of polypropylene and lubricated with silicone fluid. The plunger rod is composed of polypropylene and a white colorant. The barrel and plunger rod meet the appropriate European Directives including Regulation EU 10/2011 and EU 1935/2004/EC. The silicone fluid complies with European Pharmacopoeia monograph "Dimethicone or Silicone Oil Used as a Lubricant". The o-ring is moulded from silicone and meets appropriate Ph. Eur. requirements and European Directives, including Regulation EU 10/2011.
Dose accuracy for the dosing syringe has been demonstrated with both water and finished product in accordance with Ph. Eur. monograph 2.9.27, "Uniformity of Mass of Delivered Doses from Multidose Containers". It has been also demonstrated that the dosing instructions would yield accurate and reproducible results.

Manufacture of the product and process controls

The manufacturing process includes the manufacture of the aprepitant colloidal coating dispersion as described in the current MAA for EMEND capsules. The main manufacturing steps are: preparation of the aprepitant colloidal coating dispersion, screening (pre-sieving) of lactose, fluid bed coating, delumping, blending, sachet filling and secondary packaging.

Critical steps of the process have been identified and proven acceptable ranges (PARs) for relevant process parameters have been set. The proposed IPCs are considered adequate and the overall control strategy is deemed sufficient so that the product meets the CQAs.
According to Annex II of the process validation guideline, this type of product is not explicitly considered as a specialised pharmaceutical dose form, however the list of examples in the guideline is non exhaustive. Despite the fact that the coating layer is non-functional, it does contain the active substance, which renders it critical and more likely to give rise to scale up difficulties and therefore this type of process requires particular attention and should be designated as non-standard process.

Nevertheless the experience of the applicant/ manufacturer with this type of process, being already used to manufacture the authorised EMEND capsules (albeit with a different substrate, i.e. microcrystalline cellulose instead of lactose) has been taken into account.
Furthermore, details on several clinical, stability and development batches manufactured with the indicated process were provided. Additional batch data presented on five commercial scale fluid bed batches showed that the particle size, blend uniformity and assay are comparable to the presented development batches. When further processed (filling in sachets), the results showed assay and content uniformity results compliant with the specification. The applicant further provided an acceptable validation protocol outlining the formal process validation studies which will be conducted on production scale batches before marketing of the product.
Based on historical data, the amount of knowledge gained during the development of the product, and the experience of the applicant/ manufacturer with this type of process, it has been adequately justified that the process is standard for the proposed manufacturer. Considering the overall data and justifications the manufacturing process is considered sufficiently validated at the commercial scale.

Product specification

The finished product release and shelf life specification include appropriate tests for this kind of dosage form: appearance (visual), identity (HPLC-DAD, HPLC), assay (HPLC), degradation products (HPLC), uniformity of dosage units (HPLC), time for constitution and microbial limits (Ph. Eur.). The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

A dissolution specification for the finished product was not included in the proposed specification on the basis that the solubilisation of the aprepitant active substance occurs instantaneously and that the product dispersion in water is controlled by time for constitution testing at release and shelf life. In addition the critical quality attribute for bioavailability is the particle size distribution and not API solubility.
Given that the packaging is considered moisture impermeable, the product is considered chemically stable, and since the product is manufactured at controlled relative humidity, monitoring water activity at release and shelf-life is not required. Also omission of pH testing has been justified based on batch data.

Batch analysis results were provided for three commercial scale batches and five smaller scale development batches from a different manufacturer confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three pilot scale batches of finished product stored under long term conditions for 12 months at 30 ºC / 75% RH and for up to six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, assay, dedradation products and time for constitution. In addition to the release specification test methods, dissolution, water activity, pH, particle size distribution, moisture and microbial quality were evaluated during the formal stability studies. The analytical procedures for assay and degradation products used were shown to be stability indicating.
Results for assay under the long term conditions were found around (or above) the upper limit because these batches were manufactured near the upper bound limit, and due to analytical variability; the observed values were not the result of a stability trend. This issue was sufficiently addressed and

corrected by using the actual batch assay for fill weight. Batches produced later at commercial scale and equipment and after applying the proposed target sachet fill weight adjustment showed results ranging from 98.6% to 100.5 %, thus providing confidence that the proposed shelf-life acceptance criteria of 95.0% to 105.0% will be met.
Results on water activity are in-line with the packaging environmental control and confirm that the proposed commercial packaging provides sufficient moisture protection for the product.
All other results complied with the proposed specification. No trends were seen and no degradation products were observed above the reporting threshold.

In-use stability

In-use stability was evaluated by reconstituting the powder to oral suspension as per the SmPC instructions and holding the suspension in the sample cup for five hours under ambient light, temperature and humidity conditions. No trend was seen for assay, degradation products or suspension particle size. All results confirm an in-use stability of 30 minutes (SmPC section 6.3).

Photo-stability

EMEND powder for oral suspension is packaged in a foil sachet. Since this packaging is impervious to light, photo stability was not performed for this product.

Based on the available stability data, the proposed shelf-life of 24 months without any special temperature storage conditions but with recommendation to store in the original package in order to protect from moisture, as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Aprepitant (EMEND™) is a selective, high-affinity antagonist of human substance P/neurokinin 1 (NK1) receptors that, in combination with other antiemetic agents including a 5-HT_3 receptor antagonist and a corticosteroid, is approved for the prevention of acute and delayed nausea and vomiting due to highly emetogenic and moderately emetogenic cancer chemotherapy in adults (CINV-HEC and CINV-MEC, respectively).

In support of the new pediatric indication the Applicant has submitted two juvenile toxicity studies on aprepitant (EMEND™, oral administration) in juvenile rats and two juvenile toxicity studies on fosaprepitant (IVEMEND™, intravenous administration) in juvenile dogs. The studies on fosaprepitant are submitted because fosaprepitant is rapidly dephosphorylated *in vivo* to the active moiety aprepitant. No new nonclinical pharmacology and pharmacokinetic studies have been conducted to support the marketing application for use of aprepitant in paediatrics and only an integrated summary is presented.

An ERA including the pediatric population has also been submitted.

2.3.2. Pharmacology

Results of the nonclinical pharmacology studies with aprepitant and fosaprepitant were previously submitted and reviewed as part of initial and supplemental marketing applications for use of aprepitant in adults. No new nonclinical pharmacology studies have been conducted to support the marketing application for use of aprepitant in paediatrics.

Aprepitant is a high affinity, selective NK1 receptor antagonist that penetrates the CNS and has long central duration of activity. Aprepitant has excellent functional selectivity at NK1 receptors in vitro and in vivo against substance P challenges. Extensive cross screening revealed no significant off target activities of aprepitant or its metabolites, which suggests that the pharmacological activity observed in vivo is likely attributable to NK1 receptor antagonism. Importantly, no activity was detected at previously recognized sites (5-HT3 and dopamine D2 receptors) for anti-emetic activity. Aprepitant has excellent efficacy against acute and delayed cisplatin-induced emesis in ferrets.

2.3.3. Pharmacokinetics

Results of the nonclinical pharmacokinetics studies with aprepitant and fosaprepitant were previously submitted and reviewed as part of initial and supplemental marketing applications for use of aprepitant in adults. No new nonclinical pharmacokinetics studies have been conducted to support the marketing application for use of aprepitant in pediatrics.

The pharmacokinetics of aprepitant has been evaluated thoroughly in the rat and dog. Aprepitant is a low (dog, mouse) to moderate (rat) clearance compound in nonclinical species, with a plasma half-life of approximately 3 hours in rodents and approximately 7 hours in dogs. The plasma half-life in humans ranges from approximately 9 to 13 hours. In rats, dogs, and humans, aprepitant is cleared via metabolism and excretion of metabolites into urine and bile (or feces when bile was not collected). The major routes of metabolism involve a variety of primary and secondary oxidation pathways that lead to the formation of multiple metabolites. All metabolites observed in humans were detected in rats, mice, and/or dogs. CYP3A4 is primarily responsible for the oxidative metabolism of aprepitant in human liver microsomes. Aprepitant is a weak or a moderate inhibitor of CYP3A4 using different probe reactions

(IC50 or Ki values 2 to 21 µM) but a weak inhibitor (IC50 and Ki values >10 µM) of other CYP enzyme mediated reactions in human liver microsomes.

Systemic exposure multiples are based on the exposure in pediatric patients 6 months to <12 years of age (AUC0-24hr = 20.9 µg•hr/mL). This exposure is similar to the exposure in adult patients for the 3-day aprepitant 125/80/80 mg regimen (AUC0-24h = 19.6 µg•hr/mL and 21.2 µg•hr/mL on Day and Day 3, respectively).

2.3.4. Toxicology

Single dose toxicity

Aprepitant has a low order of acute toxicity following oral administration to rodents (approximate LD50 >2000 mg/kg).

Repeat dose toxicity

The primary treatment-related findings in the adult rat repeated-dose toxicity studies were in the liver and/or thyroid (e.g., hepatocellular hypertrophy, thyroid follicular cell hyperplasia), and were considered secondary to hepatic cytochrome P-450 enzyme induction. In rodents, aprepitant has been shown to induce hepatic cytochrome P-450 enzymes, to increase the rate of thyroxine clearance, and to induce its own metabolism. Similar changes in the liver and thyroid have been seen with structurally and pharmacologically dissimilar compounds that have been shown to induce hepatic P-450 enzymes. These rodent-specific findings are of limited toxicological significance to human risk assessment. Systemic exposures to aprepitant in these studies were approximately 2-fold (female rats) or lower than (male rats) the exposure at the recommended pediatric dose. The high dose used in these studies was the maximum feasible dose.

In repeated-dose toxicity studies in dogs with aprepitant, systemic exposure to aprepitant at the NOEL was approximately 13-fold the exposure at the recommended pediatric dose. The primary changes noted in dogs (significant decreased body weight gain or body weight loss, testicular degeneration, and prostatic atrophy) occurred at systemic exposures >30-fold the exposure at the recommended pediatric dose, and are of minimal toxicological significance to human risk assessment.

Genotoxicity

Aprepitant was shown to be neither mutagenic nor genotoxic in assays conducted to detect mutagenicity, DNA strand breaks, and chromosomal aberrations.

Carcinogenicity

Although carcinogenicity studies are not required for a CINV indication due to the limited and episodic duration of patient treatment, studies in mice and rats were conducted up to the maximum feasible dose to support other potential therapeutic indications. Treatment-related neoplastic changes were limited to increased incidences of hepatocellular adenomas and/or carcinomas (mice and rats) and thyroid follicular cell adenomas and/or carcinomas (rats). These findings in the liver and/or thyroid were considered to be secondary to hepatic P-450 enzyme induction. This tumor promotion phenomena observed in rodents caused by hepatic cytochrome P-450 enzyme inducers has not been shown to occur in humans. Systemic exposures to aprepitant in these studies were up to approximately 3-fold higher (mice), approximately 1.5-fold (female rats), or less than (male rats) the exposure at the recommended pediatric dose.

Reproduction Toxicity

Aprepitant had no effects on female or male fertility in rats at systemic exposures approximately 1.5-fold (females) or less than (males) the exposure at the recommended pediatric dose. Aprepitant was not teratogenic nor did it cause any embryo-fetal toxicity in rats or rabbits at doses in which transplacental exposures were demonstrated. Maternal systemic exposures were approximately 1.3-fold the exposure at the recommended pediatric dose. In addition, no effects on pre- and post-weaning development of the F1 generation were seen in rats. Significant lactational transfer of aprepitant was demonstrated.

Juvenile toxicity studies

Study TT #08-7605 (aprepitant) and study TT #10-9013 (fosaperepitant) are non-GLP dose-range finding studies in rat and dog, respectively. The pivotal studies TT #09-7200 (aprepitant) and TT #10-9017 (fosaperepitant) are GLP-complient toxicity studies in rat and dog, respectively. The studies are summarized in the table below.

Table 1. Summary of the toxicity studies performed with aprepitant and fosaprepitant in juvenile animals.

Type of study, study number / GLP	Organ system evaluated / Species	Dose / number of animals per group and sex Administration / duration	Major findings
Aprepitant			
TT #08-7605 Non-GLP	Crl:CD(SD) rat	0, 5, 125, 500, 1000 mg/kg, b.i.d., (second dose 6 hours after first dose), oral gavage, PND 10 through PNW 9 TK evaluated PNW 4 and PNW 9 15 pups/sex/group Controls: 20% sucrose/4% HPC/0.19 % SLS in deionized water	**Parameters studied:** mortality, physical signs and body weights Mortality: Males, at 5 mg/kg b.i.d., 2 rats at PNW 4 and at 125 mg/kg b.i.d., 1 rat at PNW 4 and at 500 mg/kg b.i.d., 3 rats at PNW 4 and at 1000 mg/kg b.i.d., 2 rats at PNW 4 and 9, respectively. Females, 1 control at PNW 5 and at 5 mg/kg b.i.d., 1 rat at PNW 3 and at 125 mg/kg b.i.d., 1 rat at PNW 4. Not-dose-related and considered not treatment-related. Body weight: Decreased body weight gain in female and male rats in the 125-, 500-, and 1000 mg/kg b.i.d. groups (24%, 50%, 54%, respectively, compared to controls) between PND 10 and 14. Thereafter body weight gains were similar to control. Kinetics: For TK-parameters, see table 3 below. NOAEL: ≥1000 mg/kg, b.i.d.

TT #09-7200 GLP	Crl:CD(SD) rat	0, 10, 250, 1000 mg/kg, b.i.d (second dose 6 hours after first dose), oral gavage, PND 10 through PNW 9, 2 months recovery period (through PNW 17) Interim necropsy in PNW 9 (10 rats/sex/group) and final necropsy in PNW 14 (7-10 rats/sex/group) TK evaluated PNW 6 40 pups/sex/group Controls: 20% sucrose/4% HPC/0.19 % SLS in deionized water	**Parameters studied:** mortality, physical signs, body weights, food observations, developmental landmarks (vaginal opening and preputial separation), ophthalmic examinations, clinical and anatomic pathology evaluations, behavioral assessment (motor activity, auditory startle habituation, and passive avoidance), and reproductive performance (assessments of mating performance, fertility, and embryonic/fetal survival on GD 15 to 17). Mortality: 9 deaths; 5 controls, 3 in the 10 mg/kg b.i.d group (one due to an intubation accident) and 1 in the 1000 mg/kg b.i.d. Body weight: Decreased body weight gain from PND 10 to 12 in all aprepitant-treated groups (female/male: 26%/20%, 66%/64%, and 78%/77% below control in the 10-, 250-, and 1000-mg/kg b.i.d. groups, respectively). Thereafter body weight gains were similar to control. Developmental landmarks: All female rats in the 250-mg/kg b.i.d. and 1000-mg/kg b.i.d. groups displayed vaginal opening compared to 20% in controls at PND 28, first day of observation. The mean day of occurrence in the 10-mg/kg b.i.d. group (PND 32.8 ± 2.7) was similar to the control group (PND 31.7 ± 2.8). In male rats, the mean days of appearance of preputial separation in the 10-, 250-, and 1000-mg/kg b.i.d. groups (PND 46.2 ± 2.9, 47.4 ± 2.9, 48.2 ± 3.1, respectively) were delayed 2, 3, and 4 days compared to controls (PND 44.2 ± 3.1). Clinical pathology: Treatment-related changes in all dose groups, shown in table 2 below. Anatomic pathology: Interim necropsy in PNW 9: increased hepatic weights (males and females, from 10 mg/kg b.i.d) that correlated with hepatocellular hypertrophy and increased thyroid weights (males and females, from 250 mg/kg b.i.d.) that correlated with follicular cell hypertrophy. Final necropsy in PNW 14: no gross or histomorphologic changes. Kinetics: For TK-parameters, see table 4 below. NOAEL: <10 mg/kg, b.i.d.

Fosaprepitant			
TT #10-9013 Non-GLP	Dog/beagle	0, 2, 4, 6 mg/kg/day, IV, 1 week, PND 14 through PND 20 4 pups/group (2 males and 2 females in the control and high dose group and 3 males and 1 female in the low-, and mid-dose group). Controls: 0.125 mg/ml EDTA in 0.9% sodium chloride injection	**Parameters studied:** mortality, physical signs, body weight, electrocardiography, blood pressure, clinical pathology, and macroscopic observations at necropsy. Mortality: None No treatment-related effects. NOEL= 6 mg/kg/day
TT #10-9017 GLP	Dog/beagle	0, 2, 4, 6 mg/kg/day, IV, 4 weeks, PND 14 through PND 41 4 pups/sex/group Controls: 0.125 mg/ml EDTA in 0.9% sodium chloride injection TK evaluated PNW 6 (PND 41)	**Parameters studied:** mortality, physical signs, body weight, cardiovascular parameters (blood pressure, heart rate, and electrocardiography recorded pretest and on PND 14, 21, 28, 35, and 40 beginning immediately after dosing), clinical and anatomic pathology evaluations. Mortality: None Body weight: Decreased body weight gain (PND 14 to PND 42) by 18% for males at 6 mg/kg/day and by 32% and 15% for females at 4 and 6 mg/kg/day, respectively, compared to controls. Anatomic pathology: Decreased testicular weight and reduced size of Leydig cells in 4 males at 6 mg/kg/day. Endometrial and myometrial hypertrophy of the uterine horns and body associated with increased uterine weight, hypertrophy of the cervical muscularis and edema of the lamina propria and submucosa of the vagina in 1 female at 4 mg/kg/day and 4 females at 6 mg/kg/day. Decreased heart to brain weight in males at 6 mg/kg/day (23% below control values) and in females at 4 and 6 mg/kg/day (heart to brain weight 30% and 24%, respectively, below control values). Injection sites effects: intimal proliferation within the cephalic veins at ≥2 mg/kg/day and inflammation within or adjacent to the injected vein in all groups with increased incidence and severity of inflammation at ≥2 mg/kg/day. Kinetics: For TK-parameters, see table 5 below. NOAEL=2 mg/kg/day for females, 4 mg/kg/day for males

b.i.d. = Twice daily; PND = Postnatal Day; PNW = Postnatal Week; TK=Toxikokinetics

2.3.5. Ecotoxicity / environmental risk assessment

Summary of main study results

Substance (INN / Invented Name): aprepitant					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	Log Kow 4.27-4.75			Potential PBT (Y)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	Log Kow 4.27-4.75			B
	BCF	39.2-47.9			not B
Persistence	DT50 or ready biodegradability	Not readily biodegradable DT50 whole system not calculated			P
Toxicity	NOEC or CMR				not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.82	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =2.26 to 2.30			Terrestrial assessment not required
Ready Biodegradability Test	OECD 314	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 7.5 and 13.8 days $DT_{50, sediment}$ = not calculated > 10% shifting to sediment			P?
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	0.184	mg/ L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.018	mg/ L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	0.195	mg/ L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} (3 hour)	>100	mg/ L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	39.2-47.9	L/kg	%lipids: 1.96
Sediment dwelling organism	OECD 218	NOEC	100	mg/ kg	*Chironomus riparius*

An adequate ERA in accordance with available guidance was performed. All studies submitted were performed in accordance with GLP.

Initially the log Kow of 4.75 at pH 7 indicated potential for bioaccumulation, however based on the results of a bioconcentration study in fish where the BCF_{ss} was in the range of 39.2-47.9 it can be concluded that aprepitant has little potential to bioaccumulate. Therefore, aprepitant is not considered as a PBT substance. Aprepitant showed potential to adsorb to organic matter in soil, however the log Koc sludge value is less than the trigger value of 4 and terrestrial studies are not required.

Aprepitant was not readily biodegraded and a DT_{50} for the whole system in the OECD 308 study was not reproted due to steadily increase of test item in the sediment compartment. However, the DT50 of the whole system was calculated to 388 and 1131 d (12°C). Thus, aprepitant is considered as very persistent even though evidence of some degradation was observed. There was significant shifting to the sediment compartment and a sediment risk assessment was conducted.

Aprepitant was of low toxicity to microbials, algae, *Daphnia*, fish and *Chironomus riparius*. In addition to the required chronic tests acute toxicity studies were submitted for *Daphnia* and fish. These studies are of low relevance to the overall risk assessment.

All PEC/PNEC quotients were below 1 (0.1 for micro-organisms) indicating that aprepitant, in the proposed use, does not pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Two juvenile toxicity studies on aprepitant in juvenile rats and two juvenile toxicity studies on fosaprepitant in juvenile dogs have been submitted. The studies on fosaprepitant in dogs are submitted because fosaprepitant is rapidly dephosphorylated in vivo to the active moiety aprepitant.

In the pivotal study on aprepitant the rats were dosed by oral gavage at 10, 250 and 1000 mg/kg, b.i.d. between PND 10 and PNW 9, followed by a 2 months recovery period.

There was a decreased body weight gain from PND 10 to 12 in all aprepitant-treated groups (female/male: 26%/20%, 66%/64%, and 78%/77% below control in the 10-, 250-, and 1000-mg/kg b.i.d. groups, respectively). However thereafter body weight gains were similar to control.

At PND 28, the first day of observation, all female rats in the 250-mg/kg b.i.d. and 1000-mg/kg b.i.d. groups displayed vaginal opening compared to 20% in controls, i.e. aprepitant treatment led to an earlier vaginal opening. The mean day of occurrence in the 10-mg/kg b.i.d. group (PND 32.8 ± 2.7) was similar to the control group (PND 31.7 ± 2.8). In male rats, the mean days of appearance of preputial separation in the 10-, 250-, and 1000-mg/kg b.i.d. groups (PND 46.2 ± 2.9, 47.4 ± 2.9, 48.2 ± 3.1, respectively) were delayed 2, 3, and 4 days compared to controls (PND 44.2 ± 3.1). There were, however, no treatment-related effects on mating performance, fertility or embryonic/fetal survival and no pathological changes in the reproductive organs at necropsy.

At interim necropsy in PNW 9, increased hepatic weights (males and females, from 10 mg/kg b.i.d) that correlated with hepatocellular hypertrophy and increased thyroid weights (males and females, from 250 mg/kg b.i.d.) that correlated with follicular cell hypertrophy were observed. However, at the final necropsy in PNW 14 no gross pathological or histomorphologic changes were found and there was an absence, or a notable reduction, in liver and thyroid weight increases, indicating reversibility. Similar toxicological findings in the liver and thyroid were found in previous studies in adult rats and were considered to be due to microsomal enzyme induction in the liver and a subsequent increased thyroxine clearance with compensatory TSH elevation, a well-known effect in rodents.

Review of the toxicokinetic data in rats revealed that there were consistent sex differences in systemic exposures across all dose groups (at PNW 6 and PNW 9, but not at PNW 4). Female rats had approximately 1.9-4.5 fold higher systemic exposure values compared to male rats. A similar gender

difference in exposure level has been seen also in previous studies in adult rats where a higher metabolism was seen in males, possibly due to differences in P-450 enzyme expression between males and females. A plateau in systemic exposure (AUC0-24h and Cmax) was observed between 125 and 1000 mg/kg b.i.d. in PNW 4 and PNW 9 (study nr TT#08-7605) and between 250 and 1000 mg/kg b.i.d. in PNW 6 (study nr TT#09-7200). This has been observed previously also in adult rats as a result of saturation of absorption of aprepitant.

The exposure in rats at 10 mg/kg b.i.d. (NOAEL=<10 mg/kg b.i.d. in study nr TT#09-7200), AUC0-24h level of 7.33 µg*h/ml in males and 13.8 µg*h/ml in females, gives margins to clinically relevant exposure of less than 1 in both males and females, based on 20.9 µg*h/ml, mean AUC in pediatric human subjects given 3 mg/kg aprepitant (day 1).

In adult rats after repeated dosing the target organs were the thyroid and the liver and there were a number of changes in clinical pathology parameters (similar as in the juvenile animals), at exposure levels similar to, or lower, than the clinically relevant exposure.

In the pivotal study on fosaprepitant in juvenile dogs there was a decreased body weight gain (PND 14 to PND 42) by 18% for males at 6 mg/kg/day and by 32% and 15% for females at 4 and 6 mg/kg/day, respectively, compared to controls.

A decreased heart to brain weight was observed in males at 6 mg/kg/day (23% below control values) and in females at 4 and 6 mg/kg/day (30% and 24%, respectively, below control values). However, there were no histomorphologial changes in the heart and no electrocardiographic changes.

A decreased testicular weight and a reduced size of Leydig cells were seen in 4 males at 6 mg/kg/day. The exposure in males at 4 mg/kg/day (NOAEL) of 35.8 µg*h/ml gives a margin to clinically relevant exposure of approximately 1.7 based on 20.9 µg*h/ml, mean AUC in pediatric human subjects 6 months-<12 years given 3 mg/kg aprepitant (day 1). Endometrial and myometrial hypertrophy of the uterine horns and body associated with increased uterine weight, hypertrophy of the cervical muscularis, and edema of the lamina propria and submucosa of the vagina were seen in 1 female at 4 mg/kg/day and in 4 females at 6 mg/kg/day. The exposure level at 2 mg/kg/day fosaprepitant (NOAEL), AUC0-24h level of approximately 15.9 µg*h/ml, gives a margin to clinically relevant exposure of less than 1, based on 20.9 µg*h/ml, mean AUC in pediatric human subjects 6 months-<12 years given 3 mg/kg aprepitant (day 1).

In previous studies in adult dogs (oral administration of aprepitant) the target organs were the reproductive organs (prostate, testis and ovaries). Testicular degeneration was seen from 25 mg/kg b.i.d. The exposure level at 5 mg/kg/day (NOAEL) gives a margin towards clinical relevant exposure of approximately 13. The findings in the female reproductive organs were not seen previously in adult animals.

Regarding the dog juvenile findings the applicant argues that since there was no disruption of tissue architecture in the reproductive organs the findings are probably reversible. This can be agreed on, however, there is no data substantiating this, as no recovery group was included in the study. The lack of histomorphological changes in both rats and dogs, and the lack of effects on reproduction performance in rats is reassuring. Of importance in the discussion on clinical relevance is the duration of treatment in children versus the animal studies. Animals were exposed for a substantial longer duration than children (49 days for rats and 28 days for dogs, versus 3 days per chemotherapy cycle for children), and therefore any possible transient effect on the endocrine system is unlikely to be of clinical relevance and will not lead to a change in the B/R of aprepitant.

Review of the toxicokinetic data in dogs showed that there was a rapid conversion in plasma of fosaprepitant to aprepitant. The mean plasma levels of fosaprepitant 5 minutes post dose were 14-46

fold lower (all dose levels) compared to the plasma level 2 minutes post dose. There were no sex differences in exposure to fosaprepitant or aprepitant.

In the pivotal study in juvenile rats, they were evaluated from PND 10 to PNW 9, consequently the corresponding early stage (1 month to 12 years) of development in humans is considered covered (the pivotal study on fosaprepitant in dogs, treatment time PND 14-PND 42 corresponds to an age of 1 month-2 years in human). Thus, the age-group of paediatric subjects of 6 months to <12 years intended for the use of the applied powder for oral suspension formulation is considered to be covered non-clinically. The Applicant also has applied for extending the indication for the already approved 80 mg and 125 mg hard capsules (approved in adults) to include paediatric patients from 12 to 17 years of age. This age group can be considered to be covered by repeat dose 5- and 27-week toxicity studies (submitted as part of the initial Marketing Authorization Application) in which the rats were approximately 40 days old at study start (corresponding to an approximate 10 year old human). In these studies, twice daily administration of aprepitant up to 1000 mg/kg/ b.i.d did not result in any histomorphological effects on any reproductive organ, mammary glands, or bone.

The findings in the reproductive organs of rat and dogs are considered unlikely to be clinically relevant at short term treatment and at recommended dose regimen; these findings are appropriately reflected in the SmPC, section 5.3.

The new powder for oral suspension formulation of aprepitant contains no excipients that could cause concern, nor are there any impurities that need toxicological qualification.

2.3.7. Conclusion on the non-clinical aspects

In a juvenile toxicity study in rats treated from post natal day 10 to day 63 aprepitant led to an earlier vaginal opening in females from 250 mg/kg b.i.d. and to a delayed preputial separation in males, from 10 mg/kg b.i.d. There were no margins to clinically relevant exposure. There were no treatment-related effects on mating, fertility or embryonic/fetal survival, and no pathological changes in the reproductive organs. In a juvenile toxicity study in dogs treated from post natal day 14 to day 42, a decreased testicular weight and Leydig cell size were seen in the males at 6 mg/kg/d and increased uterine weight, hypertrophy of the uterus and cervix, and oedema of vaginal tissues were seen in females from 4 mg/kg/day. There were no margins to clinically relevant exposure of aprepitant. For short term treatment according to recommended dose regimen these findings are considered unlikely to be clinically relevant. These findings are appropriately reflected in the SmPC, section 5.3.

Considering the above data, aprepitant is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Study P208 - pivotal *Trial ID: 2011-000651-16*

Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
III	Worldwide	A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial, Conducted Under In-House Blinding Conditions, to Examine the Efficacy and Safety of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Patients	Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial, Conducted Under In-House Blinding Conditions	**Cycle 1** **Aprepitant Regimen** Patients 12-17 years of age: Day 1: aprepitant 125 capsule PO + ondansetron (Zofran™) Days 2 and 3: aprepitant 80 capsule PO Patients <12 years of age: Day 1: aprepitant powder-for-suspension (PFS): 3.0 mg/kg (up to 125 mg) + ondansetron (Zofran™) Days 2 and 3: aprepitant PFS: 2.0 mg/kg (up to 80 mg) **Control Regimen** Patients 12 – 17 years of age: Day 1: matching placebo for aprepitant 125 mg capsule PO + ondansetron (Zofran™) Days 2 and 3: matching placebo for aprepitant 80 mg capsule PO Patients <12 years of age: Day 1: matching placebo for aprepitant PFS: 3.0 mg/kg (up to 125 mg) + ondansetron (Zofran™) Days 2 and 3: matching placebo for aprepitant PFS: 2.0 mg/kg (up to 80 mg) **Optional Cycles 2-6** Patients 12-17 years of age: Day 1: aprepitant 125 mg capsule PO + ondansetron Days 2 and 3: aprepitant 80 capsule PO Patients < 12 years of age: Day 1: aprepitant PFS: 3.0 mg/kg (up to 125 mg) + ondansetron Days 2 and 3: aprepitant PFS: 2.0 mg/kg (up to 80 mg)	Males/females Age: 6 months to 17 years scheduled to receive emetogenic chemotherapy for documented malignancy.	**Cycle 1** Aprepitant regimen: 152 pts Control regimen: 150 pts

Study P134 *Trial ID: 2006-005515-10*

Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
I	Australia, Brazil, Canada, Colombia, France, Germany, Hungary, Israel, Mexico, Norway, Peru, Poland, Spain, Sweden, Switzerland, USA	A Multi-center, Open-label, 5-Part Study to Evaluate the Pharmocokinetics, Safety, and Tolerability of Aprepitant and Fosaprepitant Dimeglumine in Pediatric Patients Receiving Emetogenic Chemotherapy	Multi-center, open-label, 5-part study	**Part IA:** Subjects 12-17 years of age. Day 1: 115 mg IV fosaprepitant with IV ondansetron ±IV dexamethasone. Days 2 and 3: 80 mg oral aprepitant and IV ondansetron ±IV dexamethasone. **Part IB:** Subjects 12-17 years of age. Day 1: 150 mg IV fosaprepitant with IV ondansetron ±IV dexamethasone. **Part IIA:** Subjects <12 years of age. Day 1: Oral aprepitant dose equivalent to 80 mg in adults with IV ondansetron ±IV dexamethasone. **Part IIB:** Subjects <12 years of age. Day 1: Oral aprepitant dose equivalent to 125 mg in adults with IV ondansetron ±IV dexamethasone. **Part III**: Subjects <12 years of age. Days 1-3: IV ondansetron ±IV dexamethasone. **Part IV:** Subjects <12 years of age. Day 1: Oral aprepitant at a dose equivalent to 125 mg in adults with IV ondansetron ± IV dexamethasone. Days 2 and 3: Oral aprepitant at a dose equivalent to 80 mg in adults with IV ondansetron ± IV dexamethasone. **Part V:** Subjects 6 months to <12 years of age. Day 1: IV fosaprepitant at a dose equivalent to 150 mg in adults with IV ondansetron ±IV dexamethasone.	Males/females Age: birth to 17 years of age scheduled to receive moderately or highly emetogenetic chemotherapy or a chemotherapy regimen not previously tolerated due to nausea and/or vomiting for a documented malignancy.	**Part IA** Three day regimen (fosaprepitant on Day 1 and aprepitant on Days 2 and 3, along with ondansetron): 12 subjects **Part IB** Single day regimen of fosaprepitant: 11 subjects **Part IIA** Single day regimen of aprepitant: 19 subjects **Part IIB** Single day regimen of aprepitant: 19 subjects **Part III** Three day regimen of ondansetron: 19 subjects **Part IV** Three day regimen of aprepitant: 20 subjects **Part V** Single day regimen of fosaprepitant: 23 subjects

Study P097 *Trial ID: 0869-097*

Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
III	Australia, Brazil, United States	A Randomized, double-blind, placebo-controlled, parallel-group study, conducted under in-house blinding conditions to examine the safety, tolerability, and efficacy of aprepitant for the prevention of nausea and vomiting associated with emetogenic chemotherapy in adolescent patients.	Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions	**Cycle 1 – Part I** Aprepitant Regimen Day 1: aprepitant 125 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 8 mg, PO Day 2: aprepitant 80 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 4 mg, PO Day 3: aprepitant 80 mg capsule PO + dexamethasone 4 mg PO Day 4: dexamethasone 4 mg PO Standard Therapy Day 1: dexamethasone 16 mg PO + ondansetron (0.15 mg/kg x 3 doses) IV Day 2: dexamethasone 8 mg PO + ondansetron (0.15 mg/kg x 3 doses) IV Days 3 and 4: dexamethasone 8mg PO **Cycle 1 – Part II** Open-label Aprepitant Regimen Day 1: aprepitant 125mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 8mg, PO Days 2: aprepitant 80 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 4 mg, PO Day 3: aprepitant 80 mg capsule PO + dexamethasone 4 mg PO Day 4: dexamethasone 4 mg PO **Optional Cycles 2-10** Day 1: aprepitant 125 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 8 mg, PO Day 2: aprepitant 80 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 4 mg, PO Day 3: aprepitant 80 mg capsule PO + dexamethasone 4 mg PO Day 4: dexamethasone 4 mg PO	Male and female adolescent patients aged 12 to 17 with confirmed malignancies being treated with an emetogenic chemotherapy regimen.	**Cycle 1** Aprepitant regimen: 32 pts Standard Regimen: 18 pts

Study P148 *Trial ID: 2008-0031-78-17*

Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
I	Worldwide	A Multicenter, 2-Part Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Aprepitant in Pediatric Patients Undergoing Surgery	2-Part Study: Part I: Open and Part II: Blinded	Part I: aprepitant 40 mg PO. Part II: aprepitant 40 mg PO+ondansetron IV. Aprepitant 15 mg +1.1 mg/kg PO+ondansetron IV	Males/females Age: 6 months to 17 years scheduled to under surgery. Age groups: 12 to 17 yrs 6 to <12 yrs 2 to <6 yrs 6 mos <2 yrs	Part I: 46 subjects exposed to aprepitant Part II: 27 subjects exposed to aprepitant, 25 subjects exposed to ondansetron

2.4.2. Pharmacokinetics

Paediatric pharmacokinetic data for aprepitant were obtained from studies 134 and 097 (CINV), and from study 148 (PONV).

Biopharmaceutics

No biopharmaceutic studies have been performed to characterise the new powder for oral suspension (PFS), i.e. there is no comparative bioavailability study vs. the capsules and no food effect study. The bioavailability for the previously approved 80 mg and 125 mg capsules is about 60-70%. Data in the original application for the capsules demonstrated that the bioavailability of aprepitant is dependent on the particle size of the active pharmaceutical ingredient. Introduction of the aprepitant colloidal

dispersion greatly increased the bioavailability from the capsule as compared with early tablet formulations. The active pharmaceutical ingredient (aprepitant colloidal dispersion with controlled particle size) is the same. Importantly, all pharmacokinetic, safety and efficacy data for the paediatric patient population <12 years, for which the PFS is indicated, was obtained using the final PFS formulation. Furthermore, the capsule and the PFS are not intended to be interchangeable.

Based on data in the original application, the food effect for aprepitant appears also to be largely dependent on particle size of the active substance. The bioavailability of the capsules increased 40%, i.e. is expected to be about 100% with a standard breakfast. This effect is not considered clinically relevant and the capsules can be administered with or without food. Assuming similar fasting bioavailability for the PFS, the food effect cannot be relevantly larger for the PFS. The PFS was administered without regard to concomitant food in the pivotal study.

Pharmacokinetics in target population

The Applicant has proposed dosing per kg bodyweight in paediatric patients <12 years, while the adult flat dose is proposed for adolescent patients. Pharmacokinetic data with the proposed body-weight based dosing to children <12 years is relatively limited. However, based on more extensive pharmacokinetic data from three different paediatric studies covering the age range 0.5-17 years and different dosing regimens, the Applicant developed a population pharmacokinetic model. The model adequately describes the observed data across all age categories. There was no significant residual trend in IIV of CL vs age suggesting that the included maturation function on CL is sufficient to describe the change in CL with age over the whole age span.

The population pharmacokinetic model was used to simulate exposure with the proposed body-weight based dose in children <12 years as well as the flat dose in adolescents. Pharmacokinetic data, observed as well as simulated, demonstrate that with these doses, mean exposure (AUC) is somewhat lower in paediatric patients and adolescents than what has previously been observed in adult cancer patients. The lowest simulated mean AUC was seen in patients aged 6-<12 years. Mean Cmin values were generally lower in children < 12 years than in adults and adolescents. Simulated pharmacokinetic parameters are shown in Figure 1 to Figure 4.

Figure 1. Comparison of model-predicted pharmacokinetic parameters in children and adolescents and observational data in adult healthy volunteers and adult cancer patients (far right)

$AUC_{0\text{-}24\ hr.}$

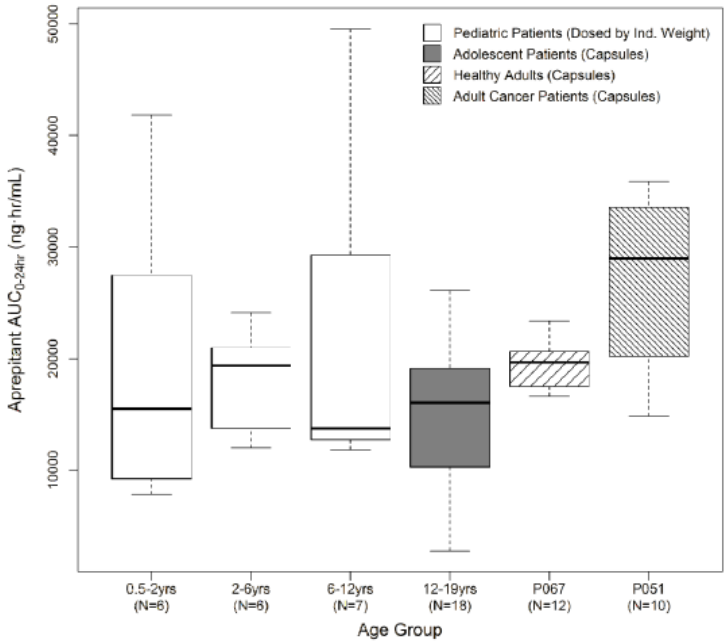


Figure 2. Comparison of model-predicted pharmacokinetic parameters in children and adolescents and observational data in adult healthy volunteers and adult cancer patients

C_{24hr}

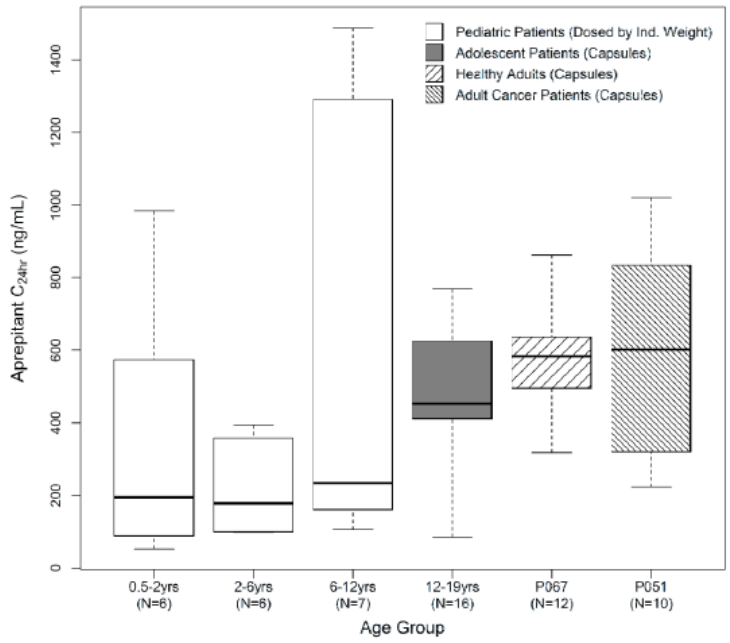


Figure 3. Comparison of model-predicted pharmacokinetic parameters in children and adolescents and observational data in adult healthy volunteers and adult cancer patients

C_{48hr}

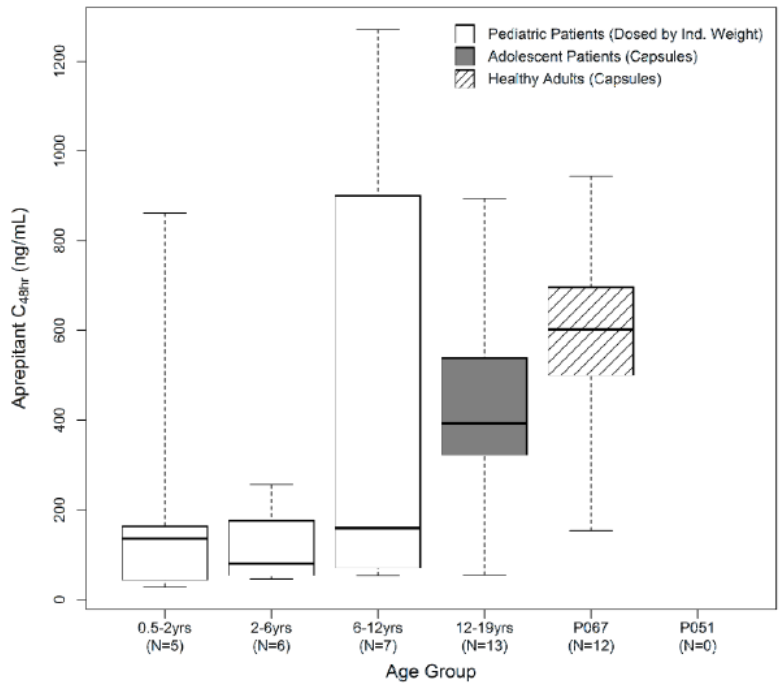
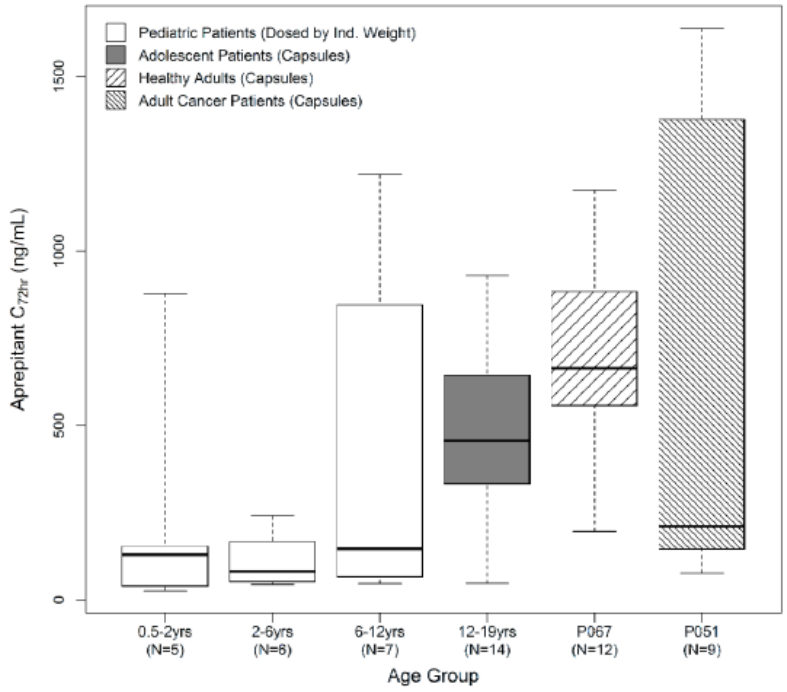


Figure 4. Comparison of model-predicted pharmacokinetic parameters in children and adolescents and observational data in adult healthy volunteers and adult cancer patients

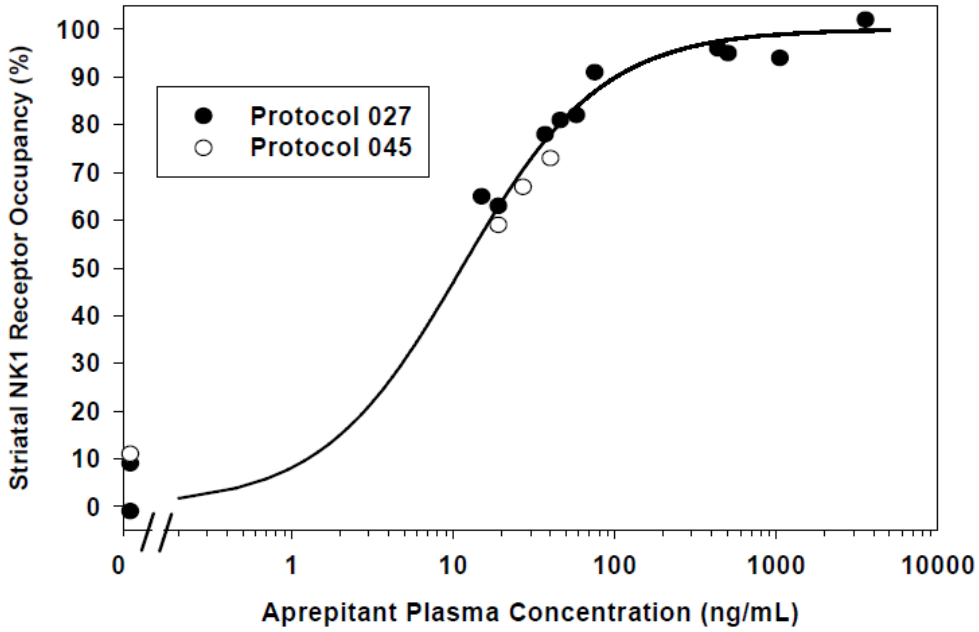
C_{72hr}



The Applicant suggests that the observed Cmin values in paediatric patients are at the plateau of the previously established (in adults) concentration-response curve in terms of receptor occupancy and

that based on trough concentrations of about 100 ng/ml, at least 90% receptor occupancy can be expected in paediatric patients < 12 years (Figure 5). Therefore, and as efficacy was demonstrated in the pivotal efficacy trial, the Applicant suggests that the pharmacokinetic differences between paediatric and adult patients is not clinically relevant.

Figure 5. Correlation of plasma aprepitant concentration with binding of aprepitant to striatal NK1 receptors (previous, adult data)



Proposed dose nomogram

In the pivotal efficacy and safety study, aprepitant was dosed strictly according to bodyweight in the children <12 years. However, in order to facilitate dosing in clinical practice, the Applicant has proposed a dose nomogram for the SmPC, where dosing is proposed over a small range of weights ("bins"). The relative difference between the low and high end of the weights within each range, or bin, is between ~20-30%. The basis for the doses is predicated upon the weight-based regimen (3.0 mg/kg on Day 1 followed by 2.0 mg/kg on Days 2 and 3) applied to the highest weight in the range with small adjustments owing to the volume and precision of the oral dispenser (5 mL) required for administration. Considering that the efficacy of lower aprepitant exposures in children has not been determined, and that aprepitant appears to have a good clinical margin of safety and tolerability, the application of 3 mg/kg on Day 1 followed by 2 mg/kg on Days 2 and 3 was targeted to the upper end of each weight range in order to maintain the clinical benefit demonstrated in the clinical trials.

In order to support the proposed dose nomogram, which has not been verified in a clinical trial, the Applicant performed a series of simulations of the predicted exposure, using the population pharmacokinetic model based on paediatric data from studies P097, P134 and P148.

The simulations indicate that using the nomogram results in slightly higher (~30%) aprepitant exposures compared to the individualised weight-based regimen.

Special populations
No data in paediatric patients with hepatic or renal impairment which is acceptable. The population pharmacokinetic analysis indicated no clinically relevant effect of gender or race on aprepitant pharmacokinetics in paediatric patients.

Pharmacokinetic interaction studies
No new interaction studies in paediatric patients were submitted

2.4.3. Pharmacodynamics

Mechanism of action
Aprepitant (EMEND) is a selective, high-affinity antagonist of human substance P/neurokinin 1 (NK1) receptors.

The mechanism of emesis is believed to be similar in adults and children, that is a complex process between neurotransmitters and receptors in both the central and peripheral nervous systems initiated by the stimulation of dopamine, opiate, histamine, acetylcholine, neurokinin (NK1) and/or serotonin type-3 (5-HT3) receptors. Neurokinin-1 (NK1) receptor antagonists have been identified as a novel class of anti-emetics. Substance P is the preferred agonist for NK1 receptors and belongs to a family of neuropeptides known as tachykinins. In experimental models, NK1 receptor antagonists have been shown to have potent and usually long-lasting, anti-emetic activity against a broad spectrum of both central and peripheral emetogens whereas 5-HT3 antagonists show a more limited spectrum of activity with efficacy mostly against peripheral emetogens.

Primary and Secondary pharmacology
For children, no new pharmacodynamic data are submitted. The pharmacodynamic profile is sufficiently investigated in adults. The absence of news data is acceptable.

2.4.4. Discussion on clinical pharmacology

Biopharmaceutics

The lack of biopharmaceutic studies for the new PFS is acceptable. It is agreed that based on the similarity of the PFS with the previously approved capsule and in particular the colloidal dispersion of the active substance, which is identical, bioavailability can be expected to be in the same range for the two formulations. Even if there would be a small difference, strict bioequivalence between the two is not necessary. All efficacy and safety data for paediatric patients < 12 years (for which the PFS is indicated) were obtained using the final market formulation of the PFS, and the PFS and the capsules are not intended to be used interchangeably. It is also agreed that a clinically relevant food effect for the PFS is unlikely.

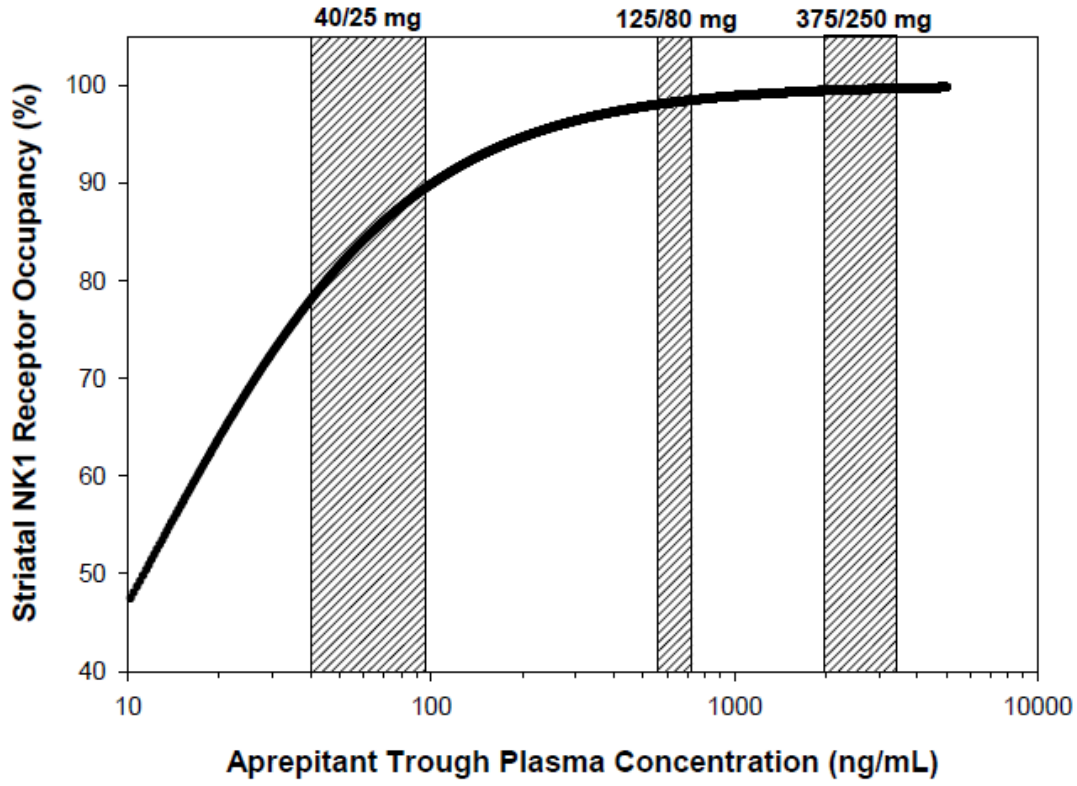
Pharmacokinetics in target population

The population pharmacokinetic model adequately describes the change in CL over the whole paediatric age span and is considered adequate for simulations. The pharmacokinetic data, observed as well as simulated, indicate that mean exposure (AUC0-24) is lower in paediatric patients (0.5-17 years) than that previously observed in adults. Trough (Cmin) values were lower in paediatric patients

<12 years than in adults, while adolescents had trough values in the same range as adults at the 125/80/80 mg dose regimen.

Based on a previously established PKPD relationship, the Applicant suggests that the trough concentrations seen in paediatric patients at the proposed doses are sufficient to obtain at least 90% receptor occupancy and therefore sufficient anti-emetic efficacy may still be expected. However, the Applicant has in a previous application presented an analysis (Figure 6), where the upper part of the established PKPD curve on receptor occupancy vs. concentration (depicted in Figure 5 above) is super-imposed with the observed trough concentration ranges in adults at different dosing regimens (shaded bars in Figure 6 below). It is noted that trough concentrations of around 100 ng/ml, obtained at the proposed doses for children < 12 years, are between a regimen that produced sub-maximal efficiency in CINV in adults in early studies (40 mg/25 mg) and regimens shown to be maximally effective in CINV in adults (125/80/80 mg and 375/250 mg).

Figure 6. Striatal NK1-Receptor Occupancy and Ranges of Mean Aprepitant Trough Plasma Concentrations Achieved With Different Chemotherapy-Induced Nausea and Vomiting (CINV) Dosing Regimens for Aprepitant



The shaded bars represent the range of the mean trough plasma concentrations of aprepitant achieved on each of Days 1 through 5 with aprepitant 375 mg/250 mg, 125 mg/80 mg, and 40 mg/25 mg regimens from Protocol 041 in healthy volunteers.

Thus, pharmacokinetic data cannot be considered fully supportive of the chosen dose regimens for paediatric patients. In response to questions, the Applicant simulated exposure and Cmin (C48 and C72) values at higher dose regimens in children <12 years. A regimen of 4/3/3 mg/kg on Day 1, 2 and 3, respectively, would give concentrations that are significantly higher than what has previously been established as safe in adults and is not relevant to consider. A regimen of 3/3/3 mg/kg on each of Day 1, 2 and 3 could possibly give C48 and C72 levels more in the range of what has been observed in adults at efficacious doses than the currently proposed doses of 2 mg/kg on Days 2 and 3. However, there were also other differences than pharmacokinetics between the study populations in the

paediatric and adult studies that may have affected treatment outcome. Available data are therefore not sufficient to determine whether the pharmacokinetic differences are of clinical importance. As the currently proposed dose regimen led to clinically relevant response rates in all age groups, it is considered acceptable (see discussion of clinical efficacy below).

Proposed dose nomogram

The dose nomogram proposed for the SmPC has not been confirmed in a clinical trial. Simulations indicate that using the nomogram results in slightly higher (~30%) aprepitant exposures compared to the individualised weight-based regimen. This was not unexpected, as the dose per weight group was set to aim for target exposure at the highest weight in each group. The approach is acceptable, given the somewhat lower exposure seen in paediatric patients as compared with adults with the strict bodyweight-based dosing, and the favourable safety profile of aprepitant. The increase in exposure when using the nomogram is not larger than other exposure changes that have been considered not clinically relevant, e.g. the food effect of 40%. The proposed nomogram is therefore acceptable.

Interactions

As aprepitant is a substrate for as well as an inhibitor of CYP3A4 and an inducer via PXR (e.g. CYP2C9 and 3A4), its pharmacokinetic profile (characterised in adults by auto-inhibition and auto-induction) and interaction potential may be somewhat different in the smallest children, in which enzyme maturation is ongoing. Overall, however, the interaction potential is expected to be largely similar in children, adolescents and adults. Interaction studies cannot be required in small children. A statement that interaction data in children is not available has been added to section 4.5 of the SmPC, which is adequate.

It was previously shown that addition of dexamethasone, a mild to moderate inducer, to aprepitant treatment did not relevantly affect aprepitant exposure in adults. On the other hand, aprepitant increased the exposure to dexamethasone, and the dexamethasone dose should be reduced if co-administered with aprepitant as reflected in the SmPC.

2.4.5. Conclusions on clinical pharmacology

Aprepitant is a neurokinin 1 (NK1) receptor antagonist. The pharmacodynamics has been thoroughly assessed in previous Market authorisation applications for adult indications. Aprepitant is recommended to be given in combination with 5HT3 inhibitors for optimal antiemetic effect. The pharmacodynamics of aprepitant is believed to be the same in children and adults and the aim of the paediatric dose finding was therefore to obtain similar exposure in children as in adults.

Over the whole age range, paediatric patients (0.5 – 17 years) receiving the proposed doses of 3/2/2 mg/kg in children <12 years and 125/80/80 mg in adolescents are predicted to have lower exposure on Day 1 (AUC_{0-24}) than what has previously been observed in adults. Cmin (C_{48} and C_{72}) values are predicted to be lower in the children < 12 years than in adults. However, as the studied dose regimen led to clinically relevant response rates in all paediatric age groups (see Clinical Efficacy), the observed pharmacokinetic differences do not give raise to objections against the proposed dose regimen.

The biopharmaceutic characterisation of the new paediatric powder for oral suspension is considered sufficient.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

The general approach to dose selection for the paediatric trials taken by the applicant was to match drug exposures to those previously demonstrated to be safe and efficacious in adults. In adults, plasma exposures associated with the approved adult dosing regimen of 125 mg aprepitant on Day 1 followed by 80 mg aprepitant on Days 2 to 3 (125/80/80 mg regimen) result in CNS NK1 receptor occupancy >95%. Doses higher than the 125/80/80 mg regimen were not associated with greater efficacy in a clinical study, whereas doses associated with CNS NK1 receptor occupancy <80 to 85% were submaximally efficacious. The Applicant therefore considered it reasonable and prudent to assess whether a positive benefit-risk relationship in children could be demonstrated at exposures similar to those shown to be well tolerated and maximally efficacious in adults.

The initial aprepitant paediatric study conducted was Protocol 097 (P097), which was a double-blind, Phase III pharmacokinetics (PK), safety, and exploratory efficacy study for the prevention of CINV in adolescent subjects 12 to 17 years of age. This study utilized the approved adult dosing regimen of 125 mg aprepitant on Day 1 followed by 80 mg aprepitant on Days 2 to 3, administered concomitantly with ondansetron and dexamethasone. The results of this study suggested that PK parameters in adolescents were similar to those in adults and that aprepitant was generally well-tolerated, and therefore further evaluation of the adult regimen in adolescents was reasonable.

The second study conducted, Protocol 134 (P134), was an open-label, Phase I study that evaluated the PK, safety, tolerability, and exploratory efficacy in subjects 6 months to 17 years of age. This study consisted of five parts, described below (Supportive studies), evaluating oral aprepitant in either a poweder for solution (PFS) or capsule formulation and fosaprepitant dimeglumine, an intravenous (IV) prodrug of aprepitant.

Pharmacokinetic data from Protocols 097 and 134, as well as PK data from a separate paediatric PONV trial that studied a single lower dose of aprepitant, Protocol 148 (P148), were used to develop a population PK model. This model was used to conduct simulations on paediatric dose adjustments for subjects 6 months to <12 years of age that would approximate PK parameters associated with safe and efficacious exposures in adults. This efficacy and safety of this dose regimen was further evaluated within Protocol 134 (Part IV) as well as Protocol 208 as noted below.

The results of the population PK model supported the doses chosen for the confirmatory phase 3 study P208.

2.5.2. Main study(ies)

A Phase III, Randomized, Double-Blind, Active Comparator- Controlled Clinical Trial, Conducted Under In-House Blinding Conditions, to Examine the Efficacy and Safety of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Patients.

Methods

Study Participants

Study P208 included patients 6 months-17 years of age with a documented malignancy and life expectancy of ≥3 months who were scheduled to receive chemotherapeutic agent(s) associated with

moderate, high risk or very high risk of emetogenicity, or a chemotherapy regimen not previously tolerated due to vomiting, for which ondansetron treatment should be planned. Patients scheduled for stem cell rescue therapy in conjunction with study related course(s) of emetogenic chemotherapy were excluded, as were patients who had received or would receive radiation therapy to the abdomen or pelvis in the week prior to Treatment Day 1 and/or during the course of the study. Patients with symptomatic CNS malignancy causing nausea or vomiting were also excluded. Excluded medications were: CYP3A4 inducers, substrates and inhibitors, anti-emetics, and products with QT prolongation, among others.

Table 2. Inclusion and exclusion criteria, P208.

Inclusion Criteria for Cycle 1	Exclusion Criteria
1. Patient is 6 months to 17 years of age at time of study entry. 2. Parent/guardian (legally authorized representative) agrees to the patient's participation as indicated by parent/legal guardian signature on the informed consent form. Patients 12 to 17 years of age, or as required by local regulation, assents and has the ability to understand the nature and intent of the study including the ability to comply with study procedures, complete study diary, and is willing to keep scheduled study visits. 3. Patient is scheduled to receive chemotherapeutic agent(s) associated with moderate, high risk or very high risk of emetogenicity for a documented malignancy, or a chemotherapy regimen not previously tolerated due to vomiting. 4. Patient is expected to receive ondansetron as part of their antiemetic regimen. 5. Female patient who has begun menses has a negative urine pregnancy test prior to randomization. A female patient who is of reproductive potential agrees to remain abstinent or use a barrier form of contraception for at least 14 days prior to, throughout, and for at least one month following the last dose of study medication. Women taking oral contraception must agree to add a barrier form of contraception. For countries where abstinence is not considered an acceptable method of birth control, a locally acceptable birth control method must be used. 6. Patient aged >10 years has a Karnofsky score≥ 60; patient aged ≤10 years has a Lansky Play Performance score ≥ 60 (as displayed in Appendix 6.2 of the protocol). 7. Patient has a predicted life expectancy of ≥3 months.	1. Patient has vomited in the 24 hours prior to Treatment Day 1. 2. Patient is currently a user of any illicit drugs or has current evidence of alcohol abuse (defined using DSM-IV criteria) as determined by the investigator. 3. Patient is scheduled to receive stem cell rescue therapy in conjunction with study related course(s) of emetogenic chemotherapy. 4. Patient has received or will receive radiation therapy to the abdomen or pelvis in the week prior to Treatment Day 1 and/or during the course of the study. 5. Patient is pregnant or breast feeding. (Females of child bearing potential are required to have a negative urine pregnancy test prior to entering the study.) 6. Patient is allergic to aprepitant, ondansetron, or any other 5-HT3 antagonist. 7. Patient has a symptomatic primary or metastatic CNS malignancy causing nausea and/or vomiting. Patient who is asymptomatic is allowed to participate. 8. Patient has abnormal laboratory values as follows (deviations from these guidelines require discussion with the Merck Clinical Monitor): a. Bone Marrow Function: i. Peripheral absolute neutrophil count (ANC) <1000/mm3 ii. Platelet count <100,000/ mm3 b. Liver Function i. AST >5.0 x upper limit of normal (ULN) for age ii. ALT >5.0 x upper limit of normal (ULN) for age iii. Bilirubin > 1.5 x upper limit of normal (ULN) for age c. Renal function i. A serum creatinine > 1.5 x upper limit of normal (ULN) for age 9. Patient has a known history of QT prolongation or is currently taking other medicinal products that lead to QT prolongation. 10. Patient has an active infection (e.g., pneumonia), congestive heart failure (CHF), bradyarrythmia, or any uncontrolled disease (e.g., diabetic ketoacidosis, gastrointestinal obstruction) except for malignancy, or has a history of any illness which, in the opinion of the investigator, might confound the results of the study or pose unwarranted risk in administering study drug or concomitant therapy to the patient. 11. Patient has had benzodiazepine or opioid therapy initiated within 48 hours of study drug administration, except for single daily doses of triazolam, temazepam,
Additional Inclusion Criteria for the Optional Cycles (Cycles 2-6) These criteria will be used in addition to the Cycle 1 inclusion criteria: a. Parent/guardian (legally authorized representative) agrees to the patient's participation as indicated by parent/legal guardian signature on the informed consent form. Patients 12 to 17 years of age, or as required by local regulation, assents and has the ability to understand the nature and intent of the study including the ability to comply with study procedures and is willing to keep scheduled study visits. b. Participation in the study during a subsequent cycle	

of chemotherapy is considered appropriate by the investigator and will not pose unwarranted risk to the patient. c. Patient has, in the opinion of the investigator, completed the preceding cycle of chemotherapy and related study procedures satisfactorily. If a patient experiences vomiting or uses rescue medication during a study cycle, they are permitted to participate in a subsequent study cycle provided they have complied with all required study procedures.	or midazolam. -Continuation of chronic benzodiazepine or opioid therapy is permitted provided it was initiated at least 48 hours prior to study drug administration. 12. Patient has been started on systemic corticosteroid therapy within 72 hours prior to study drug administration or is planned to receive a corticosteroid as part of the chemotherapy regimen. Exceptions: • Patients who are receiving chronic (>72 hours), daily steroid therapy can be enrolled provided the steroid dose is not >0.14 mg/kg (up to 10 mg) of prednisone daily or equivalent. • For supportive care, patients are permitted to receive a single dose of corticosteroid within 3 days prior (but not on the day of study drug administration) provided it is < the equivalent of 20 mg of prednisone. 13. Patient is currently taking warfarin. 14. Patient has ever participated in a study with aprepitant or fosaprepitant, or has taken a non-approved (investigational drug) within the last 4 weeks. Note: Patients in investigational studies with marketed chemotherapeutic agents (whether explicitly for children or only marketed for adults and usually administered to children with the appropriate dose adjustments) are allowed to enroll if they fulfil all other entry criteria. 15. - 18. Other Excluded Medications: CYP3A4 inducers, substrates and inhibitors, and Anti-emetics, according to non-exhaustive list (Table 9-3 in CSR). The Sponsor should be consulted in individual cases where the patient is taking a CYP3A4 or anti-emetic not listed.

The eligibility criteria appear relevant and sufficient to allow conclusions regarding the efficacy of apreptitant while excluding main potential confounding factors.

The Applicant has clarified that the additional inclusion criteria (c.) for entry into the optional open label extension was included to ensure subjects considering participation in the extension had first completed all the protocol required procedures in Cycle 1. Regardless of whether a subject had Complete Response or not in Cycle 1, they could be considered for inclusion in the extension.

Treatments

Table 3. Study treatments, P208

Regimen (N)	Study Medication	Subject Age	Day 1 Dose	Day 2 Dose	Day 3 Dose
Aprepitant [A] (150)	Aprepitant	12 to 17 years	125 mg capsule PO 60 minutes prior to initiation of chemotherapy	80 mg capsule PO[B]	80 mg capsule PO[B]
		6 months to <12 years	3.0 mg/kg (up to 125 mg) powder for suspension (PFS) PO 60 minutes prior to initiation of chemotherapy	2.0 mg/kg (up to 80 mg) PFS PO[B]	2.0 mg/kg (up to 80 mg) PFS PO[B]
	Ondansetron[C]	6 months to 17 years	administered according to the product label for pediatric usage or local standard of care[D]		
Control [A] (150)	Placebo for aprepitant	12 to 17 years	125 mg placebo capsule PO 60 minutes prior to initiation of chemotherapy	80 mg Placebo capsule PO[B]	80 mg Placebo capsule PO[B]
		6 months to <12 years	3.0 mg/kg (up to 125 mg) placebo PFS PO 60 minutes prior to initiation of chemotherapy	2.0 mg/kg (up to 80 mg) placebo PFS PO[B]	2.0 mg/kg (up to 80 mg) placebo PFS PO[B]
	Ondansetron[C]	6 months to 17 years	administered according to the product label for pediatric usage or local standard of care[D]		

A Intravenous dexamethasone was permitted to be administered to both treatment arms as part of the anti-emetic regimen, at the discretion of the investigator. If dexamethasone was administered as part of the anti-emetic regimen for patients receiving aprepitant, dexamethasone was to be administered at 50% of the established dose in children.

B For patients receiving chemotherapy on Days 2 or 3, aprepitant was to be administered 60 minutes prior to initiation of chemotherapy.

C Branded ondansetron (Zofran™) was required for Cycle 1 of this study. Zofran™ was not be supplied by the SPONSOR, meaning Merck Headquarters or IVRS. Zofran™ was to be provided by the subsidiary or the site. If procurement of Zofran™ was not feasible, discussion with the Merck Clinical Monitor and/or delegate was required. Generic ondansetron was permitted during the Optional Cycles 2-6.

D Preventative antiemetic treatment with ondansetron was permitted ONLY on days that chemotherapy is administered. Once the chemotherapy treatment regimen was complete, ondansetron was no longer permitted as prophylactic treatment.

It is noted, based on prescribed dosing volumes in SmPC 4.2, that patients <12 years of age and >30 kg will be dosed with aprepitant powder for suspension at 125 mg on day 1 and 80 on day 2 and 3, corresponding to the dose of the adult regimen with125/80 mg capsules. In the absence of specific trial data demonstrating interchangeability between the capsule and PFS formulations, the proposed labelling that does not mention any possibility of choice between the two formulations which is considered appropriate.

Objectives

See section below.

Outcomes / endpoints

Table 4. Objectives and endpoints P208

Primary objective and hypothesis	**Endpoint**
Efficacy: To compare the three-day oral aprepitant regimen (aprepitant plus ondansetron), to ondansetron alone with respect to the efficacy endpoint of Complete Response in the 25 to 120 hours following the initiation of emetogenic chemotherapy in **Cycle 1** (**delayed phase**). **Hypothesis:** superiority	**Complete Response**: The proportion of patients with no vomiting, no retching, and no use of rescue medication.
Secondary objectives	**Endpoint**
Efficacy: To compare the three-day oral aprepitant regimen, to the control regimen with respect to the efficacy endpoint of Complete Response in the 0 to 24 hours following the initiation of emetogenic chemotherapy in **Cycle 1** (**acute phase**).	**Complete Response**: The proportion of patients with no vomiting, no retching, and no use of rescue medication.
Efficacy: To compare the three-day oral aprepitant regimen, to the control regimen with respect to the efficacy endpoint of Complete Response in the 0-120 hours following the initiation of emetogenic chemotherapy in **Cycle 1** (**overall phase**).	**Complete Response**: The proportion of patients with no vomiting, no retching, and no use of rescue medication.
Efficacy: To compare the three-day oral aprepitant regimen, to the control regimen with respect to the efficacy endpoint of No Vomiting, regardless of rescue medication use, in the 120 hours following the initiation of emetogenic chemotherapy in **Cycle 1** (**overall phase**).	**No Vomiting**: The proportion of patients with no vomiting, irrespective of use of rescue medication.
Safety: To assess the safety and tolerability of the three-day oral aprepitant regimen in patients from 6 months to 17 years of age who are receiving emetogenic chemotherapy in **Cycle 1**.	Clinical and laboratory adverse events that are considered drug-related, serious, serious drug-related, or lead to discontinuation of study therapy. There are no pre-specified events of clinical interest (ECI) for this study, other than the Merck-standard ECIs of overdose and Drug-Induced Liver Injury events.
Exploratory objectives and endpoints	
Efficacy: The number of emetic episodes in the 120 hours following initiation of emetogenic chemotherapy (overall phase);	
Efficacy: The time to first rescue medication in the 120 hours following initiation of emetogenic chemotherapy (overall phase);	
Efficacy: The time to first vomiting in the 120 hours following initiation of emetogenic chemotherapy (overall phase);	

Efficacy: The number of patients with no use of rescue medication in the 120 hours following initiation of emetogenic chemotherapy (overall phase).
Safety: To describe the adverse event profile of the aprepitant regimen when administered to paediatric cancer patients receiving **additional cycles** of emetogenic chemotherapy.

Vomiting Assessment: A vomiting episode was defined as one or more episodes of emesis (expulsion of stomach contents through the mouth) or retches (an attempt to vomit that is not productive of stomach contents). Distinct vomiting episodes are, by definition, separated by the absence of emesis and retching for at least one minute. The timing (date and time) of each vomiting episode was recorded by the patient/parent/guardian in the diary at the time of the occurrence.

Sample size

This study was planned to randomize approximately 150 patients into the aprepitant regimen group and 150 patients into the control regimen group and has 80% power to demonstrate the superiority of the aprepitant regimen over the control regimen at an overall one-sided, 2.5% alpha-level, if the underlying treatment difference in Complete Response is 15 percentage points. The power and sample size are based on the following assumptions: 1) an approximately 3% (overall) dropout rate, and 2) an underlying response rate of 60% for the control regimen. The minimum criterion for success is that the one-sided p-value < 0.025.

Randomisation

Subjects who satisfied the inclusion and exclusion criteria were randomized centrally and assigned to one of the two treatment regimens via the IVRS. At the time of randomization via IVRS, subjects were stratified by age on Day 1 of Cycle 1 into the appropriate age cohort (6 months to < 2 years; 2 to < 6 years; 6 to <12 years; or 12 to 17 years).

Patients were further stratified based on planned use of a chemotherapy agent associated with a Very High Risk of emetogenicity in Cycle 1 (Yes or No) and planned use of dexamethasone as an antiemetic in Cycle 1 (Yes or No).

Blinding (masking)

This was a double-blind study, conducted under in-house blinding conditions. The study medication for Cycle 1 was supplied in a blinded manner based on a Component Identification Number (CID). At the time of subject randomization, the IVRS assigned a CID number for the randomized subjects. Site staff retrieved the corresponding clinical supply (identified via the CID) for administration to the subject. Unblinded personnel were not required to prepare the study medication as the study medication for Cycle 1 (aprepitant and placebo) was supplied in a blinded manner.

Clinical supplies for Cycles 2-6 were open-label.

Dexamethasone, when administered, was sourced locally and prepared by the unblinded pharmacist in order to maintain the blind. A dose reduction of dexamethasone was required for patients in the aprepitant regimen; as such, unblinded personnel was required to prepare the dexamethasone according to the patient's treatment group assignment. The unblinded pharmacist or designee prepared the intravenous dexamethasone in a manner that allowed site staff to remain blinded when administering the corticosteroid.

Zofran™/ondansetron was sourced locally and was open-label for all study cycles.

Statistical methods

Nominal p-values were computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. Unless otherwise stated, all statistical tests were conducted at the α=0.05 (2- sided) level.

The treatment comparisons for Complete Response and No Vomiting was made using the Cochran-Mantel-Haenzel (CMH) test stratified by age (<2 years, 2 to 17 years), use of dexamethasone as an antiemetic in Cycle 1 (yes, no), and receipt of very high risk emetogenic chemotherapy agent in Cycle 1 (yes, no). The superiority hypotheses will be evaluated by comparing the 1-tailed p-value to 0.025 and significance declared if the p-value was≤0.025.

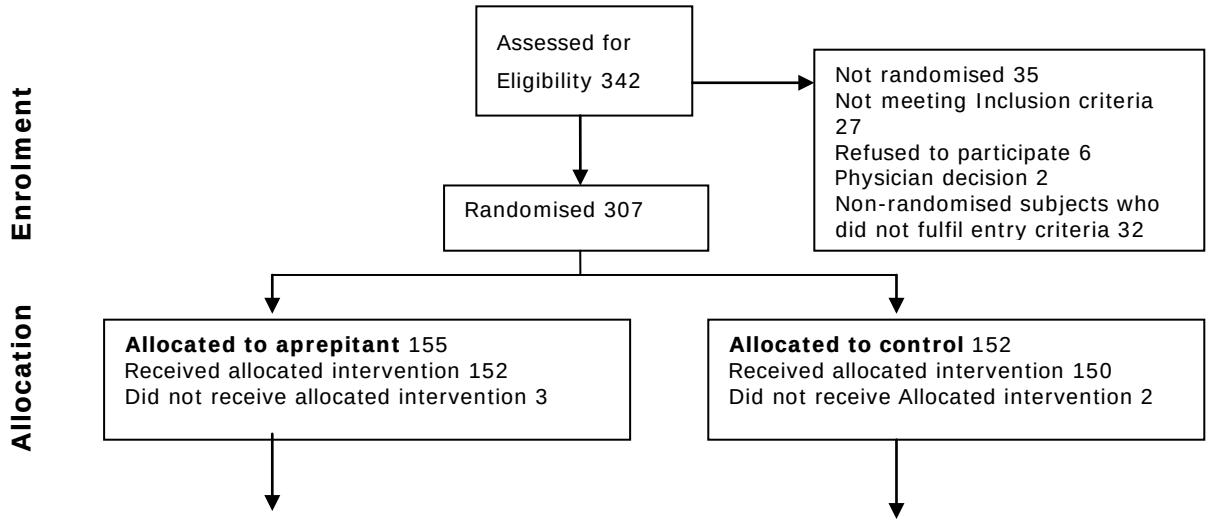
A supportive analysis was performed using a logistic regression model that included terms for treatment (aprepitant regimen, control regimen), use of dexamethasone as an antiemetic in Cycle 1 (yes, no), receipt of a very high risk emetogenic chemotherapy agent in Cycle 1 (yes, no), and age (<2 years, 2 to 17 years). The final model did not include treatment interaction terms.

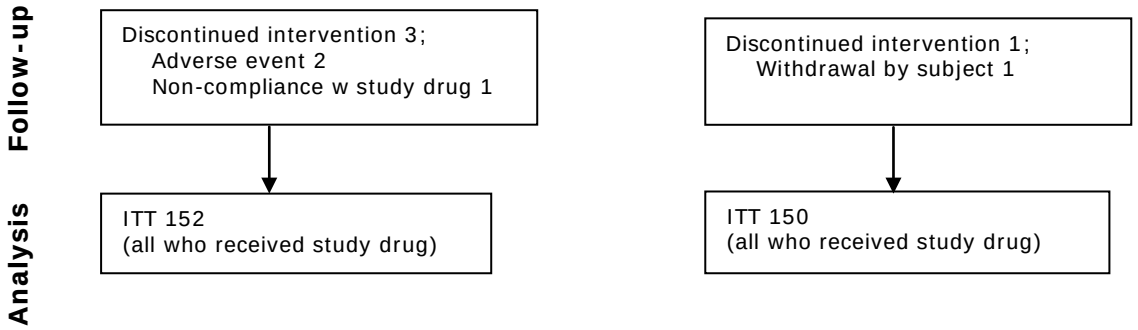
Any vomiting, retching, dry heaves, or use of rescue therapy within a phase (acute or delayed) would define a patient as having an unfavorable response for that phase and for the overall analysis (regardless of missing data at other time points) for all 3 efficacy patient populations (ITT, FAS, and PP). In the ITT and FAS, response to therapy in a particular phase was to be assessed based on the observed data in that phase. Patients with missing binary data for the primary and secondary endpoints were to be classified as non-responder/failure in both the ITT and FAS efficacy analyses. In the PP population, any missing data (in the absence of vomiting or use of rescue therapy at another time point) would exclude the patient from the analysis for that phase and for the overall analysis.

For the exploratory analysis of time to first use of rescue medication, Kaplan-Meier curves depicting the percentage of patients who did not use rescue medication, since the initiation of emetogenic chemotherapy, were presented. Kaplan-Meier curves depicting the percentage of patients who are vomiting-free, ignoring rescue, since the initiation of emetogenic chemotherapy were also be presented

Results

Participant flow





Source: Study P208 CSR, Table 10-4.

Recruitment

Trial Initiation Date 22-Sep-2011, Trial Completion Date 16-Aug-2013.

Conduct of the study

Study P208 underwent three protocol amendments. The first and third were minor.

The second amendment (11 July 2012) included changes made in response to regulatory agency feedback obtained after the trial began. These included interchange of primary and secondary objectives (following advice from FDA), change of primary analysis population to the Intent-to-treat (ITT) population, change of primary analysis method to Cochran-Mantel-Haenzel (CMH) test, and change minimum age for inclusion from 0 to 6 months.

The changes to the protocol did not affect the study results or interpretation thereof. A rationale for excluding patients below the age of 6 months were given in the context of the Paediatric Investigation Plan (PIP): “A waiver was granted for the development of the product from birth to less than 6 months based on the grounds of safety concerns since it will be difficult standardizing the dose in subjects less than 6 months of age due to unpredictable cytochrome P450 enzyme levels compared to patients > 6 months.”

Baseline data

Somewhat more male than female patients were enrolled, 54 vs. 46%. With regard to age group, the youngest age group represented nearly 12% of study participants while the other three age groups represented approximately 30% each. A majority of patients were white (76%).

With regard to stratification factors (concerning planned use), a majority of patients actually received chemotherapy with very high risk of emetogenicity (66.2%), while a majority of patients did not receive dexamethasone as part of the antiemetic regimen in Cycle 1 (71.5%).

Table 5. Baseline characteristics, P208

	Aprepitant Regimen		Control Regimen		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	152		150		302	
Gender						
Male	84	(55.3)	79	(52.7)	163	(54.0)
Female	68	(44.7)	71	(47.3)	139	(46.0)
Age (Months)						
6 months to <2 years	19	(12.5)	16	(10.7)	35	(11.6)
2 years to <6 years	45	(29.6)	43	(28.7)	88	(29.1)
6 years to <12 years	41	(27.0)	43	(28.7)	84	(27.8)
12 years to 17 years	47	(30.9)	48	(32.0)	95	(31.5)
Mean	97.7		99.4		98.5	
SD	63.2		60.9		62.0	
Median	86.5		91.5		89.5	
Range	6 to 213		6 to 214		6 to 214	
Race						
American Indian Or Alaska Native	2	(1.3)	0	(0.0)	2	(0.7)
Asian	11	(7.2)	16	(10.7)	27	(8.9)
Black Or African American	0	(0.0)	2	(1.3)	2	(0.7)
Multiple	20	(13.2)	22	(14.7)	42	(13.9)
White	119	(78.3)	110	(73.3)	229	(75.8)
Ethnicity						
Hispanic Or Latino	36	(23.7)	32	(21.3)	68	(22.5)
Not Hispanic Or Latino	111	(73.0)	112	(74.7)	223	(73.8)
Not Reported	2	(1.3)	4	(2.7)	6	(2.0)
Unknown	3	(2.0)	2	(1.3)	5	(1.7)
Use of Dexamethasone as Part of the Antiemetic Regimen in Cycle 1						
Yes	44	(28.9)	42	(28.0)	86	(28.5)
No	108	(71.1)	108	(72.0)	216	(71.5)
Very High Risk Emetogenicity Chemotherapy						
Yes	99	(65.1)	101	(67.3)	200	(66.2)
No	53	(34.9)	49	(32.7)	102	(33.8)

Tumour type

The most common primary malignancies were Ewing's sarcoma and osteosarcoma (~11%), followed by rhabdomyosarcoma and neuroblastoma, representing approximately 8% of the population and medullablastoma and acute lymphocytic leukaemia, which represented 7% of the population. In general, the treatment groups were balanced with regard to primary malignancies.

Overall, the baseline demographic and disease characteristics, as well as use of dexamethasone and very high emetogenic chemotherapy (VHEC) were balanced across study arms.

Table 6. Disposition of subjects, Cycle 1, Study P208

	Aprepitant Regimen		Control Regimen		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	155		152		307	
Study Disposition						
Completed	150	(96.8)	149	(98.0)	299	(97.4)
Discontinued	5	(3.2)	3	(2.0)	8	(2.6)
Adverse Event	2	(1.3)	0	(0.0)	2	(0.7)
Physician Decision	0	(0.0)	1	(0.7)	1	(0.3)
Protocol Violation	2	(1.3)	0	(0.0)	2	(0.7)
Withdrawal By Subject	1	(0.6)	2	(1.3)	3	(1.0)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)
Study Medication Disposition						
Completed	149	(96.1)	149	(98.0)	298	(97.1)
Did Not Take Study Medication	3	(1.9)	2	(1.3)	5	(1.6)
Discontinued	3	(1.9)	1	(0.7)	4	(1.3)
Adverse Event	2	(1.3)	0	(0.0)	2	(0.7)
Non-Compliance With Study Drug	1	(0.6)	0	(0.0)	1	(0.3)
Withdrawal By Subject	0	(0.0)	1	(0.7)	1	(0.3)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)
Each subject is counted once for Study Disposition, Study Medication Disposition based on the latest corresponding disposition record.						
Unknown: A disposition record did not exist at the time of reporting.						

Following Cycle 1, 171 subjects elected to participate in the **optional cycles (Cycles 2-6)**. Of those, all but one subject received study medication in Cycle 2. This patient was excluded from further efficacy and safety analyses.

Table 7. Disposition of subjects, Cycle 2-6, Study P208

	Aprepitant Regimen	
	n	(%)
Subjects in population	171	
Trial Disposition		
Completed	46	(26.9)
Discontinued	125	(73.1)
Adverse Event	2	(1.2)
Completed Chemotherapy Regimen	51	(29.8)
Did Not Meet Additional Criteria	25	(14.6)
Did Not Respond To Chemotherapy Regimen	4	(2.3)
Lack Of Efficacy	1	(0.6)
Lost To Follow-Up	1	(0.6)
Physician Decision	19	(11.1)
Protocol Violation	4	(2.3)
Withdrawal By Subject	18	(10.5)
Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.		

Thus, 27% of the patients included in Cycle 1 also completed all Cycles 2-6. For 30 % of patients this was explained by the fact that they completed the chemotherapy regimen before a total of 6 cycles had been administered. Another large proportion (15%) did not fulfil the additional inclusion criteria for cycle 2-6. Only 1% discontinued due to adverse event.

Numbers analysed

Table 8. Analysis populations and numbers, P208

Analysis population: n	Description	Excluded
Randomised: 307	All randomised patients	-
ITT: 302 Intent-to-treat	All patients who received at least one dose of study medication (aprepitant/control).	5 randomised patients did not receive study medication and were excluded from the ITT, FAS, and PP
FAS: 301 Full analysis set	All randomized patients who: (1) received chemotherapy, (2) received at least one dose of study medication, and (3) had at least one post-treatment efficacy assessment.	1 patient did not have a post-treatment efficacy assessment and is excluded from the FAS and PP analyses and will be considered as having an unfavorable response in the ITT analysis
PP: Per protocol	All patients who did not have a protocol violation that was deemed likely to confound the analysis of efficacy endpoints	63 patients with protocol violation were excluded (from one or all analysis phases).
APaT: All patients as treated	All randomized subjects who received at least one dose of study treatment. Analysis by which study drug the patients actually received, regardless of randomised group.	

Outcomes and estimation

Primary endpoint – Complete response

Table 9.Number (%) of Patients with Complete Response by Phase and Treatment Group (CMH Method) - Cycle 1 (Intent to Treat Population) Protocol 208

	Aprepitant Regimen n/m (%)	Control Regimen n/m (%)
Acute Phase	101 / 152 (66.4) *	78 / 150 (52.0)
Delayed Phase	77 / 152 (50.7) **	39 / 150 (26.0)
Overall Phase	61 / 152 (40.1) **	30 / 150 (20.0)

* p<0.05 when compared with Control Regimen.

** p<0.01 when compared with Control Regimen.

[†] Complete Response = no vomiting or retching and no use of rescue medication.

Treatment comparison is made using the CMH test stratified by age group, use of dexamethasone as an antiemetic in Cycle 1, and receipt of a Very High Risk emetogenic chemotherapy agent in Cycle 1.

n/m = Number of patients with desired response/number of patients included in time point

Acute Phase: 0 to 24 hours following initiation of chemotherapy.

Delayed Phase (Primary Endpoint): 25 to 120 hours following initiation of chemotherapy.

Overall Phase: 0 to 120 hours following initiation of chemotherapy.

In the delayed phase, significantly (p<0.0001) more patients on the aprepitant regimen had Complete Response compared to those on the control regimen. The aprepitant regimen was also more effective than the control regimen in the acute phase (nominal p=0.0135) and the overall phase (nominal p=0.0002).

The result in the primary endpoint, the delayed phase, was statistically significant well above the threshold for superiority. Similarly, the results in the acute and overall phases both had nominal p-values < 0.02. The difference between arms in the proportion of patients with complete response is considered clinically relevant with the responding portion approximately doubled in the overall phase (absolute difference 20%), as well as in the delayed phase (absolute difference 25%), and increased by more than ¼ in the acute phase (absolute difference 14%).

The corresponding table for the primary endpoint in the FAS population (ITT minus one patient) showed nearly identical figures, percentages and annotations, except for one less patient included in the control arm (m= 149 instead of 150), thus supporting the primary analysis (not shown).

In addition, analysis of Complete response in the ITT population was performed using the originally planned logistic regression model resulted in the same frequencies and achievement of clinical significance (not shown).

The results in the PP population were very similar to the primary analysis in the ITT, thereby supporting the results (see table below).

Table 10. Number (%) of Patients with Complete Response by Phase and Treatment Group (CMH Method) - Cycle 1 (Per Protocol Patient Population) P208

	Aprepitant Regimen n/m (%)	Control Regimen n/m (%)
Acute Phase	91 / 140 (65.0) *	67 / 130 (51.5)
Delayed Phase	63 / 126 (50.0) **	33 / 119 (27.7)
Overall Phase	52 / 126 (41.3) **	25 / 118 (21.2)

* p<0.05 when compared with Control Regimen.
** p<0.01 when compared with Control Regimen.
† Complete Response = No vomiting or retching and no use of rescue medication.
Treatment comparison is made using the CMH test stratified by age group, use of dexamethasone as an antiemetic in Cycle 1, and receipt of Very High Risk emetogenic chemotherapy agent in Cycle 1.
n/m = Number of patients with desired response/number of patients included in time point.
Acute Phase: 0 to 24 hours following initiation of chemotherapy.
Delayed Phase: 25 to 120 hours following initiation of chemotherapy.
Overall Phase: 0 to 120 hours following initiation of chemotherapy.

Secondary endpoint – No vomiting

(Regardless of rescue therapy.)

Table 11. Number (%) of Patients with No Vomiting by Phase and Treatment Group (CMH Method) - Cycle 1 (Intent to Treat Population) Protocol 208

	Aprepitant Regimen n/m (%)	Control Regimen n/m (%)
Acute Phase	108 / 152 (71.1) **	80 / 150 (53.3)
Delayed Phase	84 / 152 (55.3) **	42 / 150 (28.0)
Overall Phase	71 / 152 (46.7) **	32 / 150 (21.3)

* p<0.05 when compared with Control Regimen.

** p<0.01 when compared with Control Regimen.

† No Vomiting = No emesis or retching or dry heaves.

Treatment comparison is made using the CMH test stratified by age group, use of dexamethasone as an antiemetic in Cycle 1, and receipt of a Very High Risk emetogenic chemotherapy agent in Cycle 1.

n/m = Number of patients with desired response/number of patients included in time point

Acute Phase: 0 to 24 hours following initiation of chemotherapy.

Delayed Phase: 25 to 120 hours following initiation of chemotherapy.

Overall Phase: 0 to 120 hours following initiation of chemotherapy.

In the overall phase, more subjects on the aprepitant regimen reported No Vomiting compared to those on the control regimen (nominal p=<0.0001). The aprepitant regimen was also more effective than the control regimen in the acute phase (nominal p=0.0023) and the delayed phase (nominal p=<0.0001).

With regard to No vomiting, the difference between arms in the proportions responding is very similar (slightly larger) in all three phases compared with the primary endpoint (Complete response), supporting the primary endpoint.

Secondary endpoint – Number of Emetic Episodes

Details for acute and delayed phase, respectively, are shown in the tables below.

Table 12. Number (%) of Patients With Vomiting During the Acute Phase by Frequency and Treatment Group - Cycle 1 (Intent to Treat Population)

	Aprepitant Regimen n/m (%)	Control Regimen n/m (%)
No vomiting	108/152 (71.1)	80/150 (53.3)
1 episode of vomiting	22/152 (14.5)	24/150 (16.0)
2 episodes of vomiting	5/152 (3.3)	12/150 (8.0)
3 episodes of vomiting	7/152 (4.6)	7/150 (4.7)
>3 episodes of vomiting	10/152 (6.6)	26/150 (17.3)

† Acute Phase: 0 to 24 hours following initiation of chemotherapy.

n/m = Number of patients with desired response/number of patients included in time point.

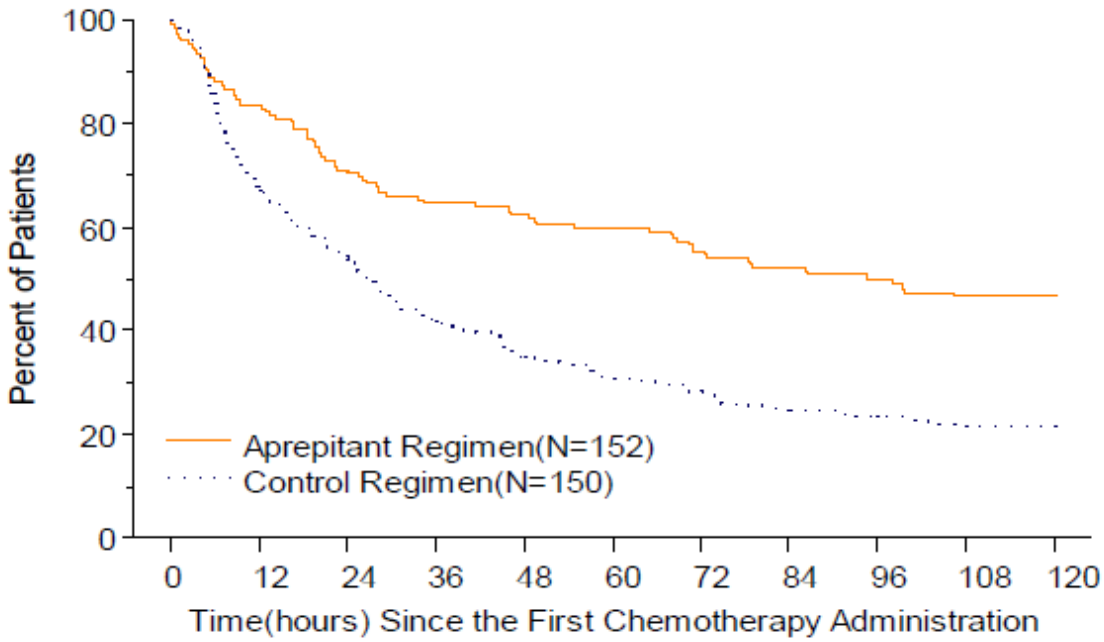
Table 13. Number (%) of Patients With Vomiting During the Delayed Phase by Frequency and Treatment Group - Cycle 1 (Intent to Treat Population)

	Aprepitant Regimen n/m (%)	Control Regimen n/m (%)
No vomiting	84/152 (55.3)	42/150 (28.0)
1 episode of vomiting	18/152 (11.8)	17/150 (11.3)
2 episodes of vomiting	9/152 (5.9)	16/150 (10.7)
3 episodes of vomiting	11/152 (7.2)	12/150 (8.0)
>3 episodes of vomiting	30/152 (19.7)	62/150 (41.3)
[T] Delayed Phase: 25 to 120 hours following initiation of chemotherapy. n/m = Number of patients with desired response/number of patients included in time point.		

In both phases (acute and delayed), the largest difference between arms were seen in the categories with 2 episodes of vomiting and particularly in the group with >3 emetic episodes.

Secondary endpoint – Time to First Vomiting

Figure 7. Kaplan-Meier Curves for Time to First Vomiting Episode From Start of Chemotherapy Administration in the Overall Phase-Cycle 1 (Intent to Treat population) P208



The estimated median time to first vomiting was 94.5 hours in the aprepitant regimen group compared with 26.0 hours in the control regimen group (nominal p<0.0001, based on log-rank test).

The difference in vomiting-free time appears clearly clinically relevant. In the first 8 hours there appears to be no added benefit from aprepitant for this outcome measure, in line with the lower difference in responders in the acute phase observed for other endpoints.

Secondary endpoint –No Use of Rescue Medication

Table 14. Number (%) of Patients with No Use of Rescue Therapy by Phase and Treatment Group - Cycle 1 (Intent to Treat Population)

	Aprepitant Regimen n/m (%)	Control Regimen n/m (%)
Acute Phase	133 / 152 (87.5)	115 / 150 (76.7)
Delayed Phase	110 / 152 (72.4)	81 / 150 (54.0)
Overall Phase	101 / 152 (66.4)	73 / 150 (48.7)

n/m = Number of patients with desired response/number of patients included in time point
Acute Phase: 0 to 24 hours following initiation of chemotherapy.
Delayed Phase: 25 to 120 hours following initiation of chemotherapy.
Overall Phase: 0 to 120 hours following initiation of chemotherapy.

With regard to No use of rescue medicine, the difference in proportions between arms is similar, although somewhat smaller, in all phases than for the primary endpoint, the former being a less frequent event.

Ancillary analyses

Subgroup analyses

Table 15. Number (%) of Patients With Complete Response in the Overall Phase by Subgroup and Treatment Group - Cycle 1 (Intent to Treat Population) P208

	Aprepitant Regimen n/m (%)	Control Regimen n/m (%)
Age Group		
6 months to <2 years	9/19 (47.4)	4/16 (25.0)
2 years to <6 years	22/45 (48.9)	13/43 (30.2)
6 years to <12 years	12/41 (29.3)	9/43 (20.9)
12 years to 17 years	18/47 (38.3)	4/48 (8.3)
Gender Group		
Male	39/84 (46.4)	15/79 (19.0)
Female	22/68 (32.4)	15/71 (21.1)
Race Group		
White	47/119 (39.5)	24/110 (21.8)
Black	0/0	0/2 (0.0)
Asian	1/11 (9.1)	2/16 (12.5)
Multi-Racial	12/20 (60.0)	4/22 (18.2)
Other	1/2 (50.0)	0/0
Use of Dexamethasone as an Antiemetic in Cycle 1		
Yes	15/44 (34.1)	7/42 (16.7)
No	46/108 (42.6)	23/108 (21.3)
Receipt of a Very High Risk Emetogenic Chemotherapy Agent in Cycle 1		
Yes	35/99 (35.4)	14/101 (13.9)
No	26/53 (49.1)	16/49 (32.7)
Chemotherapy Duration in Cycle 1		
One Day of Chemotherapy	15/26 (57.7)	2/16 (12.5)
More Than 1 Day of Chemotherapy	46/126 (36.5)	28/134 (20.9)

† Complete Response = No vomiting or retching and no use of rescue medication.
‡ Overall Phase: 0 to 120 hours following initiation of chemotherapy.
n/m = Number of patients with desired response/number of patients included in time point

Table 16. Number (%) of Patients With Complete Response in the Delayed Phase by Subgroup and Treatment Group - Cycle 1 (Intent to Treat Population) P208

	Aprepitant Regimen n/m (%)	Control Regimen n/m (%)
Age Group		
6 months to <2 years	9/19 (47.4)	4/16 (25.0)
2 years to <6 years	25/45 (55.6)	16/43 (37.2)
6 years to <12 years	19/41 (46.3)	14/43 (32.6)
12 years to 17 years	24/47 (51.1)	5/48 (10.4)
Gender Group		
Male	47/84 (56.0)	19/79 (24.1)
Female	30/68 (44.1)	20/71 (28.2)
Race Group		
White	59/119 (49.6)	32/110 (29.1)
Black	0/0	0/2 (0.0)
Asian	2/11 (18.2)	2/16 (12.5)
Multi-Racial	14/20 (70.0)	5/22 (22.7)
Other	2/2 (100.0)	0/0
Use of Dexamethasone as an Antiemetic in Cycle 1		
Yes	16/44 (36.4)	9/42 (21.4)
No	61/108 (56.5)	30/108 (27.8)
Receipt of a Very High Risk Emetogenic Chemotherapy Agent in Cycle 1		
Yes	42/99 (42.4)	20/101 (19.8)
No	35/53 (66.0)	19/49 (38.8)
Chemotherapy Duration in Cycle 1		
One Day of Chemotherapy	21/26 (80.8)	5/16 (31.3)
More Than 1 Day of Chemotherapy	56/126 (44.4)	34/134 (25.4)
†Complete Response = No vomiting or retching and no use of rescue medication. ‡Delayed Phase: 25 to 120 hours following initiation of chemotherapy. n/m = Number of patients with desired response/number of patients included in time point		

Table 17.Number (%) of Patients With Complete Response in the Acute Phase by Subgroup and Treatment Group - Cycle 1 (Intent to Treat Population) P208

	Aprepitant Regimen n/m (%)	Control Regimen n/m (%)
Age Group		
6 months to <2 years	16/19 (84.2)	10/16 (62.5)
2 years to <6 years	36/45 (80.0)	33/43 (76.7)
6 years to <12 years	23/41 (56.1)	17/43 (39.5)
12 years to 17 years	26/47 (55.3)	18/48 (37.5)
Gender Group		
Male	59/84 (70.2)	42/79 (53.2)
Female	42/68 (61.8)	36/71 (50.7)
Race Group		
White	81/119 (68.1)	58/110 (52.7)
Black	0/0	2/2 (100.0)
Asian	5/11 (45.5)	8/16 (50.0)
Multi-Racial	14/20 (70.0)	10/22 (45.5)
Other	1/2 (50.0)	0/0
Use of Dexamethasone as an Antiemetic in Cycle 1		
Yes	31/44 (70.5)	19/42 (45.2)
No	70/108 (64.8)	59/108 (54.6)
Receipt of a Very High Risk Emetogenic Chemotherapy Agent in Cycle 1		
Yes	64/99 (64.6)	51/101 (50.5)
No	37/53 (69.8)	27/49 (55.1)
Chemotherapy Duration in Cycle 1		
One Day of Chemotherapy	19/26 (73.1)	5/16 (31.3)
More Than 1 Day of Chemotherapy	82/126 (65.1)	73/134 (54.5)
†Complete Response = No vomiting or retching and no use of rescue medication. ‡Acute Phase: 0 to 24 hours following initiation of chemotherapy. n/m = Number of patients with desired response/number of patients included in time point		

Sex

Male patients in the aprepitant arm responded in a higher frequency than female patients in all study phases, which was not the case in the control arm.

Use of corticosteroid and VHEC

The add-on efficacy of aprepitant was consistent in patients receiving and not receiving dexamethasone as anti-emetic in Cycle1, with around 20% additional responding patients in both groups in the overall phase. The add-on efficacy of aprepitant was also largely consistent in patients receiving and not receiving Very High Risk Emetogenic Chemotherapy (VHEC) in Cycle1, with 16-21% additional patients achieving Complete response in the overall phase.

Within each age group, the number of subjects who received ondansetron and dexamethasone was comparable between the 2 treatment groups. In addition, the mean daily doses for ondansetron and dexamethasone were either similar between treatment groups or higher in the control regimen group. The one exception is in the 12 to 17 age group where the mean daily ondansetron dose was higher in the aprepitant regimen group than in the control regimen group (14.6 vs. 11.9 mg), but the difference in effect between treatment arms in this age group was large and not likely explained by the difference in ondansetron use. As expected, the mean daily doses increased with increasing age. Differences in ondansetron or dexamethasone dosing are considered unlikely to have biased the interpretation of the clinical trial results in favour of aprepitant.

Duration of chemotherapy

The add-on efficacy was clearly higher in patients receiving a 1-day chemotherapy regimen (approximately 40-50% difference in Complete response in the three study phases) compared with chemotherapy regimens over more than one day (11-19% difference between arms in the three study phases).

Age

Different patterns of efficacy and add-on benefit of aprepitant were observed for all age groups with regard to proportions achieving Complete response in the three study phases:

The benefit of aprepitant was clearly clinically relevant in all three study phases in the 12-17 year age group, receiving the adult aprepitant regimen. The difference between arms in terms of complete response was thus 18%, 41% (an increase x 5 from 10 to 51%) and 30% for the acute, delayed and overall phases, respectively.

In the 6-11 year old group, the efficacy in the overall phase appears low, with only 8% difference between arms. However, in the acute and delayed phases the difference was larger, 14% and 17%, respectively. This pattern indicates that the patients failing in the acute phase were others than those failing in the delayed phase.

In the 2-5 year age group, the efficacy in the acute phase was high for both regimens (80.0% and 76.7%, respectively), resulting in a very small difference of 3% between regimens. For the delayed phase an 18% difference favouring aprepitant was seen, however, which was further propelled to the overall phase.

For the youngest group, 6 months – 1 year olds, the add-on benefit of aprepitant was consistently 22% in all three study phases, indicating that largely the same patients failed in the acute and delayed phase.

Overall, the demonstrated add-on efficacy in terms of Complete response is considered clinically relevant, with differences compared with the control arm at around 20% or above in the delayed and overall phases, while often smaller in the acute phase. In the age group 6-11 years (n=84), the add-on benefit of aprepitant appeared somewhat lower, however, coinciding with a lower mean AUC

predicted in this age group, compared with the other age groups by the population PK model based on studies P134, P097 and P148. However, other differences between adults and children than PK, such as chemotherapy regimens, may also have affected outcomes, and the effect observed at present dose is considered clinically relevant in all age groups.

Summary of main study(ies)

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

Summary of Efficacy for trial MK-0869-208

<table>
<tr><td colspan="3"><u>Title:</u>
A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial, Conducted Under In-House Blinding Conditions, to Examine the Efficacy and Safety of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Patients</td></tr>
<tr><td>Study identifier</td><td colspan="2">Protocol 208

EudraCT number: 2011-00651-16</td></tr>
<tr><td rowspan="2">Design</td><td colspan="2">A worldwide, multi-center, phase III, randomized, double-blind, parallel-group study with in-house blinding to assess the efficacy and safety or oral aprepitant for the prevention of CINV in pediatric patients aged 6 months to 17 years, receiving emetogenic chemotherapy for a documented malignancy.

Eligible patients were male or female, 6 months to 17 years of age, with documented malignancy at either original diagnosis or relapse, and scheduled to receive chemotherapeutic agent(s) associated with moderate, high risk, or very high risk of emetogenicity.</td></tr>
<tr><td>Duration of main phase:
Duration of Run-in phase:
Duration of Extension phase:</td><td>19 - 29 Days
Maximum of -28 days
Maximum of 6 months</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Primary Efficacy Hypothesis: The three-day oral aprepitant regimen will provide superior control of CINV compared to the control regimen as measured by the proportion of patients with Complete Response in the 25 to 120 hours following the initiation of emetogenic chemotherapy in Cycle 1.</td></tr>
</table>

Treatments groups	Aprepitant Regimen		Subjects 12 to 17 years of age: Day 1: aprepitant 125 mg capsule PO, 60 minutes prior to initiation of chemotherapy + ondansetron, at least 30 minutes prior to initiation of chemotherapy Days 2-3: aprepitant 80 mg PO Subjects <12 years of age: Day 1: aprepitant powder-for-suspension (PFS): 3.0 mg/kg (up to 125 mg), 60 minutes prior to initiation of chemotherapy + ondansetron, at least 30 minutes prior to initiation of chemotherapy Days 2-3: aprepitant (PFS): 2.0 mg/kg (up to 80 mg) Note: Intravenous dexamethasone was permitted as part of the antiemetic regimen for subjects in both treatment groups, at the discretion of the investigator. A dose reduction (50%) of dexamethasone was required for subjects in the aprepitant regimen.
	Control Regimen		Subjects 12 to 17 years of age: Day 1: matching placebo for aprepitant 125 mg capsule PO, 60 minutes prior to initiation of chemotherapy + ondansetron, at least 30 minutes prior to initiation of chemotherapy Days 2-3: matching placebo aprepitant 80 mg PO Subjects <12 years of age: Day 1: matching placebo aprepitant powder-for-suspension (PFS): 3.0 mg/kg (up to 125 mg), 60 minutes prior to initiation of chemotherapy + ondansetron, at least 30 minutes prior to initiation of chemotherapy Days 2-3: matching placebo aprepitant (PFS): 2.0 mg/kg (up to 80 mg) Note: Intravenous dexamethasone was permitted as part of the antiemetic regimen for subjects in both treatment groups, at the discretion of the investigator. No dose reduction of dexamethasone was required for subjects in the control regimen.
Endpoints and definitions	Primary endpoint	Complete Response – delayed phase	No vomiting, retching or dry heaves and no use of rescue medication in the 25 to 120 hours following the initiation of emetogenic chemotherapy
	Secondary endpoint	Complete Response – acute phase	No vomiting, retching or dry heaves and no use of rescue medication up to 24 hours following the initiation of emetogenic chemotherapy
	Secondary endpoint	Complete Response – overall phase	No vomiting, retching or dry heaves and no use of rescue medication up to 120 hours following the initiation of emetogenic chemotherapy
	Secondary endpoint	No Vomiting – overall phase	No emesis, retching, or dry heaves (regardless of use of rescue medication) up to 120 hours following the initiation of emetogenic chemotherapy

	Secondary endpoint	Safety and Tolerability	The broad clinical and laboratory adverse event (AE) categories consisting of patients with any AE, a drug related AE, a serious AE, and AE which is both drug-related and serious, and who discontinued due to an AE.	
Statistical methods	The treatment comparisons for Complete Response and No Vomiting was made using the Cochran-Mantel-Haenzel (CMH) test stratified by age (<2 years, 2 to 17 years), use of dexamethasone as an antiemetic in Cycle 1 (yes, no), and receipt of very high risk emetogenic chemotherapy agent in Cycle 1 (yes, no). CMH utilized the 1-tailed p-value and significance declared if the p-value was ≤0.025.			
Database lock	**29-Aug-2013**			

Results and Analysis

All analyses for efficacy and safety were performed according to the protocol.

Analysis description	**Primary Analysis:** Complete Response – delayed phase			
Analysis population and time point description	The Intent-to-Treat (ITT) population which consists of all patients randomized and who received study drug was the primary efficacy analysis population. In the ITT population response to therapy in a particular phase was assessed based on the observed data in that phase. Patients with missing binary data for the primary and secondary endpoints were classified as non-responder/failure in the ITT efficacy analyses. Definition of Complete response and Delayed phase, see above.			
Effect estimate per comparison	Complete Response – delayed phase (25 to 120 hours)	Comparison groups	Aprepitant Regimen (Cycle 1) n / m (%)	Control Regimen (Cycle 1) n / m (%)
		Superiority hypothesis done by comparing 1-tailed p-value to 0.025 and significance declared if p-value was ≤0.025	77 / 152 (50.7)	39 / 150 (26.0)
		P-value *(CMH test)*	p<0.0001	
Notes	n / m = number of patients with desired response/number of patients included in time point			
Analysis description	**Secondary analysis:** Complete Response – acute phase			
Analysis population and time point description	The Intent-to-Treat (ITT) population: all patients randomized and who received study drug. Definition of Complete response and Acute phase, see Endpoints and definitions above.			
Effect estimate per comparison	Complete Response – acute phase (0 to 24 hours)	Comparison groups	Aprepitant Regimen (Cycle 1)	Control Regimen (Cycle 1)
		n / m (%)	101 / 152 (66.4)	78 / 150 (52.0)
		P-value *(CMH test)*	nominal p=0.0135	

Notes	n / m = number of patients with desired response/number of patients included in time point			
Analysis description	**Secondary analysis:** Complete Response – overall phase			
Analysis population and time point description	The Intent-to-Treat (ITT) population: all patients randomized and who received study drug. Definition of Complete response and Overall phase, see Endpoints and definitions above.			
Effect estimate per comparison	Complete Response – overall phase (0 to 120 hours)	Comparison groups	Aprepitant Regimen (Cycle 1)	Control Regimen (Cycle 1)
		n / m (%)	61 / 152 (40.1)	30 / 150 (20.0)
		P-value *(CMH test)*	nominal p=0.0002	
Notes	n / m = number of patients with desired response/number of patients included in time point			
Analysis description	**Secondary analysis:** No Vomiting – overall phase			
Analysis population and time point description	The Intent-to-Treat (ITT) population: all patients randomized and who received study drug. Definition of No vomiting and Overall phase, see Endpoints and definitions above.			
Effect estimate per comparison	No Vomiting – overall phase (0 to 120 hours)	Comparison groups	Aprepitant Regimen (Cycle 1)	Control Regimen (Cycle 1)
		n / m (%)	71 / 152 (46.7)	32 / 150 (21.3)
		P-value *(CMH test)*	nominal p=<0.0001	
	No Vomiting – acute phase (0 to 24 hours)	n / m (%)	108 / 152 (71.1)	80 / 150 (53.3)
		P-value *(CMH test)*	nominal p=0.0023	
	No Vomiting – delayed phase (25 to 120 hours)	n / m (%)	84 / 152 (55.3)	42 / 150 (28.0)
		P-value *(CMH test)*	nominal p=<0.0001	
Notes	n / m = number of patients with desired response/number of patients included in time point			

Analysis description	**Secondary analysis**: Safety and Tolerability (Cycle 1)			
Analysis population and time point description	The All Patients as Treated (APaT) population which consists of all randomized patients who received at least one dose of study drug was used for the analysis of safety data.			
Effect estimate per comparison	Safety and Tolerability (Cycle 1)	Comparison groups	Aprepitant Regimen (Cycle 1)	Control Regimen (Cycle 1)
		Number of subjects	152 n (%)	150 n (%)
		with one or more adverse events	120 (78.9)	116 (77.3)
		Difference in % vs Control Regimen (Estimate 95% CI)	1.6 (-7.8, 11.0)	
		with no adverse events	32 (21.1)	34 (22.7)
		with drug-related adverse events	5 (3.3)	3 (2.0)
		Difference in % vs Control Regimen (Estimate 95% CI)	1.3 (-2.8, 5.7)	
		with serious adverse events	46 (30.3)	41 (27.3)
		Difference in % vs Control Regimen (Estimate 95% CI)	2.9 (-7.3, 13.1)	
		with serious drug-related adverse events	2 (1.3)	0 (0.0)
		Difference in % vs Control Regimen (Estimate 95% CI)	1.3 (-1.2, 4.7)	
		who died	1 (0.7)	0 (0.0)
		discontinued due to an adverse event	2 (1.3)	0 (0.0)
		Difference in % vs Control Regimen (Estimate 95% CI)	1.3 (-1.2, 4.7)	

		discontinued due to a drug-related adverse event	0 (0.0)	0 (0.0)
		discontinued due to a serious adverse event	2 (1.3)	0 (0.0)
		discontinued due to a serious drug-related adverse event	0 (0.0)	0 (0.0)
Notes	CI is based on the Miettinen & Nurminen method. Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.			
Analysis description	**Secondary analysis**: Safety and Tolerability (Optional open-label Cycles 2-6)			
Analysis population and time point description	The All Patients as Treated (APaT) population which consists of all randomized patients who received at least one dose of study drug was used for the analysis of safety data.			
Descriptive statistics and estimate variability	Treatment group		Aprepitant Regimen (Cycles 2-6)	
	Number of subjects		170 n (%)	
	with one or more adverse events		149 (87.6)	
	with no adverse events		21 (12.4)	
	with drug-related adverse events		7 (4.1)	
	with serious adverse events		84 (49.4)	
	with serious drug-related adverse events		1 (0.6)	
	who died		0 (0.0)	
	discontinued due to an adverse event		4 (2.4)	
	discontinued due to a drug-related adverse event		2 (1.2)	
	discontinued due to a serious adverse event		2 (1.2)	
	discontinued due to a serious drug-related adverse event		1 (0.6)	

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

Since this application consists of one single pivotal trial (Protocol 208) and exploratory, supportive data from two smaller studies (Protocols 097 and 134), no formal pooled efficacy analyses were performed across these studies as differences in the study designs and conduct did not support such an approach.

Nevertheless, the results of the exploratory efficacy analyses from the supportive studies were generally consistent with those of the pivotal study.

For example, the observed Complete Response proportions (%) in the overall phase (0 to 120 hour following chemotherapy) for subjects treated with aprepitant were 40.1, 28.6, and 45.0 in Protocols 208, 097, and 134, respectively. Comparing the active-controlled studies only (Protocols 208 and 097), the between-group difference in proportions (i.e., the difference in percentages of subjects achieving Complete Response in the overall phase, between the aprepitant and control arms) were 20.1 and 23.0 percentage points, respectively. The corresponding values for Complete Response in the acute phase (14.4 and 21.8, respectively) and delayed phase (24. 7 and 30.1, respectively) demonstrate a similar pattern. Although the smaller study size of Protocol 097 limits the ability to interpret subgroups, Complete Response rates were consistently higher in patients treated with aprepitant, which supports the findings observed in Protocol 208. These comparisons suggest that after accounting for differences in study populations, study designs and sample size, the efficacy of aprepitant was generally consistent.

Clinical studies in special populations

This variation intends the addition of a new pharmaceutical form (125 mg powder for oral suspension) for use in paediatric subpopulations with an age of 6 months to 11 years. No new data are submitted for other age groups than the paediatric population. This is accepted.

Supportive studies

Protocol 134 (P134)

"A Multi-center, Open-label, 5-Part Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Aprepitant and Fosaprepitant Dimeglumine in Pediatric Patients Receiving Emetogenic Chemotherapy"

- In this study both oral (aprepitant), IV (fosaprepitant), and combined IV + oral regimens were studied. All patients in all study parts received concomitant ondansetron IV +/- dexamethasone IV.

Protocol 134 enrolled a total of 91 paediatric subjects across the 5 Parts of the study who were 6 months to 17 years old (enrolment of subjects from birth to <6 months old was unsuccessful, despite over 2 year enrolment period), had a documented malignancy, and were undergoing emetogenic chemotherapy (HEC or MEC). Unique subjects were enrolled in Part I (Steps A and B) and Part II (Steps A and B). Those subjects enrolled in Part III could continue into the subsequent Parts (Part IV and Part V); subjects could also enrol in Part IV and/or Part V without participating in a previous Part. Of the 19 subjects who enrolled in Part III, 15 subjects continued into Part IV and 12 of those subjects continued into Part V.

Table 18. Study p134 summary of number of patients, age groups and regimens.

Part	Step	N	Ages	Regimen*	Corresponding adult aprepitant/fosaprepitant dose and regimen
I	A	12	12-17 y	Fosaprepitant 115 mg IV (Day 1) + Aprepitant 80 mg PO (Day 2 + 3)	115 mg IV + 80 mg PO + 80 mg PO
	B	11	12-17 y	Fosaprepitant 150 mg IV (Day 1)	150 mg IV single dose
II	A	19	6 m-<12 y	Aprepitant 47 mg/m^2 PO (Day 1)	80 mg PO single dose
	B	19	6 m-<12 y	Aprepitant 74 mg/m^2 alt. 1.3 mg/kg PO (Day 1)	125 mg PO single dose
III		19	6 m-<12 y	Ondansetron IV (Day 1-3)	*"Control arm"*
IV		20	6 m-<12 y	Aprepitant 3 mg/kg PO (Day 1) + Aprepitant 2 mg/kg PO (Day 2 + 3;)	125 mg PO+ 80 mg PO + 80 mg PO
V		23	6 m-<12 y	Fosaprepitant 3 mg/kg IV (Day 1)	150 mg IV single dose

*All patients in all study parts received concomitant ondansetron IV +/- dexamethasone IV.

Baseline data

With regard to type of malignancy, the variation of diagnoses across study steps and parts was quite wide, reflecting the rareness of the conditions and the small number of patients included in each part. In part I (ages 12-17) bone sarcomas dominated, while in the younger age groups of parts II-V (6 months -12 years) different -blastomas and other visceral neoplasms were predominant.

The heterogeneity with regard to malignancies and main emetogenic chemotherapy is summarised below.

Table 19. Summary of most frequent malignancy and emetogenic chemotherapy, P134

Part	Step	N	Ages	Most frequent malignancy	Most frequent HEC/MEC in study
I	A	12	12-17 y	Ewing sarcoma + osteosarcoma	Ifosfamide
	B	11		Osteosarcoma	Doxorubicin
II	A	19	6 m-<12 y	Osteosarcoma	Cisplatin
	B	19		No particular malignancy was more frequent	Cisplatin
III		19		Medulloblastoma and neuroblastoma	Doxorubicin
IV		20		Embryonal rhabdomyosarcoma, medulloblastoma and neuroblastoma	Cyclophosphamide
V		23		Medulloblastoma and neuroblastoma	Cyclophosphamide

HEC: highly emetogenic chemotherapy, MEC: moderately emetogenic chemotherapy, m: months, y: years.

The small numbers and nonrandomised nature of the study precludes any firm conclusions with regard to efficacy and safety based on comparisons across regimens. The possibility of using of Part III as "control" is limited due to the different HEC/MEC chemotherapy, among other heterogeneities across study parts.

Complete response

Table 20. Number (%) of Subjects with Complete Response by Phase, P134

Part I		Fosaprepitant (115 mg) Regimen (Step A)		Fosaprepitant (150 mg) Regimen (Step B)	
	Phase	n/m	% (CI)	n/m	% (CI)
	Acute	7 / 11	63.6 (30.8, 89.1)	10 / 11	90.9 (58.7, 99.8)
	Delayed	3 / 12	25.0 (5.5, 57.2)	8 / 11	72.7 (39.0, 94.0)
	Overall	2 / 11	18.2 (2.3, 51.8)	8 / 11	72.7 (39.0, 94.0)
Part II		Aprepitant (80 mg eq.) Regimen (Step A)		Aprepitant (125 mg eq.) Regimen (Step B)	
	Phase	n/m	% (CI)	n/m	% (CI)
	Acute	15 / 19	78.9 (54.4, 93.9)	11 / 18	61.1 (35.7, 82.7)

Part III, IV and V		Ondansetron (Part III)		Aprepitant Regimen (Part IV)		Fosaprepitant Regimen (Part V)	
	Phase	n/m	% (CI)	n/m	% (CI)	n/m	% (CI)
	Acute	5 / 19	26.3 (9.1, 51.2)	16 / 20	80.0 (56.3, 94.3)	16 / 22	72.7 (49.8, 89.3)
	Delayed	3 / 19	15.8 (3.4, 39.6)	12 / 20	60.0 (36.1, 80.9)	4 / 22	18.2 (5.2, 40.3)
	Overall	2 / 19	10.5 (1.3, 33.1)	9 / 20	45.0 (23.1, 68.5)	4 / 22	18.2 (5.2, 40.3)

Complete Response = No vomiting and no use of rescue therapy.

Source: CSR, Table 11-25, Table 11-26, and Table 11-27.

The proportions of patients in Part IV (6 months – 11 years; Aprepitant 3 mg/kg PO Day 1 + Aprepitant 2 mg/kg PO Day 2 + 3) achieving Complete response are noted: 80% in the acute phase, 60% in the delayed phase and 45% in the overall phase. This is very similar to the two age groups 6 months -1 year and 2 -5 years in the pivotal study P208, but higher than the 6-11years group.

Subgroup analyses

Subgroup analyses were performed; however, no generalizations can be made due to the small number of subjects in each subgroup.

Protocol 097 (P097)

"A Randomized, Double-Blind, Placebo-Controlled, Parallel- Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety, Tolerability, and Efficacy of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated With Emetogenic Chemotherapy in Adolescent Patients."

- In this study the adult aprepitant regimen was tested in adolescents.

Design: Multicentre, randomized, double-blind parallel-group, placebo controlled trial with in-house blinding to assess the safety, tolerability, plasma concentration and efficacy of aprepitant in the prevention of CINV in adolescent patients with confirmed malignancies and who were treated with an emetogenic chemotherapy regimen. The protocol had 2 parts. Part One of the protocol had 2 components with 2 dosing regimens: standard therapy regimen and aprepitant triple therapy regimen. The first component, which was blinded, focused on the first cycle (Cycle 1) of chemotherapy. The second component consisted of an optional open-label multiple-cycle extension for up to 9 subsequent cycles of chemotherapy (maximum of 10 cycles total). All patients received aprepitant during the multiple-cycle extension. Part 2 of the protocol had 2 components with 1 dosing regimen: aprepitant triple therapy in both Cycle 1 and in the multiple-cycle extension. As in Part One of the protocol, the first component focused on the first cycle (Cycle 1) of chemotherapy and the second component focused on the multiple-cycle extension for up to 9 subsequent cycles of chemotherapy (for a maximum of 10 cycles total).

Objectives: Safety was the primary objective of this study. Efficacy and PK were secondary objectives.

The study had 2 treatment groups:

Aprepitant triple therapy regimen = Aprepitant 125 mg P.O. on Day 1 and 80 mg once daily on Days 2 and 3 plus ondansetron (0.15 mg/kg x 3 doses) IV on Day 1 and 2 and dexamethasone 8 mg P.O. on Day 1 and 4 mg P.O. once daily on Days 2 to 4.

Standard therapy regimen = Ondansetron (0.15 mg/kg x 3 doses) IV on Day 1 and 2 plus dexamethasone 16 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.

Numbers analysed: 50 patients were randomised, 32 to the aprepitant arm, 18 to standard therapy.

Baseline factors

The distribution of known risk factors for CINV (female gender; history of alcohol use, morning sickness, motion sickness, and prior chemotherapy-induced vomiting) and the number of patients with and without prior chemotherapy was similar between treatment groups.

Median age was 15 years. 72% were male, 28% female.

Bone sarcoma was the most common primary cancer diagnosis. Of all patients entered in the study, 32 (64%) had bone sarcoma. Bone sarcoma occurred more frequently in the standard therapy group than in the aprepitant triple therapy group (83.3% and 53.1%, respectively).

Complete response

Table 21. Number (%) of Patients With Complete Response by Treatment and Phase (Modified-Intention-to-Treat Population) - Cycle 1 Part 1, P097

	Aprepitant Triple Therapy Regimen			Standard Therapy		
	n/m	(%)	(95% CI)	n/m	(%)	(95% CI)
Overall Phase	8/28	(28.6)	(13.2, 48.7)	1/18	(5.6)	(0.1, 27.3)
Acute Phase	17/28	(60.7)	(40.6, 78.5)	7/18	(38.9)	(17.3, 64.3)
Delayed Phase	10/28	(35.7)	(18.6, 55.9)	1/18	(5.6)	(0.1, 27.3)

† Complete Response = No vomiting and no use of rescue medicine.

n/m = Number of patients with desired response/number of patients included in time point.

Aprepitant Regimen = **Day 1:** Aprepitant 125 mg P.O., dexamethasone 8 mg P.O. and 3 doses of ondansetron 0.15 mg/kg IV (maximum total daily dose 32 mg); **Day 2:** Aprepitant 80 mg P.O., dexamethasone 4 mg P.O. and 3 doses of ondansetron 0.15 mg/kg IV (maximum total daily dose 32 mg) **Day 3:** Aprepitant 80 mg P.O., dexamethasone 4 mg P.O.; **Day 4:** Dexamethasone 4 mg P.O.

Standard Therapy = **Day 1:** Placebo for aprepitant 125 mg P.O., dexamethasone 16 mg P.O. and 3 doses of ondansetron 0.15 mg/kg IV (maximum total daily dose 32 mg) **Day 2:** Placebo for aprepitant 80 mg P.O., dexamethasone 8 mg P.O. and 3 doses of ondansetron 0.15 mg/kg IV (maximum total daily dose 32 mg); **Day 3:** Placebo for aprepitant 80 mg P.O., dexamethasone 8 mg P.O.; **Day 4:** Dexamethasone 8 mg P.O.

P.O. = By mouth; IV = Intravenous.

Overall Phase = 0 to 120 hours following initiation of emetogenic chemotherapy.

Acute Phase = 0 to 24 hours following initiation of emetogenic chemotherapy.

Delayed Phase = 25 to 120 hours following initiation of emetogenic chemotherapy.

The response rates in P097are *roughly* around similar levels as those in the pivotal study P208. (P208 Complete response frequencies for aprepitant (ITT): Overall 40%, Delayed 51%, Acute 66%).

Studies P134 and P097 are considered supportive of the results of the pivotal study P208.

Protocol 148 (P148)

In Protocol 148 Part II, 5-8 patients in each age group (6 months-<2 years; 2-6 years; 6-<12 years; 12-17 years) were randomized to receive a single oral dose of aprepitant (total N=27) or intravenous ondansetron (total N=25) prior to surgery. Ondansetron was administered as a single dose of

0.1mg/kg IV for patients weighing <40kg, and as a single fixed dose of 4mg IV for patients weighing ≥40kg. The dose of aprepitant administered in Part II was based upon the PK assessment for each age group in Part I: 15 mg + 1.1 mg/kg of aprepitant for patients 6 months to <12 years. Patients 12-17 years of age received 40 mg of aprepitant.

The efficacy assessment in Protocol 148 was exploratory. No Vomiting (No Vomiting, retching or dry heaves) and Complete Response (No Vomiting and no use of rescue medication) over the first 24 hours following surgery were the endpoints of primary interest. The Full Analysis Set (FAS) population served as the primary population for the analysis of efficacy data in this study. The FAS population was as a subset of all enrolled patients with subjects excluded for the following reasons: (1) failure to receive a full dose of active study therapy; (2) failure to have the surgery; and (3) lack of at least one post - treatment efficacy assessment.

Complete response

Table 22. Number (%) of Subjects with Complete Response in the 24 and 48 Hours Following End of Surgery by Treatment Group <FAS population - Part II>

24 Hours:

Complete Response	n/m	(%)	EXACT 95% CI[†]
Aprepitant	19/25	(76.0)	(54.9, 90.6)
Ondansetron	20/25	(80.0)	(59.3, 93.2)

CI = confidence interval.
[†]95% CI based on Clopper-Pearson exact CI method for proportions.

48 Hours:

Complete Response	n/m	(%)	EXACT 95% CI[†]
Aprepitant	17/25	(68.0)	(46.5, 85.1)
Ondansetron	20/25	(80.0)	(59.3, 93.2)

CI = confidence interval.
[†]95% CI based on Clopper-Pearson exact CI method for proportions.

P148 is not considered supportive with regard to efficacy for the present extension application (powder for solution) or the new sought paediatric indications, since used in a different indication (PONV). The data were not sufficient to determine a final dosing recommendation in this indication and no benefit compared with ondansetron was shown. Nevertheless the CHMP considers study P148 adequate to support the suggested SmPC updates (inclusion of the study results into sections 5.1 and 5.2) for the EMEND 40 mg capsules (PONV indication), where no new indication or new posology is proposed.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Protocol 208 (P208) randomized 307 paediatric subjects (302 were treated) with a documented malignancy undergoing moderate – very high emetogenic chemotherapy. Subjects were randomized in a 1:1 ratio to receive either aprepitant in combination with ondansetron (aprepitant regimen) or ondansetron alone (control regimen). Intravenous (IV) dexamethasone was only administered as part of the antiemetic regimen at the discretion of the investigator. Randomization was stratified into one of four age cohorts (12 years to 17 years, 6 years to <12 years, 2 years to <6 years, and 6 months to <2 years) based on the subject's age on Day 1 of chemotherapy in Cycle 1. There was an approximately even distribution of subjects in the 2 <6 year, 6 to <12 year, and 12 to 17 year cohorts (29.1%, 27.8%, and 31.5%, respectively), with similar distribution of age in each age cohorts between

the two treatment regimens. Due to enrolment challenges, the youngest cohort (6 months to <2 years of age) enrolled 11.6% of subjects. Subjects were further stratified in Cycle 1 based on the planned use of a chemotherapy agent associated with a Very High Risk of Emetogenicity (VHEC) and planned use of dexamethasone as part of the antiemetic regimen in Cycle 1. More than half of subjects received a VHEC agent (66.2%), while only 28.5% of subjects received prophylactic dexamethasone. Use of a VHEC agent and use of prophylactic dexamethasone was approximately evenly distributed between the treatment regimens.

P208 was a 1:1-randomised double-blind trial. The predefined definition of superiority was purely statistical requiring that a one-sided p-value < 0.025 was met.

Changes were made to the study protocol during the study with regard to primary and secondary objectives (delayed vs. overall study phase), and methods for analyses. In view of the results, these changes did not affect the overall results or interpretation thereof, however. The minimum age for inclusion was also changed from 0 to 6 months, in line with a waiver in the Paediatric Investigation Plan.

Concerning the optional Cycles 2-6 it is noted that only 27% of the patients included in Cycle 1 also completed all Cycles 2-6. For 30 % of patients this was explained by the fact that they completed the chemotherapy regimen before a total of 6 cycles had been administered. Furthermore, a large proportion (15%) did not fulfil the additional inclusion criteria for cycle 2-6. Only 1% discontinued due to adverse event. Still, there remains approximately 22% who did not complete due to patient (11%) or physician decision (11%). This could lower somehow the degree of evidence gained from this part of the study, (safety objectives only) but was not considered by the CHMP to a have a significant impact on the validity of the data.

Efficacy data and additional analyses

The primary endpoint was Complete response, defined as the proportion of patients with no vomiting, no retching, and no use of rescue medication, in the 25 to 120 hours following the initiation of emetogenic chemotherapy (delayed phase) in Cycle 1. In the ITT population, complete response in the delayed phase was achieved in 50.7% vs. 26.0% (p<0.0001) of patients in the aprepitant and control regimens, respectively. I.e. the proportion with Complete response was approximately doubled (with an absolute difference of 25%). The proportion with Complete response was also doubled (from 20 to 40%, nominal p=0.0002) in the overall phase (0-120 hours after chemotherapy start), and increased by one fourth (from 52 to 66%, nominal p=0.0135) in the acute phase (0-24 hours after start).

The Complete response results for the three study phases in the ITT population by the Cochran-Mantel-Haenzel (CMH) test method (primary endpoint, primary analysis population, and primary analysis method) were supported by very similar results in the FAS and PP populations, as well as by the results using a logistic regression model initially planned. As such, the results of the primary endpoint are considered robust.

The results from the secondary endpoint No vomiting further supported the primary endpoint with very similar (slightly larger) and highly statistically significant differences (by nominal p-values) between arms in the proportions of patients responding (i.e. having no vomiting) in all three phases.

The secondary endpoint Number of emetic episodes showed that in both the acute and delayed phase, the largest difference between arms was seen in the category with more than 3 emetic episodes, while smaller differences or similar proportions were seen for the categories with1, 2 or 3 emetic episodes. Thus, there is a relevant magnitude of effect in the group with the worst problems.

The estimated median time to first vomiting was 94.5 hours in the aprepitant regimen group compared with 26.0 hours in the control regimen group (nominal p<0.0001, based on log-rank test). This

difference in vomiting-free time appears clearly clinically relevant. In the first 8 hours there appears to be no added benefit from aprepitant for this outcome measure, in line with the lower difference in responders in the acute phase observed for other endpoints.

With regard to the endpoint No use of rescue medicine, the difference in proportions between arms is similar, although somewhat smaller, in all phases compared with the primary endpoint, reflecting that use of rescue medicine is a less frequent event and being one of the components of the composite primary endpoint Complete response.

Subgroup analyses

Male patients in the aprepitant arm responded in a higher frequency than female patients in all study phases, which was not the case in the control arm.

The add-on efficacy of aprepitant was consistent in patients receiving and not receiving dexamethasone as anti-emetic in Cycle1, with around 20% additional responding patients in both groups in the overall phase. The add-on efficacy of aprepitant was also largely consistent in patients receiving and not receiving Very High Risk Emetogenic Chemotherapy (VHEC) in Cycle1, with 16-21% additional patients achieving Complete response in the overall phase.

The add-on efficacy was clearly higher in patients receiving a 1-day chemotherapy regimen (approximately 40-50% difference in Complete response in the three study phases) compared with chemotherapy regimens over more than one day (11-19% difference between arms in the three study phases).

Different patterns of efficacy and add-on benefit of aprepitant were observed for all age groups with regard to proportions achieving Complete response in the three study phases.

Overall across age groups, the demonstrated add-on efficacy in terms of Complete response is considered clinically relevant, with differences compared with the control arm at around 20% or above in the delayed and overall phases, while often smaller in the acute phase.

The largest treatment effects were observed in the 12-17 year age group, receiving the adult aprepitant regimen, with absolute differences between arms of approximately 30% for the overall phase and 40% for the delayed phase (increased x 5, from 10 to 51%).

In the age group 6-11 years (n=84), the add-on benefit of aprepitant appeared generally somewhat lower, however, with 14% difference between arms in the delayed phase, compared to 22, 18, and 41% differences in the other age groups (6 m-2 y, 2-6y, 12-17y, respectively). This observation coincides with a lower mean AUC predicted in this age group compared with the other paediatric age groups by the population PK model based on studies P134, P097 and P148. Further PK-PD modelling analysis indicated that increasing doses on Day 2 and 3 in children under the age of 12 could increase concentrations to be more in the adult range; however available data are not sufficient to conclude that this would lead to clinically relevant improvements in outcomes. No change in dosing recommendations is therefore requested.

Supportive studies

The results of studies P134 (subset of main interest was part IV in ages 6-months-11 years receiving powder for oral solution) and P097 (adolescents receiving adult aprepitant regimen), both in the CINV indication, are considered supportive of the results of the pivotal study P208. Efficacy endpoints were exploratory in these studies.

The results from P148 were not sufficient to determine a final paediatric dosing recommendation in the PONV indication and did not indicate superior efficacy compared with ondansetron. With regard to efficacy, P148 is only relevant to the suggested SmPC changes for the EMEND 40 mg capsules (PONV

indication), where no new indication or new posology is proposed. The outcomes of the study are considered appropriately reflected in the SmPC.

2.5.4. Conclusions on the clinical efficacy

The demonstrated add-on efficacy of EMEND (aprepitant) to an antiemetic regimen consisting of the 5-HT3 inhibitor ondansetron with or without dexamethasone in paediatric patients in terms of Complete response (no vomiting/retching and no use of rescue medication) is considered clinically relevant, with increased proportions around 20% or more in the delayed and overall phases. The differences between arms were larger for the secondary endpoint No vomiting, where supportive rescue medication was not included as an event.

The superiority criterion for the primary objective was met (one-sided p-value < 0.025). While some differences in the magnitude of effect were seen in subgroups, the overall results of the pivotal study P208 are consistent across endpoints, study phases, analysis populations and methods, and therefore considered robust and convincing for the proposed extension of indication.

2.6. Clinical safety

The purpose of this application is to support approval for the use of aprepitant for the prevention of chemotherapy-induced nausea and vomiting (CINV) in the pediatric population. Exposure to aprepitant in this application includes a 3-day oral regimen with aprepitant in a powder for suspension (PFS) for children 6 months to <12 years of age and the oral aprepitant capsules (adult formulation) in adolescents 12 to 17 years of age along with a 5-HT3 antagonist with or without dexamethasone. This regimen was investigated in 3 clinical studies:

Table 23. Studies included in the Safety Discussion

Study Number, Phase, and Description	Dosing Regimen	Subject Study Medication Exposure
MK-0869-208 **(Phase III, Efficacy and Safety)** Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial, Conducted Worldwide, Under In-House Blinding Conditions to Examine Efficacy and Safety of Aprepitant for the Prevention of CINV ClinicalTrials.gov identifier: NCT01362530 **[Ref. 5.3.5.1: P208]**	**Cycle 1** Aprepitant Regimen Subjects 12 to 17 years of age: Day 1: aprepitant 125 mg capsule by mouth (PO) + ondansetron (Zofran™) - dose determined by investigator Days 2 and 3: aprepitant 80 mg capsule PO Regimen may include dexamethasone Subjects <12 years of age: Day 1: aprepitant PFS: 3.0 mg/kg (up to 125 mg) PO + ondansetron (Zofran™) - dose determined by investigator Days 2 and 3: aprepitant PFS: 2.0 mg/kg (up to 80 mg) PO Regimen may include dexamethasone Control Regimen Subjects 12 to 17 years of age: Day 1: matching placebo for aprepitant 125 mg capsule PO + ondansetron (Zofran™) Days 2 and 3: matching placebo for aprepitant 80 mg capsule PO Regimen may include dexamethasone Subjects <12 years of age: Day 1: matching placebo for aprepitant PFS: 3.0 mg/kg (up to 125 mg) PO + ondansetron (Zofran™) - dose determined by investigator Days 2 and 3: matching placebo for aprepitant PFS: 2.0 mg/kg (up to 80 mg) PO Regimen may include dexamethasone **Optional Cycles 2-6** Subjects 12 to 17 years of age: Day 1: aprepitant 125 mg capsule PO + ondansetron - dose determined by investigator Days 2 and 3: aprepitant 80 mg capsule PO Regimen may include dexamethasone Subjects < 12 years of age: Day 1: aprepitant PFS: 3.0 mg/kg (up to 125 mg) PO + ondansetron - dose determined by investigator Days 2 and 3: aprepitant PFS: 2.0 mg/kg (up to 80 mg) PO Regimen may include dexamethasone	**Cycle 1** Aprepitant regimen: 152 subjects[a] Control regimen: 150 subjects[b]

Study Number, Phase, and Description	Dosing Regimen	Subject Study Medication Exposure
MK-0869-097 **(Phase III, PK, Safety and Exploratory Efficacy)** Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study, Conducted Worldwide, Under In-House Blinding Conditions, to Examine PK, the Safety, Tolerability, and Efficacy of Aprepitant for the Prevention of CINV in Adolescent Subjects ClinicalTrials.gov identifier: NCT00080444 **[Ref. 5.3.5.1: P097]**	Subjects 12 to 17 years old: **Cycle 1 – Part I** Aprepitant Regimen Day 1: aprepitant 125 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 8 mg, PO Day 2: aprepitant 80 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 4 mg, PO Day 3: aprepitant 80 mg capsule PO + dexamethasone 4 mg PO Day 4: dexamethasone 4 mg PO Standard Therapy Day 1: dexamethasone 16 mg PO + ondansetron (0.15 mg/kg x 3 doses) IV Day 2: dexamethasone 8 mg PO + ondansetron (0.15 mg/kg x 3 doses) IV Days 3 and 4: dexamethasone 8mg PO **Cycle 1 – Part II** Open-label Aprepitant Regimen Day 1: aprepitant 125mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 8mg, PO Days 2: aprepitant 80 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 4 mg, PO Day 3: aprepitant 80 mg capsule PO + dexamethasone 4 mg PO Day 4: dexamethasone 4 mg PO **Optional Cycles 2-10** Day 1: aprepitant 125 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 8 mg, PO Day 2: aprepitant 80 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 4 mg, PO Day 3: aprepitant 80 mg capsule PO + dexamethasone 4 mg PO Day 4: dexamethasone 4 mg PO	**Cycle 1 – Part I** Aprepitant regimen: 28 subjects Control regimen: 18 subjects **Cycle 1 – Part II** Aprepitant regimen: 4 subjects

Study Number, Phase, and Description	Dosing Regimen	Subject Study Medication Exposure
MK-0869-134 **(Phase I, PK, Safety and Exploratory Efficacy)** A Multicenter, Open-label, 5-Part Study, Conducted Worldwide to Evaluate the Pharmacokinetics, Safety, and Tolerability of Aprepitant and Fosaprepitant Dimeglumine in Pediatric Subjects Receiving Emetogenic Chemotherapy[c] ClinicalTrials.gov identifier: NCT00818259 **[Ref. 5.3.3.2: P134]**	**Part I Step A** Subjects 12 to 17 years of age: Day 1: fosaprepitant 115 mg IV + ondansetron IV- dose determined by investigator Days 2 and 3: aprepitant PFS 80 mg PO + ondansetron IV - dose determined by investigator Regimen may include dexamethasone **Part IIA** Subjects 6 months to < 12 years of age: Day 1: aprepitant PFS dose equivalent to 80 mg PO with IV ondansetron- dose determined by investigator Regimen may include dexamethasone **Part IIB** Subjects 6 months to < 12 years of age: Day 1: aprepitant PFS dose equivalent to 125 mg PO with IV ondansetron - dose determined by investigator Regimen may include dexamethasone **Part IV** Subjects 6 months to <12 years of age: Day 1: aprepitant PFS at a dose equivalent to 125 mg with IV ondansetron - dose determined by investigator Days 2 and 3: oral aprepitant PFS at a dose equivalent to 80 mg with IV ondansetron - dose determined by investigator Regimen may include dexamethasone	**Part IA** Aprepitant on Days 2 and 3: 11 subjects[d] **Part IIA** Single-day regimen of aprepitant: 19 subjects **Part IIB** Single-day regimen of aprepitant: 19 subjects **Part IV** 3-day regimen of aprepitant: 20 subjects

[a] Three additional subjects were randomized but did not receive study medication.
[b] Two additional subjects were randomized but did not receive study medication.
[c] For the purposes of this document, only Part IV of Protocol 134 safety data is summarized since the 3 day aprepitant regimen was used. Safety data from Parts I and II are not included but can be found in the Clinical Study Report [Ref. 5.3.3.2: P134].
[d] One additional subject did not receive oral aprepitant on Days 2 or 3 of the treatment regimen. The subject received study medication on Day 1 (fosaprepitant) and was discontinued.

As the MK-0869-208 (Phase III, Efficacy and Safety) is the pivotal study and comprises the majority of patients, main focus will be on this study whereas data from MK-0869-097 and MK-0869-134 will be regarded as supportive.

Data presented below refers to study 208 unless otherwise noted.

Patient exposure

Table 24. Extent of Exposure to Aprepitant by Dose <Cycle 1>, Study 208

Aprepitant	1 Day	2 Days	3 Days	> 3 Days	Total Subjects	Duration Range	Mean Duration
Any Dose	2	1	149	0	152	1 to 3 days	3.0 days

A table showing exposure in the various age groups (6 months to<2y, 2y to <6y, etc) may have been more relevant, but almost all patients in study 208 fulfilled study treatment in Cycle 1 as seen in the table.

In the table below from module 2.7.4, exposure in the various paediatric age-groups is shown. For the combined group of patients from studies 208 and 097, all patients <12 years of age are from study 208 as study 097 enrolled only adolescents 12 to 17 years.

Table 25. Number of Subjects Exposed to Aprepitant By Age Category Protocols 208, 097 Combined (Cycles 1 to 10), and 134 (Parts I, II, and IV)

		Aprepitant Exposure†			
Age Group	PN208 and PN097 Combined (Cycles 1-10)	PN134 (Part I)	PN134 (Part II)	PN134 (Part IV)	Total
6 months to < 2 years	31	0	11	7	49
2 years to < 6 years	63	0	15	6	84
6 years to < 12 years	72	0	12	7	91
12 years to < 18 years	120	11	0	0	131
18 years to 19 years	2	0	0	0	2
Total	288	11	38	20	357
†Number of subjects who received at least one dose of aprepitant.					

† Number of subjects who received at least one dose of aprepitant.

Subjects in Part IV of Study 134 were 6 months to <12 years of age and received aprepitant in the same regimen as in Studies 208 and 097.

Extent of Exposure - Ondansetron Cycle 1

All randomized subjects were required to receive ondansetron on Day 1; branded ondansetron (ZofranTM) was required in Cycle 1. The dose of ondansetron was determined by the investigator based on the product label for pediatric usage or local standard of care.

Table 26. Extent of Exposure to Ondansetron by Dose for Aprepitant Regimen <Cycle 1>

Ondansetron	1 Day	2 Days	3 Days	4 Days	5 Days	> 5 Days	Total Subjects	Duration Range	Mean Duration
Any Dose	41	21	37	31	10	12	152	1 to 9 days	3.0 days

Source: CSR, Table 12-2

Table 27. Extent of Exposure to Ondansetron by Dose for Control Regimen <Cycle 1>

Ondansetron	1 Day	2 Days	3 Days	4 Days	5 Days	> 5 Days	Total Subjects	Duration Range	Mean Duration
Any Dose	49	20	33	23	15	10	150	1 to 8 days	2.8 days

Subjects receiving multi-day chemotherapy were permitted to receive preventative antiemetic treatment with ondansetron after Day 1 on days that chemotherapy was administered, if clinically

indicated and consistent with local standard of care. Once the chemotherapy regimen was complete, ondansetron was no longer permitted as prophylactic treatment. Ondansetron exposure when used as rescue medication is not reflected in this table.

Extent of Exposure - Dexamethasone Cycle 1

Subjects in both treatment regimens were permitted to receive preventative antiemetic treatment with intravenous dexamethasone on each day that chemotherapy was administered, at the discretion of the investigator. Once the chemotherapy regimen was complete, dexamethasone was no longer permitted as prophylactic treatment.

The dose of dexamethasone was determined by the investigator based on the product label for pediatric usage or local standard of care. If dexamethasone was administered to a subject randomized to receive aprepitant, the dose of intravenous dexamethasone to be administered was reduced by 50% on Days 1-4 due to the effects of aprepitant on the pharmacokinetics of dexamethasone

Table 28. Extent of Exposure to Dexamethasone by Dose for Aprepitant Regimen <Cycle 1>

Dexamethasone	1 Day	2 Days	3 Days	4 Days	5 Days	> 5 Days	Total Subjects	Duration Range	Mean Duration
Any Dose	10	4	12	9	4	3	42	1 to 7 days	3.1 days

Table 29. Extent of Exposure to Dexamethasone by Dose for Control Regimen <Cycle 1>

Dexamethasone	1 Day	2 Days	3 Days	4 Days	5 Days	> 5 Days	Total Subjects	Duration Range	Mean Duration
Any Dose	7	6	21	5	3	2	44	1 to 7 days	3.0 days

Exposure of the co-medications ondansetron and dexamethasone was similar in the 2 arms during cycle 1, except the lower dose of dexamethasone prescribed for subjects in the experimental arm.

Extent of Exposure - Cycles 2 - 6

The number of subjects that entered each cycle between 2 and 6 in study 208 is displayed in Table 10-6 below.

Table 30. Study 208 Number of Subjects in Each Cycle <Cycles 2-6>

	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Number of Patients	**171**	**126**	**92**	**72**	**47**

In both protocols 208 and 097, eligible subjects had the opportunity to receive open-label aprepitant in subsequent cycles identical to the aprepitant treatment plan in Cycle 1 (up to 6 cycles in Protocol 208 and up to 10 cycles in Protocol 097), if they elected to participate. Many subjects did not participate in all additional cycles for a variety of reasons, such as completion of chemotherapy cycles, lack of response to chemotherapy, progression of cancer, and/or chemotherapy side effects.

Table 31 Clinical trial exposure to aprepitant (PFS formulation) by duration of exposure for pediatric patients (Totals for Protocols 134 (Parts IA, II and IV) and 208 (6 mos. to <12 years of age) Pediatric CINV studies and Protocol 148 Pediatric PONV study)

Minimum exposure	Persons	Person time (in years)
1 to 3 days	202	1.0
4 to 6 days	27	0.4
7 to 9 days	20	0.5
10 to 12 days	12	0.4
13 to 15 days	28	1.1
16 to 18 days	17	0.8

Table 32 Clinical trial exposure to aprepitant (all formulations) by duration of exposure for pediatric patients (6 months to 17 years of age) (Totals for Protocols 097, 134 (Parts IA, II and IV) and 208 Pediatric CINV studies and Protocol 148 Pediatric PONV study)

Minimum exposure	Persons	Person time (in years)
1 to 3 days	242	1.3
4 to 6 days	50	0.8
7 to 9 days	41	1.0
10 to 12 days	30	1.0
13 to 15 days	37	1.5
16 to 18 days	26	1.3
19 to 24 days	2	0.1
25 to 30 days	1	0.1

The duration of exposure to aprepitant has been further clarified following the D120 LoQ. Patients in P148 were exposed to aprepitant on a single day, and patients in P134 were exposed for a maximum of 3 days in conjunction with a single cycle of chemotherapy resulting in a higher number of subjects exposed from 1-3 days. Exposures in the two studies that offered an open – label extension for subsequent chemotherapy cycles allowed for exposures up to 18 days in P208 and up to 30 days in P097. This explains why the majority of paediatric subjects (comprising all studies and all formulations) had an exposure of 1-3 days.

In study 208 a similar number of subjects from each Cycle 1 treatment regimen entered the optional Cycles 2-6: 83 subjects from the aprepitant regimen and 88 subjects from the control regimen elected to participate in the optional cycles.

Table 37 Number of Subjects in Each Cycle, Cycles 2-6

	Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6	
Number of Patients	171		126		92		72		47	
	Aprepitant (A)	Control (C)	A	C	A	C	A	C	A	C
	83	88	61	65	44	48	37	35	23	24

Data Source: [Protocol 208]

The purpose of the optional extensions was primarily to provide additional supportive evidence for the safety and tolerability of the aprepitant regimen, in support of the primary evidence derived from the controlled portion of the study (Cycle 1). Discontinuations during the optional extensions could in theory bias the interpretation of these supportive data, given the overall similarities in the safety/tolerability profiles between Cycle 1 and the optional extension cycles.

Adverse events

Table 33. Analysis of Adverse Event Summary <Cycle 1>

	Aprepitant Regimen		Control Regimen		Difference in % vs Control Regimen
	n	(%)	n	(%)	Estimate (95% CI)†
Subjects in population	152		150		
with one or more adverse events	120	(78.9)	116	(77.3)	1.6 (-7.8, 11.0)
with no adverse events	32	(21.1)	34	(22.7)	
with drug-related‡ adverse events	5	(3.3)	3	(2.0)	1.3 (-2.8, 5.7)
with serious adverse events	46	(30.3)	41	(27.3)	2.9 (-7.3, 13.1)
with serious drug-related adverse events	2	(1.3)	0	(0.0)	1.3 (-1.2, 4.7)
who died	1	(0.7)	0	(0.0)	
discontinued§ due to an adverse event	2	(1.3)	0	(0.0)	1.3 (-1.2, 4.7)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	
discontinued due to a serious adverse event	2	(1.3)	0	(0.0)	
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	

† Based on Miettinen & Nurminen method.
‡ Determined by the investigator to be related to the drug.
§ Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Table 34. Adverse Event Summary by Age Category <Cycle 1>

	6 Months To <2 Years				2 To <6 Years				6 To <12 Years				12 To 17 Years			
	Aprepitant Regimen		Control Regimen		Aprepitant Regimen		Control Regimen		Aprepitant Regimen		Control Regimen		Aprepitant Regimen		Control Regimen	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	19		16		45		43		41		43		47		48	
with one or more adverse events	13	(68.4)	13	(81.3)	37	(82.2)	31	(72.1)	34	(82.9)	34	(79.1)	36	(76.6)	38	(79.2)
with no adverse event	6	(31.6)	3	(18.8)	8	(17.8)	12	(27.9)	7	(17.1)	9	(20.9)	11	(23.4)	10	(20.8)
with drug-related† adverse events	1	(5.3)	1	(6.3)	1	(2.2)	0	(0.0)	0	(0.0)	1	(2.3)	3	(6.4)	1	(2.1)
with serious adverse events	4	(21.1)	7	(43.8)	18	(40.0)	11	(25.6)	9	(22.0)	15	(34.9)	15	(31.9)	8	(16.7)
with serious drug-related adverse events	1	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)	1	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	1	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Data Source: [16.4]

Adverse events were reported by 236 (78.1%) of the 302 subjects included in the safety analysis and were comparable between the treatment regimens. In general, the adverse event profile observed was typical of a patient population with cancer receiving emetogenic chemotherapy.

Table 12-9 displays the adverse events summary by age category and treatment group. Although some variability was observed for the incidence of serious adverse events between the treatment regimens and age categories, there was no consistent pattern noted within an age category or specific adverse event. All other adverse event subgroups appear similar between treatment groups.

Table 35. Adverse Event Summary <Cycles 2-6>

	Aprepitant Regimen	
	n	(%)
Subjects in population	170	
with one or more adverse events	149	(87.6)
with no adverse event	21	(12.4)
with drug-related† adverse events	7	(4.1)
with serious adverse events	84	(49.4)
with serious drug-related adverse events	1	(0.6)
who died	0	(0.0)
discontinued‡ due to an adverse event	4	(2.4)
discontinued due to a drug-related adverse event	2	(1.2)
discontinued due to a serious adverse event	2	(1.2)
discontinued due to a serious drug-related adverse event	1	(0.6)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.

Table 36. Adverse Event Summary by Age Category <Cycles 2-6>

	Aprepitant Regimen							
	6 Months To <2 Years		2 To <6 Years		6 To <12 Years		12 To 17 Years	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	21		44		53		52	
with one or more adverse events	18	(85.7)	39	(88.6)	47	(88.7)	45	(86.5)
with no adverse event	3	(14.3)	5	(11.4)	6	(11.3)	7	(13.5)
with drug-related† adverse events	1	(4.8)	1	(2.3)	3	(5.7)	2	(3.8)
with serious adverse events	11	(52.4)	24	(54.5)	28	(52.8)	21	(40.4)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	1	(1.9)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	1	(2.3)	3	(5.7)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	2	(3.8)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	1	(2.3)	1	(1.9)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	1	(1.9)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.

Data Source: [16.4]

As for treatment cycle 1, there was no consistent pattern noted within an age category or specific adverse event. Most AE categories occurred in somewhat higher percentages during cycles 2-6 than during cycle 1, which may be expected due to the larger cumulative exposure of chemotherapy.

Following the CHMP's request during this evaluation, the MAH also provided tables summarizing incidences of severe (grade 3-5) AEs in the aprepitant and control arms, and age the groups in respective arms. A similar table has also been presented for cycles 2-6. In cycle 1 there was some variability observed for the incidence of serious adverse events between the treatment regimens and age categories, but no consistent pattern was noted within an age category or specific adverse event.

In cycles 2-6, the adverse event profile was generally similar to that observed in Cycle 1, and no new safety signals were identified based on toxicity grading.

Overall adverse events

The adverse events mentioned above occurred at similar incidence between both treatment regimens, with the exception of anemia, which occurred at a slightly higher incidence in the control regimen.

Overall, the adverse events observed were comparable to the types of adverse events observed in patients with cancer receiving emetogenic chemotherapy.

Table 37. Subjects With Specific Adverse Events By System Organ Class (Incidence ≥ 1% in One or More Treatment Groups) <Cycle 1>

	n	Aprepitant Regimen (%)	n	Control Regimen (%)
Subjects in population	152		150	
with one or more adverse events	120	(78.9)	116	(77.3)
with no adverse events	32	(21.1)	34	(22.7)
Blood and lymphatic system disorders	**60**	**(39.5)**	**64**	**(42.7)**
Anaemia	26	(17.1)	38	(25.3)
Febrile neutropenia	24	(15.8)	24	(16.0)
Leukopenia	8	(5.3)	10	(6.7)
Lymphopenia	0	(0.0)	2	(1.3)
Neutropenia	21	(13.8)	18	(12.0)
Pancytopenia	4	(2.6)	6	(4.0)
Thrombocytopenia	15	(9.9)	16	(10.7)
Ear and labyrinth disorders	**2**	**(1.3)**	**2**	**(1.3)**
Eye disorders	**5**	**(3.3)**	**1**	**(0.7)**
Conjunctivitis	2	(1.3)	0	(0.0)
Gastrointestinal disorders	**53**	**(34.9)**	**49**	**(32.7)**
Abdominal pain	11	(7.2)	10	(6.7)
Constipation	3	(2.0)	6	(4.0)
Diarrhoea	8	(5.3)	8	(5.3)
Nausea	13	(8.6)	17	(11.3)
Odynophagia	2	(1.3)	2	(1.3)
Oral pain	0	(0.0)	3	(2.0)
Proctalgia	2	(1.3)	2	(1.3)

	n	Aprepitant Regimen (%)	n	Control Regimen (%)
Stomatitis	6	(3.9)	4	(2.7)
Toothache	2	(1.3)	0	(0.0)
Vomiting	23	(15.1)	23	(15.3)
General disorders and administration site conditions	**23**	**(15.1)**	**25**	**(16.7)**
Asthenia	2	(1.3)	0	(0.0)
Fatigue	4	(2.6)	3	(2.0)
Mucosal inflammation	3	(2.0)	7	(4.7)
Oedema peripheral	2	(1.3)	0	(0.0)
Pyrexia	8	(5.3)	12	(8.0)
Immune system disorders	**3**	**(2.0)**	**2**	**(1.3)**
Hypersensitivity	1	(0.7)	2	(1.3)
Infections and infestations	**23**	**(15.1)**	**23**	**(15.3)**
Candidiasis	2	(1.3)	0	(0.0)
Device related infection	2	(1.3)	2	(1.3)
Nasopharyngitis	2	(1.3)	4	(2.7)
Oral candidiasis	2	(1.3)	0	(0.0)
Pneumonia	0	(0.0)	2	(1.3)
Rhinitis	1	(0.7)	4	(2.7)
Upper respiratory tract infection	2	(1.3)	1	(0.7)
Urinary tract infection	5	(3.3)	5	(3.3)
Injury, poisoning and procedural complications	**7**	**(4.6)**	**5**	**(3.3)**
Accidental overdose	1	(0.7)	4	(2.7)
Allergic transfusion reaction	0	(0.0)	2	(1.3)
Transfusion reaction	2	(1.3)	0	(0.0)
Investigations	**41**	**(27.0)**	**39**	**(26.0)**
Alanine aminotransferase increased	4	(2.6)	7	(4.7)
Aspartate aminotransferase increased	4	(2.6)	6	(4.0)
Blood potassium decreased	3	(2.0)	0	(0.0)
Eosinophil count increased	2	(1.3)	0	(0.0)

	n	Aprepitant Regimen (%)	n	Control Regimen (%)
Haematocrit decreased	3	(2.0)	0	(0.0)
Haemoglobin decreased	8	(5.3)	6	(4.0)
Lymphocyte count decreased	2	(1.3)	1	(0.7)
Neutrophil count decreased	13	(8.6)	19	(12.7)
Platelet count decreased	12	(7.9)	15	(10.0)
Transaminases increased	3	(2.0)	2	(1.3)
White blood cell count decreased	6	(3.9)	6	(4.0)
Metabolism and nutrition disorders	**12**	**(7.9)**	**16**	**(10.7)**
Decreased appetite	4	(2.6)	4	(2.7)
Dehydration	0	(0.0)	3	(2.0)
Hypocalcaemia	0	(0.0)	2	(1.3)
Hypokalaemia	1	(0.7)	7	(4.7)
Metabolism and nutrition disorders	**12**	**(7.9)**	**16**	**(10.7)**
Hypomagnesaemia	3	(2.0)	4	(2.7)
Hyponatraemia	2	(1.3)	3	(2.0)
Hypophosphataemia	2	(1.3)	4	(2.7)
Musculoskeletal and connective tissue disorders	**8**	**(5.3)**	**2**	**(1.3)**
Bone pain	2	(1.3)	0	(0.0)
Pain in extremity	3	(2.0)	1	(0.7)
Nervous system disorders	**16**	**(10.5)**	**13**	**(8.7)**
Dizziness	4	(2.6)	1	(0.7)
Headache	11	(7.2)	7	(4.7)
Psychiatric disorders	**2**	**(1.3)**	**1**	**(0.7)**
Renal and urinary disorders	**3**	**(2.0)**	**0**	**(0.0)**
Glycosuria	2	(1.3)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**17**	**(11.2)**	**11**	**(7.3)**
Cough	9	(5.9)	5	(3.3)
Epistaxis	3	(2.0)	3	(2.0)
Hiccups	2	(1.3)	0	(0.0)

	n	Aprepitant Regimen (%)	n	Control Regimen (%)
Rhinorrhoea	2	(1.3)	1	(0.7)
Skin and subcutaneous tissue disorders	**9**	**(5.9)**	**8**	**(5.3)**
Dermatitis allergic	2	(1.3)	1	(0.7)
Rash	2	(1.3)	2	(1.3)
Vascular disorders	**3**	**(2.0)**	**2**	**(1.3)**

Adverse Events by National Cancer Institute Toxicity Criteria – Cycle 1

The most commonly reported severe clinical adverse events (NCI Toxicity Grades 3 and 4) overall were febrile neutropenia, anaemia, and neutrophil count decrease.

Table 38. Subjects With Specific Adverse Events by Maximum Toxicity Grade (Incidence ≥5% in One or More Treatment Groups) <Cycle 1>

	Aprepitant Regimen		Control Regimen		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	152		150		302	
with one or more adverse events	120	(78.9)	116	(77.3)	236	(78.1)
with no adverse events	32	(21.1)	34	(22.7)	66	(21.9)
Blood and lymphatic system disorders	**60**	**(39.5)**	**64**	**(42.7)**	**124**	**(41.1)**
Anaemia	26	(17.1)	38	(25.3)	64	(21.2)
Grade 1	4	(2.6)	4	(2.7)	8	(2.6)
Grade 2	6	(3.9)	8	(5.3)	14	(4.6)
Grade 3	12	(7.9)	25	(16.7)	37	(12.3)
Grade 4	2	(1.3)	1	(0.7)	3	(1.0)
Unknown	2	(1.3)	0	(0.0)	2	(0.7)
Febrile neutropenia	24	(15.8)	24	(16.0)	48	(15.9)
Grade 1	0	(0.0)	2	(1.3)	2	(0.7)
Grade 2	1	(0.7)	1	(0.7)	2	(0.7)
Grade 3	19	(12.5)	17	(11.3)	36	(11.9)
Grade 4	4	(2.6)	4	(2.7)	8	(2.6)
Leukopenia	8	(5.3)	10	(6.7)	18	(6.0)
Grade 1	7	(4.6)	4	(2.7)	11	(3.6)
Grade 3	1	(0.7)	5	(3.3)	6	(2.0)
Grade 4	0	(0.0)	1	(0.7)	1	(0.3)
Neutropenia	21	(13.8)	18	(12.0)	39	(12.9)
Grade 1	2	(1.3)	1	(0.7)	3	(1.0)
Grade 2	4	(2.6)	2	(1.3)	6	(2.0)
Grade 3	7	(4.6)	7	(4.7)	14	(4.6)
Grade 4	7	(4.6)	8	(5.3)	15	(5.0)
Unknown	1	(0.7)	0	(0.0)	1	(0.3)
Thrombocytopenia	15	(9.9)	16	(10.7)	31	(10.3)
Grade 1	7	(4.6)	2	(1.3)	9	(3.0)
Grade 2	4	(2.6)	1	(0.7)	5	(1.7)
Grade 3	3	(2.0)	7	(4.7)	10	(3.3)
Grade 4	1	(0.7)	6	(4.0)	7	(2.3)
Gastrointestinal disorders	**53**	**(34.9)**	**49**	**(32.7)**	**102**	**(33.8)**
Abdominal pain	11	(7.2)	10	(6.7)	21	(7.0)
Grade 1	9	(5.9)	4	(2.7)	13	(4.3)
Grade 2	2	(1.3)	5	(3.3)	7	(2.3)
Unknown	0	(0.0)	1	(0.7)	1	(0.3)
Diarrhoea	8	(5.3)	8	(5.3)	16	(5.3)
Grade 1	7	(4.6)	5	(3.3)	12	(4.0)
Grade 2	1	(0.7)	1	(0.7)	2	(0.7)
Grade 3	0	(0.0)	1	(0.7)	1	(0.3)
Grade 4	0	(0.0)	1	(0.7)	1	(0.3)
Nausea	13	(8.6)	17	(11.3)	30	(9.9)
Grade 1	6	(3.9)	10	(6.7)	16	(5.3)
Grade 2	6	(3.9)	6	(4.0)	12	(4.0)
Grade 3	0	(0.0)	1	(0.7)	1	(0.3)
Grade 4	1	(0.7)	0	(0.0)	1	(0.3)
Vomiting	23	(15.1)	23	(15.3)	46	(15.2)
Grade 1	15	(9.9)	11	(7.3)	26	(8.6)
Grade 2	4	(2.6)	7	(4.7)	11	(3.6)
Grade 3	3	(2.0)	4	(2.7)	7	(2.3)
Grade 4	1	(0.7)	1	(0.7)	2	(0.7)
General disorders and administration site conditions	**23**	**(15.1)**	**25**	**(16.7)**	**48**	**(15.9)**
Pyrexia	8	(5.3)	12	(8.0)	20	(6.6)
Grade 1	6	(3.9)	11	(7.3)	17	(5.6)
Grade 2	2	(1.3)	0	(0.0)	2	(0.7)
Grade 3	0	(0.0)	1	(0.7)	1	(0.3)
Infections and infestations	**23**	**(15.1)**	**23**	**(15.3)**	**46**	**(15.2)**

	Aprepitant Regimen		Control Regimen		Total	
	n	(%)	n	(%)	n	(%)
Investigations	**41**	**(27.0)**	**39**	**(26.0)**	**80**	**(26.5)**
Haemoglobin decreased	8	(5.3)	6	(4.0)	14	(4.6)
Grade 1	2	(1.3)	0	(0.0)	2	(0.7)
Grade 3	6	(3.9)	6	(4.0)	12	(4.0)
Neutrophil count decreased	13	(8.6)	19	(12.7)	32	(10.6)
Grade 1	2	(1.3)	0	(0.0)	2	(0.7)
Neutrophil count decreased	13	(8.6)	19	(12.7)	32	(10.6)
Grade 2	0	(0.0)	2	(1.3)	2	(0.7)
Grade 3	3	(2.0)	3	(2.0)	6	(2.0)
Grade 4	8	(5.3)	14	(9.3)	22	(7.3)
Platelet count decreased	12	(7.9)	15	(10.0)	27	(8.9)
Grade 1	0	(0.0)	2	(1.3)	2	(0.7)
Grade 2	2	(1.3)	3	(2.0)	5	(1.7)
Grade 3	6	(3.9)	5	(3.3)	11	(3.6)
Grade 4	4	(2.6)	5	(3.3)	9	(3.0)
Metabolism and nutrition disorders	**12**	**(7.9)**	**16**	**(10.7)**	**28**	**(9.3)**
Musculoskeletal and connective tissue disorders	**8**	**(5.3)**	**2**	**(1.3)**	**10**	**(3.3)**
Nervous system disorders	**16**	**(10.5)**	**13**	**(8.7)**	**29**	**(9.6)**
Headache	11	(7.2)	7	(4.7)	18	(6.0)
Grade 1	9	(5.9)	6	(4.0)	15	(5.0)
Grade 2	2	(1.3)	1	(0.7)	3	(1.0)
Respiratory, thoracic and mediastinal disorders	**17**	**(11.2)**	**11**	**(7.3)**	**28**	**(9.3)**
Cough	9	(5.9)	5	(3.3)	14	(4.6)
Grade 1	6	(3.9)	5	(3.3)	11	(3.6)
Grade 2	3	(2.0)	0	(0.0)	3	(1.0)
Skin and subcutaneous tissue disorders	**9**	**(5.9)**	**8**	**(5.3)**	**17**	**(5.6)**

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.

Data Source: [16.4]

In the table above, specific adverse events appear if the overall incidence of the event, regardless of grade, was ≥5%. In cases where only the System Organ Class (SOC) appears, e.g., 'Infections and Infestations', the incidence of adverse events from that system organ class was ≥5%, though not one single adverse event within that SOC reached that incidence.

The severe clinical adverse events (NCI Toxicity Grades 3 and 4) seem overall similar between the arms. The incidence of the adverse event of anemia as measured by the NCI criteria was slightly higher in subjects in the control regimen as compared with subjects in the aprepitant regimen (16.7% and 7.9%, respectively) for Grade 3 toxicity. The incidence of anemia classified as a Grade 4 toxicity was similar between treatment regimens.

Adverse Events by National Cancer Institute Toxicity Criteria – Cycles 2- 6

According to the CSR 208, and as further clarified in the responses from the MAH, there were only small differences between the treatment arms for Cycle 1 and the adverse event profile in cycle 1 and cycles 2-6. The most frequently reported events were haematological (anemia, febrile neutropenia, neutropenia) and gastrointestinal (nausea and vomiting) in nature. While these events occurred at a higher incidence in cycles 2-6 compared to cycle 1, this is not unexpected given subjects receiving multiple cycles of chemotherapy are more susceptible to experience more hematologic and gastrointestinal adverse events. The most commonly reported severe clinical adverse events (NCI Toxicity Grades 3 and 4) overall were febrile neutropenia and anaemia.

Display and Analysis of Drug-Related Adverse Events – Cycle 1

Table 39. Subjects With Specific Drug-Related Adverse Events By System Organ Class (Incidence > 0% in One or More Treatment Groups) <Cycle 1>

	n	Aprepitant Regimen (%)	n	Control Regimen (%)
Subjects in population	152		150	
with one or more adverse events	5	(3.3)	3	(2.0)
with no adverse events	147	(96.7)	147	(98.0)
Gastrointestinal disorders	**2**	**(1.3)**	**1**	**(0.7)**
Constipation	1	(0.7)	0	(0.0)
Nausea	0	(0.0)	1	(0.7)
Vomiting	1	(0.7)	0	(0.0)
Infections and infestations	**1**	**(0.7)**	**0**	**(0.0)**
Clostridium difficile infection	1	(0.7)	0	(0.0)
Investigations	**2**	**(1.3)**	**2**	**(1.3)**
Alanine aminotransferase increased	0	(0.0)	2	(1.3)
Aspartate aminotransferase increased	0	(0.0)	2	(1.3)
Blood calcium decreased	1	(0.7)	0	(0.0)
Blood potassium decreased	1	(0.7)	0	(0.0)
Investigations	**2**	**(1.3)**	**2**	**(1.3)**
Electrocardiogram T wave inversion	1	(0.7)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**1**	**(0.7)**	**0**	**(0.0)**
Hiccups	1	(0.7)	0	(0.0)

Drug related AEs were infrequent in both arms. No significant differences were seen between the arms, especially considering the context of concomitant emetogenic therapy.

Drug-Related Adverse Events –Cycles 2 - 6

Seven subjects (4.1%) had an adverse event that the investigator determined to be related to study medication (aprepitant and/or ondansetron). These events were mostly singular occurrences, except for ALT and AST increased (3 subjects each) and fatigue (2 subjects).

Serious adverse event/deaths/other significant events

Serious Adverse Events – Cycle 1

Table 40. Subjects With Serious Adverse Events By System Organ Class (Incidence > 0% in One or More Treatment Groups) <Cycle 1>

	n	Aprepitant Regimen (%)	n	Control Regimen (%)
Subjects in population	152		150	
with one or more serious adverse events	46	(30.3)	41	(27.3)
with no serious adverse events	106	(69.7)	109	(72.7)
Blood and lymphatic system disorders	**29**	**(19.1)**	**31**	**(20.7)**
Anaemia	2	(1.3)	3	(2.0)
Bone marrow failure	0	(0.0)	1	(0.7)
Febrile neutropenia	23	(15.1)	22	(14.7)
Neutropenia	4	(2.6)	0	(0.0)
Pancytopenia	3	(2.0)	6	(4.0)
Thrombocytopenia	0	(0.0)	2	(1.3)
Gastrointestinal disorders	**5**	**(3.3)**	**3**	**(2.0)**
Abdominal pain	1	(0.7)	1	(0.7)
Caecitis	1	(0.7)	0	(0.0)
Stomatitis	1	(0.7)	0	(0.0)
Vomiting	2	(1.3)	3	(2.0)
General disorders and administration site conditions	**2**	**(1.3)**	**4**	**(2.7)**
Mucosal inflammation	2	(1.3)	2	(1.3)
Pyrexia	0	(0.0)	2	(1.3)
Hepatobiliary disorders	**1**	**(0.7)**	**0**	**(0.0)**
Hepatotoxicity	1	(0.7)	0	(0.0)
Immune system disorders	**3**	**(2.0)**	**0**	**(0.0)**
Anaphylactic shock	1	(0.7)	0	(0.0)
Drug hypersensitivity	1	(0.7)	0	(0.0)
Hypersensitivity	1	(0.7)	0	(0.0)
Infections and infestations	**7**	**(4.6)**	**5**	**(3.3)**
Bacillus infection	0	(0.0)	1	(0.7)

	n	Aprepitant Regimen (%)	n	Control Regimen (%)
Bronchitis	0	(0.0)	1	(0.7)
Clostridium difficile infection	1	(0.7)	0	(0.0)
Device related infection	2	(1.3)	0	(0.0)
Otitis media acute	1	(0.7)	0	(0.0)
Periorbital cellulitis	1	(0.7)	0	(0.0)
Pneumonia	0	(0.0)	1	(0.7)
Sepsis	1	(0.7)	0	(0.0)
Urinary tract infection	0	(0.0)	2	(1.3)
Varicella	1	(0.7)	0	(0.0)
Investigations	**4**	**(2.6)**	**2**	**(1.3)**
Drug clearance decreased	1	(0.7)	0	(0.0)
Electrocardiogram T wave inversion	1	(0.7)	0	(0.0)
Neutrophil count decreased	1	(0.7)	2	(1.3)
Platelet count decreased	2	(1.3)	0	(0.0)
White blood cell count decreased	1	(0.7)	0	(0.0)
Metabolism and nutrition disorders	**0**	**(0.0)**	**2**	**(1.3)**
Dehydration	0	(0.0)	1	(0.7)
Hypokalaemia	0	(0.0)	1	(0.7)
Hyponatraemia	0	(0.0)	1	(0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(0.7)**	**0**	**(0.0)**
Neuroblastoma	1	(0.7)	0	(0.0)
Nervous system disorders	**0**	**(0.0)**	**1**	**(0.7)**
Presyncope	0	(0.0)	1	(0.7)
Vascular disorders	**0**	**(0.0)**	**1**	**(0.7)**
Hypotension	0	(0.0)	1	(0.7)

Two subjects in the aprepitant regimen had a serious adverse event that was determined by the investigator to be drug-related. A summary review of the serious drug-related adverse events is provided below:

- A 1.2 year old female subject with a diagnosis of Yolk Sac tumor had a serious drug-related adverse event of Clostridium Difficile infection that occurred on the 3rd day post initiation of study medication (Day 3). The investigator considered this event related to aprepitant and ondansetron. The subject completed Cycle 1 then discontinued from the study.
- A 16 year old female subject with a diagnosis of osteosarcoma had a serious drug-related adverse event of electrocardiogram T wave inversion that occurred on the 8th day post initiation of study medication (Day 8), 5 days after the last dose of study medication. No concomitant medication or treatment was given to the subject for this event. The adverse event of “T wave inversion” was considered an “other important medical event”; the intensity of this event was mild and the NCI toxicity grade was 1. On Day 20, the subject’s ECG tracing spontaneously returned to baseline. The investigator considered this event possibly related to aprepitant and chemotherapy agents doxorubicin and cisplatin. The subject completed Cycle 1 then discontinued from the study.

No patients in the control regimen experienced a serious adverse event that was considered drug-related.

Serious Adverse Events - Cycles 2 - 6

Table 41. Subjects With Specific Serious Adverse Events By System Organ Class (Incidence > 0% in One or More Treatment Groups) <Cycles 2-6>

	Aprepitant Regimen	
	n	(%)
Subjects in population	170	
with one or more adverse events	84	(49.4)
with no adverse events	86	(50.6)
Blood and lymphatic system disorders	**63**	**(37.1)**
Agranulocytosis	1	(0.6)
Anaemia	9	(5.3)
Bone marrow failure	1	(0.6)
Febrile neutropenia	53	(31.2)
Leukopenia	2	(1.2)
Neutropenia	4	(2.4)
Pancytopenia	4	(2.4)
Thrombocytopenia	3	(1.8)
Gastrointestinal disorders	**12**	**(7.1)**
Duodenitis	1	(0.6)
Gastritis erosive	1	(0.6)
Haematochezia	1	(0.6)
Intestinal obstruction	1	(0.6)
Oesophagitis	1	(0.6)
Stomatitis	1	(0.6)
Vomiting	8	(4.7)
General disorders and administration site conditions	**13**	**(7.6)**
Catheter site pain	1	(0.6)
Chills	1	(0.6)
Mucosal inflammation	3	(1.8)
Pain	1	(0.6)
Pyrexia	8	(4.7)
Thrombosis in device	1	(0.6)
Immune system disorders	**1**	**(0.6)**
Anaphylactic shock	1	(0.6)
Infections and infestations	**15**	**(8.8)**
Balanoposthitis infective	1	(0.6)
Infections and infestations	**15**	**(8.8)**
Cellulitis	1	(0.6)
Cystitis	1	(0.6)
Enterobiasis	1	(0.6)
Enterococcal sepsis	1	(0.6)
Gastroenteritis clostridial	1	(0.6)
Gastrointestinal infection	1	(0.6)
Pneumonia	1	(0.6)
Postoperative wound infection	1	(0.6)
Sepsis	1	(0.6)
Upper respiratory tract infection	1	(0.6)
Urinary tract infection	3	(1.8)
Viral infection	1	(0.6)
Wound infection	2	(1.2)
Injury, poisoning and procedural complications	**5**	**(2.9)**
Postoperative wound complication	1	(0.6)
Toxicity to various agents	2	(1.2)
Wound dehiscence	2	(1.2)
Investigations	**5**	**(2.9)**
Blood creatinine increased	1	(0.6)
Neutrophil count decreased	4	(2.4)
Platelet count decreased	1	(0.6)

	Aprepitant Regimen	
	n	(%)
Metabolism and nutrition disorders	**8**	**(4.7)**
Decreased appetite	3	(1.8)
Dehydration	4	(2.4)
Hypokalaemia	1	(0.6)
Hypomagnesaemia	1	(0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3**	**(1.8)**
Epithelioid sarcoma	1	(0.6)
Osteosarcoma recurrent	1	(0.6)
Tumour haemorrhage	1	(0.6)
Nervous system disorders	**2**	**(1.2)**
Convulsion	1	(0.6)
Headache	1	(0.6)
Renal and urinary disorders	**3**	**(1.8)**
Haematuria	1	(0.6)
Renal failure acute	1	(0.6)
Renal tubular disorder	1	(0.6)
Reproductive system and breast disorders	**1**	**(0.6)**
Menorrhagia	1	(0.6)
Respiratory, thoracic and mediastinal disorders	**2**	**(1.2)**
Pulmonary oedema	1	(0.6)
Tracheal inflammation	1	(0.6)
Vascular disorders	**1**	**(0.6)**
Hypotension	1	(0.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Data Source: [16.4]

In general, the serious adverse event profile was typical of a patient population with cancer receiving multiple cycles of chemotherapy.

The most commonly reported serious adverse events occurred in the blood and lymphatic system organ class, with febrile neutropenia occurring most frequently.

One subject had a serious adverse event that was determined by the investigator to be drug- related:

- A 9 year old female subject with a diagnosis of osteosarcoma had a serious drug- related adverse event of anaphylactic shock that occurred on the 1st day of study medication in Cycle 2. On Day 1 of Cycle 2, the subject received open-label aprepitant (3.48 mL powder-for-suspension) and 12,000.00 mg of intravenous methotrexate. At the end of the methotrexate infusion, the subject experienced anaphylactic shock; the exact onset time of the adverse event relative to aprepitant and methotrexate administration was not provided. The intensity of this event was severe and the NCI toxicity grade was 4. The subject was treated with corticosteroids and recovered from the event in approximately 1 hour. One day later, the subject had another serious adverse event, which was methotrexate toxicity ("toxicity to various agents"). The intensity was moderate and the NCI toxicity was 2. The patient received hydration and leucovorin calcium and recovered within 8 days. The investigator considered both events (the anaphylactic shock and methotrexate toxicity) related to aprepitant and methotrexate. The subject was discontinued from study medication on Day 1 of Cycle 2.

For adjudication of the possible relation of the anaphylactic shock described above and aprepitant, it has been clarified that the patient did not receive aprepitant in cycle 1.

A combined table listing the most frequent SAEs for cycle 1 and cycles 2-6, respectively, has been provided by the Applicant following CHMP request. Similar to the non-serious adverse events, there were only small differences between the 2 treatment arms for Cycle 1. Incidence of SAEs were

generally more frequent in Cycles 2-6, as expected due to the longer exposure both to aprepitant and to chemotherapeutic agents.

Deaths

One subject on the aprepitant regimen died:

- A 6 year old male subject with a diagnosis of neuroblastoma experienced a seizure 4 days post initiation of study medication in Cycle 1 (Day 4), one day after the last dose of aprepitant, which resolved spontaneously within 30 seconds. The adverse event diagnosis was 'worsening neuroblastoma'. The investigator did not consider this event related to study medication. The subject completed Cycle 1, then discontinued from the study. The subject did not participate in Cycles 2-6. The AE of 'worsening neuroblastoma' was not resolved at the time the subject discontinued from the study. The subject died approximately 9 months after the subject discontinued from the study (298 days after the last dose of study medication was administered).

There were no deaths in Cycles 2-6.

Laboratory findings

Laboratory Values Over Time – Cycle 1

Summary statistics (mean and standard deviation) were calculated for baseline and post-treatment laboratory tests (selected tests only) for Days 6-8 and Days 19-29. No formal hypotheses testing was performed. Differences were noted from baseline for many of the laboratory safety tests, which were not unexpected given the effects of chemotherapy on bone marrow and liver function. Common changes for Days 6-8 included increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and decrease in platelet count. A small numerical difference in the mean change for ALT and AST is noted between the treatment arms, with the subjects in the aprepitant treatment regimen experiencing a greater change from baseline to post-treatment.

There were no notable differences between groups with respect to mean alkaline phosphatase or total bilirubin. The mean change for platelet count decrease was generally similar between the treatment regimens. Changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and platelet count were less prominent by the Day 19 to 29 visit.

The increase in AST Days 6-8 appear to be of the same magnitude as that of ALT, both here and when results are combined with study 097 (module 2.7.4, Table 55). Differences between the two treatment arms were less pronounced on Day 19-29. In the overall AEs (see above) there were no notable differences regarding elevation of liver parameters.

National Cancer Institute (NCI) Toxicity Rating – Cycle 1

Data from the protocol-specified laboratory safety tests performed at baseline (prior to study medication) and at the Day 6 to 8 and Day 19 to 29 visits were summarized using NCI toxicity criteria. Although tests were scheduled to be performed on Days 6 to 8 and Days 19 to 29, the visits may include lab data captured outside the scheduled visit window.

The severity of laboratory safety test results were categorized using the standardized NCI common toxicity criteria. No formal hypothesis testing was performed. Based on the NCI toxicity criteria, the

treatment regimens were generally similar across laboratory tests when taking into account differences at baseline.

The laboratory tests with the greatest increase in NCI toxicity grade incidence from baseline to follow-up were white blood cell (WBC) count (grade 4), hemoglobin (grade 3), neutrophil count (grade 4), and platelet count (grade 4). The increase in incidence for these laboratory tests were similar between the treatment regimens and are generally considered an expected result for patients receiving chemotherapy.

Clinically Significant Laboratory Abnormalities - Cycle 1

The number of subjects whose laboratory values were outside pre-specified limits, as determined by using the NCI Common Terminology Criteria for Adverse Events (grade 3 and 4), for the period between Days 6 and 29 is presented in Table 12-24.

Table 42. Number (%) of Subjects with a Clinically Significant Laboratory Abnormalities (CSLA) - Cycle 1 Days 6 to 29

Lab Test	CSLA Criteria	Number (%) with CSLA			
		Aprepitant Regimen		Control Regimen	
		n/m	(%)	n/m	(%)
BLOOD CHEMISTRY					
Serum Albumin	<2 gm/dL	4/149	(2.7)	3/148	(2.0)
Serum Glucose	>250 gm/dL	1/150	(0.7)	0/149	(0.0)
Serum Glucose	<40 gm/dL	1/150	(0.7)	0/149	(0.0)
Serum Potassium	>6.0 mEq/L	0/151	(0.0)	0/149	(0.0)
Serum Potassium	<3.0 mEq/L	6/151	(4.0)	7/149	(4.7)
Serum Sodium	>155 mEq/L	0/151	(0.0)	0/149	(0.0)
Serum Sodium	<130 mEq/L	3/151	(2.0)	4/149	(2.7)
HEMATOLOGY					
Hemoglobin	<8.0 gm/dL	26/151	(17.2)	39/149	(26.2)
WBC Count	<2.0 x 10[3]/microL	71/151	(47.0)	81/149	(54.4)
Neutrophil Count	<1.0 x 10[3]/microL	86/145	(59.3)	80/146	(54.8)
Platelet Count	<50.0 x 10[3]/microL	31/151	(20.5)	36/149	(24.2)
HEPATIC FUNCTION					
Serum Alanine Aminotransferase	>5.0 x ULN	11/149	(7.4)	10/149	(6.7)
Serum Alkaline Phosphatase	>5.0 x ULN	0/146	(0.0)	0/146	(0.0)
Serum Aspartate Aminotransfera	>5.0 x ULN	3/149	(2.0)	3/148	(2.0)
Total Serum Bilirubin	>3.0 x ULN	0/148	(0.0)	0/149	(0.0)
RENAL FUNCTION					
Serum Creatinine	>3.0 x ULN	2/151	(1.3)	1/149	(0.7)
Serum Creatinine	>3.0 x baseline	1/151	(0.7)	1/149	(0.7)

n/m = Number of randomized Cycle 1 patients in each treatment group with a CSLA/number of randomized Cycle 1 patients in each treatment group with lab data.

Data Source: [16.4]

Though some numerical differences in CSLA are seen, the changes are those generally expected in this population.

Clinically Significant Laboratory Abnormalities – Cycles 2- 6

Table 43. Number (%) of Subjects with a Clinically Significant Laboratory Abnormality (CSLA) <Cycles 2-6>

Lab Test	CSLA Criteria	Number (%) with CSLA	
		Aprepitant Regimen	
		n/m	(%)
BLOOD CHEMISTRY			
Serum Albumin	<2 gm/dL	0/166	(0.0)
Serum Glucose	>250 gm/dL	1/164	(0.6)
Serum Glucose	<40 gm/dL	0/164	(0.0)
Serum Potassium	>6.0 mEq/L	0/167	(0.0)
Serum Potassium	<3.0 mEq/L	8/167	(4.8)
Serum Sodium	>155 mEq/L	0/167	(0.0)
Serum Sodium	<130 mEq/L	2/167	(1.2)
HEMATOLOGY			
Hemoglobin	<8.0 gm/dL	60/169	(35.5)
WBC Count	<2.0 x 10[3]/microL	95/170	(55.9)
Neutrophil Count	<1.0 x 10[3]/microL	104/168	(61.9)
Platelet Count	<50.0 x 10[3]/microL	53/169	(31.4)
HEPATIC FUNCTION			
Serum Alanine Aminotransferase	>5.0 x ULN	5/168	(3.0)
Serum Alkaline Phosphatase	>5.0 x ULN	1/166	(0.6)
Serum Aspartate Aminotransfera	>5.0 x ULN	1/165	(0.6)
Total Serum Bilirubin	>3.0 x ULN	0/165	(0.0)
RENAL FUNCTION			
Serum Creatinine	>3.0 x ULN	3/167	(1.8)

n/m = Number of treated Cycles 2-6 patients in each treatment group with a CSLA/number of treated Cycles 2-6 patients in each treatment group with lab data.

Data Source: [16.4]

As for cycle 1, the CSLA seen during cycles 2-6 were those expected considering the background chemotherapy.

Laboratory Findings That Met Predetermined Criteria: Hepatic Safety – Cycle 1

Table 44. Subjects With Liver Function Laboratory Findings That Met Predetermined Criteria All Subjects as Treated (ASaT) Population <Cycle 1 Treatment and Follow-Up Phase>

Criteria	Aprepitant Regimen		Control Regimen		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
Alanine Aminotransferase						
>5 x ULN	11/151	(7.3)	12/149	(8.1)	23/300	(7.7)
≥10 x ULN	7/151	(4.6)	3/149	(2.0)	10/300	(3.3)
≥20 x ULN	3/151	(2.0)	1/149	(0.7)	4/300	(1.3)
Aspartate Aminotransferase						
>5 x ULN	5/151	(3.3)	4/149	(2.7)	9/300	(3.0)
≥10 x ULN	2/151	(1.3)	2/149	(1.3)	4/300	(1.3)
≥20 x ULN	2/151	(1.3)	1/149	(0.7)	3/300	(1.0)
Aminotransferase (ALT or AST)						
>5 x ULN	11/151	(7.3)	12/149	(8.1)	23/300	(7.7)
≥10 x ULN	7/151	(4.6)	4/149	(2.7)	11/300	(3.7)
≥20 x ULN	3/151	(2.0)	1/149	(0.7)	4/300	(1.3)
Bilirubin						
≥2 x ULN	0/149	(0.0)	0/149	(0.0)	0/298	(0.0)
Alkaline Phosphatase						
≥1.5 x ULN	5/148	(3.4)	8/146	(5.5)	13/294	(4.4)
Aminotransferase (ALT or AST) and Bilirubin						
AT ≥3 x ULN and BILI ≥1.5 x ULN	1/151	(0.7)	0/149	(0.0)	1/300	(0.3)
AT ≥3 x ULN and BILI ≥2 x ULN	0/151	(0.0)	0/149	(0.0)	0/300	(0.0)
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase						
AT ≥3 x ULN and BILI ≥2 x ULN and ALP <2 x ULN	0/151	(0.0)	0/149	(0.0)	0/300	(0.0)

n = Number of Subjects with postbaseline test results (or combination of test results from the same day) that met predetermined criteria.
m = Number of Subjects with at least one postbaseline test result or combination of test results from the same day.
ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; AT = Aminotransferase (ALT or AST); BILI = Bilirubin; ULN = Upper limit of normal range.

Data Source: [16.4]

Table 12-26 displays the number of subjects with a liver function test result during the treatment and/or follow-up period met pre-determined criteria. The normal range was defined at a site level by the site's local laboratory. The incidences of subjects with alanine aminotransferase levels (ALT) >10X and >20X the upper limit of normal were slightly higher in the aprepitant group (7/151 [4.6%] and 3/151 [2.0%]) compared to the control group (3/149 [2.0%] and 1/149 [0.7%]). Of those with an elevation >20 times the upper limit of normal, all 4 subjects were treated with methotrexate, which is known to cause hepatotoxicity. No other hepatic parameter imbalances were noted.

Thus, there was no patient with liver function test aberrations fulfilling Hy's law.

Table 45. Subjects With Liver Function Laboratory Findings That Met Predetermined Criteria All Subjects as Treated (ASaT) Population <Cycles 2-6>

Criteria	Aprepitant Regimen	
	n/m	(%)
Alanine Aminotransferase		
>5 x ULN	7/168	(4.2)
≥10 x ULN	3/168	(1.8)
≥20 x ULN	1/168	(0.6)
Aspartate Aminotransferase		
>5 x ULN	3/165	(1.8)
≥10 x ULN	1/165	(0.6)
≥20 x ULN	0/165	(0.0)
Aminotransferase (ALT or AST)		
>5 x ULN	8/165	(4.8)
≥10 x ULN	3/165	(1.8)
≥20 x ULN	1/165	(0.6)
Bilirubin		
≥2 x ULN	0/165	(0.0)
Alkaline Phosphatase		
≥1.5 x ULN	9/166	(5.4)
Aminotransferase (ALT or AST) and Bilirubin		
AT ≥3 x ULN and BILI ≥1.5 x ULN	2/166	(1.2)
AT ≥3 x ULN and BILI ≥2 x ULN	0/166	(0.0)
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase		
AT ≥3 x ULN and BILI ≥2 x ULN and ALP <2 x ULN	0/166	(0.0)

n = Number of Subjects with postbaseline test results (or combination of test results from the same day) that met predetermined criteria.
m = Number of Subjects with at least one postbaseline test result or combination of test results from the same day.
ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; AT = Aminotransferase (ALT or AST); BILI = Bilirubin; ULN = Upper limit of normal range.

Considering the concomitant chemotherapy given, the observed changes do not seem unexpected.

Safety in special populations

No dose adjustment of oral aprepitant is required based on gender, age, body weight or race. Additionally, no dose adjustment is necessary for subjects with renal insufficiency or for subjects with end stage renal disease undergoing hemodialysis, or for subjects with mild to moderate hepatic insufficiency (Child-Pugh score 5 to 9). There are no clinical data in subjects with severe hepatic insufficiency (Child-Pugh score >9).

Immunological events

Listings of subjects with hypersensitivity Adverse Events from the paediatric trials have been provided by the Applicant following the D120 LoQ. This includes a variety of AEs (eg “dermatitis allergic”, “rash”, “urticaria”) where only a single event is termed “anaphylactic shock”. In study 208, 10/19 hypersensitivity AEs occurred in Cycle 1. In the listings of all AEs no clear difference is seen regarding hypersensitivity reactions between the 2 treatment arms and the causal relation to aprepitant remains uncertain. The current SmPC includes a precaution against hypersensitivity adverse events such as isolated reports of immediate hypersensitivity reactions including flushing, erythema, and dyspnea have occurred during infusion of fosaprepitant.

Safety related to drug-drug interactions and other interactions

Current prescribing information contains extensive information on drug interactions for oral aprepitant in adults. The findings in adults are expected to be sufficient and relevant to the paediatric population.

Discontinuation due to adverse events

Four subjects who participated in the open-label cycles discontinued study medication due to an adverse event:

- A 4 year old male subject with a diagnosis of alveolar rhabdomyosarcoma experienced febrile neutropenia 11 days post initiation of study medication in Cycle 3 (Day 11). The subject received 1.8 mL of aprepitant PFS on Day 1, then 1.2 mL on Days 2 and 3. The adverse event of 'febrile neutropenia' was considered a serious adverse event, moderate in intensity, with a toxicity grade of 3. The investigator did not consider the event to be related to study medication. The study medication in Cycle 3 was completed 9 days prior to the onset of the event; no action was taken with the study medication. The subject completed Cycle 3, then discontinued from the study. The subject was treated with cefotaxime sodium, amikacin, platelets, red blood cells, and acetaminophen, The subject recovered from the event of febrile neutropenia in 5 days.
- A 9 year old male subject with a diagnosis of osteosarcoma experienced four adverse events in Cycle 2, which led to discontinuation of study medication. On Day 1 of Cycle 2, the subject received open-label aprepitant (3.92 mL PFS) and methotrexate (13200.00 mg). On the same day, the subject experienced alanine aminotransferase increase (ALT; 2238.0 IU/L), aspartate aminotransferase increase (AST; 2738.0 IU/L), and lactate dehydrogenase increase. On the following day (Day 2 of Cycle 2), the patient experienced blood bilirubin increase (2.18 mg/dL). The adverse event of 'ALT increase' was considered moderate in intensity, with a toxicity grade of 4, and resolved in 21 days. The adverse event of 'AST increase' was considered moderate in intensity, with a toxicity grade of 4, and resolved in 15 days. The adverse event of 'lactate dehydrogenase increase' was considered moderate in intensity, with a toxicity grade of 3, and resolved in 21 days. The adverse event of 'blood bilirubin increase' was considered mild in intensity, with a toxicity grade of 1, and resolved in 8 days. The investigator considered all four events related to study medication. Study medication was discontinued on Day 1 of Cycle 2. The subject discontinued from the study after the Cycle 2 follow-up visit.
- A 9 year old female subject with a diagnosis of osteogenic sarcoma [mentioned earlier under 'Serious AEs'] experienced four adverse events in Cycle 2, which led to discontinuation of study medication. On Day 1 of Cycle 2, the subject received open-label aprepitant (3.48 mL PFS) and methotrexate (12000.0 mg). One the same day, the subject experienced ALT increase (1059.0 IU/L), AST increase (2031.0 IU/L), lactate dehydrogenase increase (1070.0 IU/L), and anaphylactic shock. The adverse event of 'ALT increase' was considered moderate in intensity, with a toxicity grade of 4, and resolved in 16 days. The adverse event of 'AST increase' was considered moderate in intensity, with a toxicity grade of 4, and resolved in 11 days. The adverse event of 'lactate dehydrogenase increase' was considered moderate in intensity, with a toxicity grade of 1, and resolved in 10 days. The adverse event of 'anaphylactic shock' was considered severe in intensity, with a toxicity grade of 4, and resolved in 1 hour. The investigator considered all four events related to study medication. Study medication was discontinued on Day 1 of Cycle 2. The subject discontinued from the study after the Cycle 2 follow-up visit.
- A 6 year old female subject with a diagnosis of gliosarcoma experienced a convulsion in Cycle 2, which led to discontinuation of study medication. The event of 'convulsion' was considered moderate in intensity, with a toxicity grade of 1. The investigator considered the event related to study medication. The study medication was discontinued on Day 2. The subject was treated with acetazolamide, carbamazepine, and topiramate. The subject discontinued from the study after the Cycle 2 follow-up visit. The event of convulsion resolved in 2 days.

In 3 of the 4 cases the investigator considered that the AEs were related to aprepitant, but it is not clear whether a causal relation was classified as possible, probable, or certain. In each case, the withdrawal of the patient from study seems reasonable as an act of caution. However, it seems likely that other factors, notably the patient's medical condition and/or concomitant chemotherapy, may at least have contributed to these adverse events.

Post marketing experience

From post-marketing experience of aprepitant, a total of 47 reports contained 90 (28; [31%] serious) adverse events in the pediatric population. Most reported events were single occurrences, many of which are already labelled, and the findings do not by themselves suggest the existence of significant unidentified risks.

2.6.1. Discussion on clinical safety

In the paediatric studies in CINV 208, 097 and Part IV of 134, a total of 308 paediatric patients have been exposed to aprepitant. During cycle 1, aprepitant was always combined with ondansetron and sometimes with dexamethasone. In study 208, AEs were recorded in 79 % and 77 % in the aprepitant and control arm, respectively. Serious AEs were observed in 30 % of subjects in the aprepitant arm and 27 % of subjects in the control arm. There were no clear differences in the incidence of severe AEs, ie grade ≥3, in the two arms or in separate age groups. Likewise there are no obvious differences seen when the incidence of various AEs are presented by Maximum Toxicity Grade.

No clear differences between the aprepitant and control arms are seen when AEs are summarised by system organ class. The most commonly reported adverse events from both treatment groups were within the blood and lymphatic system organ class, most notably anemia (20.9%), febrile neutropenia (15.9%), and neutropenia (12.9%), as well as gastrointestinal disorder of vomiting (15.2%). Vomiting was only reported as an adverse event if the vomiting episode occurred outside of the efficacy assessment period, or if the vomiting met the criteria of a serious adverse event.

The adverse events mentioned above occurred at similar incidence between both treatment regimens, with the exception of anemia, which occurred at a slightly numerically higher incidence in the control regimen.

Overall, the adverse events observed were comparable to the types of adverse events expected in patients with cancer receiving emetogenic chemotherapy. Listings of subjects with hypersensitivity Adverse Events from the paediatric trials have been provided. This includes a variety of AEs (eg "dermatitis allergic", "rash", "urticaria") where only a single event is termed "anaphylactic shock". In study 208, 10/19 hypersensitivity AEs occurred in Cycle 1. In the listings of all AEs no clear difference is seen regarding hypersensitivity reactions between the 2 treatment arms and the causal relation to aprepitant remains uncertain. The current SmPC includes a precaution against hypersensitivity adverse events such as isolated reports of immediate hypersensitivity reactions including flushing, erythema, and dyspnea have occurred during infusion of fosaprepitant.

Transaminase increases in the aprepitant arm, >10X and >20X the upper limit of normal were slightly higher in the aprepitant group (7/151 [4.6%] and 3/151 [2.0%]) compared to the control group (3/149 [2.0%] and 1/149 [0.7%]). Of those with an elevation >20 times the upper limit of normal, all 4 subjects were treated with methotrexate, which is known to cause hepatotoxicity.

In general, the differences in AEs between the arms in study 208 were small and of doubtful significance, not least in regard of concomitant chemotherapy. However, the clinical studies only describe short-term exposure to aprepitant.

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

2.6.2. Conclusions on the clinical safety

In the clinical paediatric studies of aprepitant for the treatment of CINV, safety and tolerability of aprepitant combined with ondansetron and optional dexamethasone seems moderate and on par with that of only ondansetron with optional dexamethasone. The toxicity profile of aprepitant includes anemia, febrile neutropenia, vomiting, neutropenia, nausea, and neutrophil count decreased reflecting a typical patient population with cancer receiving chemotherapy. The somewhat higher incidences of anemia and neutrophil count decrease (control regimen) and dizziness (aprepitant regimen) do not lead to a concern. No new safety concerns in paediatric subjects as compared to adults were identified in the current clinical studies.

2.7. Risk Management Plan

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

The PRAC considered that the risk management plan version 4.1 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.1 with the following content, with changes made in the current application highlighted in grey:

Safety concerns

Important identified risks	• Hypersensitivity • Drug interaction: hormonal contraceptives
Important potential risks	• Potential for medication errors
Missing information	• Use in pregnancy • Use in patients < 6 months of age or < 6 kg • Use in patients with moderate or severe hepatic impairment

Pharmacovigilance plan

Study / Activity	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim / Final Reports (target dates)
• Clinical Trial (PN-219) • (MK-0869 in PONV) • Study to Evaluate the Pharmacokinetics/Pharmacodynamics, Safety, and Tolerability of Aprepitant in Pediatric Patients for PONV • (Category 3)	To determine the appropriate dosing regimen of aprepitant for the prevention of post-operative nausea and vomiting in pediatric patients birth to 17 years of age by assessing pharmacokinetics (PK) and pharmacodynamics (PD) parameters, and monitoring safety and tolerability of the administered dose(s).	• Exposure in pediatric population	• Ongoing	1Q-2017

Risk minimisation measures

• Safety concern	• Routine risk minimization measures	• Additional risk minimization measures
• **Important identified risks**		
• Hypersensitivity	• Hypersensitivity is considered to be adequately addressed in SPC Sections 4.3, and 4.8.	• None
• Drug interaction: reduction of efficacy hormonal contraceptives	• Drug interaction (reduction of efficacy of hormonal contraceptives) is considered to be adequately addressed in SPC Sections 4.4 and 4.5	• None
• **Important potential risks**		
• Potential for medication error	• Potential for medication error is considered to be adequately addressed in SPC Section 4.2.	• None
• **Missing information**		
• Use in pregnancy	• Use in pregnancy is considered to be adequately addressed in SPC Sections 4.6 and 5.3.	• None
Use in patients < 6 months of age or weighing <6 kg •	Based on the risk/benefit assessment, product labeling is deemed adequate to address the risk of use of aprepitant in patients < 6 months of age or weighing <6 kg. The actions described in the pharmacovigilance	• None

• Safety concern	• Routine risk minimization measures	• Additional risk minimization measures
	plan are appropriate to address the risk of use in this population. •	
• Use in patients with moderate or severe hepatic impairment	• Use in patients with moderate or severe hepatic impairment is considered to be adequately addressed in SPC Sections 4.2, 4.4, and 5.2.	• None

2.8. Pharmacovigilance

Pharmacovigilance system

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

2.9. Significance of paediatric studies

The CHMP is of the opinion that study P097 and study P134 which are contained in the agreed Paediatric Investigation Plan, P/0008/2014 and have been completed after 26 January 2007, are considered as significant.

According to the criteria for assessing the significance of studies pursuant to article 45(3) of the paediatric regulation it is concluded that study P097 fulfils the following criterion for “significance”:

- *comparative efficacy studies (randomised/active control or placebo)*

According to the criteria for assessing the significance of studies pursuant to article 45(3) of the paediatric regulation it is thus concluded that Study P134 fulfils two of the criteria for “significance”:

- *dose-finding studies;*
- *studies to obtain a new age-appropriate formulation, if this is expected to be of clinical relevance for the safe and effective use of the medicinal product in the paediatric population*

P134 cover several paediatric subsets, except the one for which a waiver has been granted (0-6 months). Both studies P097 and P134 are considered supportive for the claimed indication.

2.10. Product information

2.10.1. User consultation

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

3. Benefit-Risk Balance

The pivotal study for the present application is Protocol 208 (P208). This was a 1:1-randomised, double-blind, phase III, multicentre study that included paediatric patients aged 6 months - 17 years of age with a documented malignancy undergoing moderate – very high emetogenic chemotherapy (VHEC). Subjects were randomized to receive either aprepitant in combination with ondansetron (aprepitant regimen) or ondansetron alone (control regimen). Children less than 12 years of age received aprepitant as a new liquid oral formulation, powder for suspension (PFS), while patients aged 12-17 received the adult regimen with hard capsules. All subjects received 3 days of aprepitant. Intravenous (IV) dexamethasone was given at the discretion of the investigator. Randomization was stratified into one of four age cohorts, and further by planned use of a VHEC chemotherapy agent and planned use of dexamethasone as part of the antiemetic regimen in Cycle 1. Efficacy was evaluated in a single cycle (Cycle 1). Optional open-label aprepitant was offered in the extension phase (Cycles 2 to 6). The predefined definition of superiority was purely statistical requiring that a one-sided p-value < 0.025 was met.

Benefits

Beneficial effects

The primary endpoint was Complete response, defined as the proportion of patients with no vomiting, no retching or dry heaves, and no use of rescue medication in the 25 to 120 hours following the initiation of emetogenic chemotherapy (delayed phase) of Cycle 1. In the ITT population, complete response in the delayed phase was achieved in 50.7% vs. 26.0% ($p<0.0001$) of patients in the aprepitant and control regimens, respectively. I.e. the proportion with Complete response was approximately doubled (with an absolute difference of 25%). The proportion with Complete response was also doubled (from 20 to 40%, nominal $p=0.0002$) in the overall phase (0-120 hours after chemotherapy start), and increased by one fourth (from 52 to 66%, nominal $p=0.0135$) in the acute phase (0-24 hours after start).

The Complete response results for the three study phases in the ITT population by the Cochran-Mantel-Haenzel (CMH) test method (primary endpoint, primary analysis population, and primary analysis method) were supported by very similar results in the FAS and PP populations, as well as by the results achieved using a logistic regression model. As such, the results of the primary endpoint are considered robust.

The results from the secondary endpoint No vomiting further supported the primary endpoint with very similar (slightly larger) and highly statistically significant differences (by nominal p-values only) between arms in the proportions of patients responding (i.e. having no vomiting) in all three phases.

The secondary endpoint Number of emetic episodes showed that in both the acute and delayed phase, the largest difference between arms was seen in the category with more than 3 emetic episodes, while smaller differences or similar proportions were seen for the categories with 1, 2 or 3 emetic episodes. Thus, there is a relevant magnitude of effect in the group with the worst problems.

The estimated median time to first vomiting was 94.5 hours in the aprepitant regimen group compared with 26.0 hours in the control regimen group (nominal $p<0.0001$, based on log-rank test).

Subgroup analyses

The add-on effect of aprepitant was generally somewhat smaller in the acute phase compared with the delayed and overall phases, in females than in males, and in patients receiving chemotherapy over

more than one day compared with 1-day regimens. The magnitude of effect was largest in the 12-17 age group (including an x 5 increase from 10 to 51% in the delayed phase), and appeared smaller in the group aged 6-11 years, with only 8% absolute difference between arms in the overall phase. The difference in the acute and delayed phases was larger, however, 14% and 17%, respectively.

Supportive studies

The exploratory efficacy results of studies P134 (including patients 6-months-11 of age years receiving powder for oral solution) and P097 (adolescents receiving adult aprepitant regimen), both in the CINV indication, are considered supportive of the results of the pivotal study P208.

Concerning post-operative nausea and vomiting (PONV), the results from P148 were not sufficient to determine a final paediatric dosing recommendation for aprepitant in this indication and no benefit compared with head-to head ondansetron was shown. No new indication or new posology is proposed for PONV but the outcomes of the study are considered appropriately reflected in the SmPC.

Uncertainty in the knowledge about the beneficial effects

Pharmacokinetic data indicated lower exposure (AUC_{0-24}) in all paediatric groups than what has previously been observed in adults, with the lowest mean AUC seen in the group aged 6-11 years, which also had the lowest response rate in the pivotal trial. Overall, children <12 years had lower C_{min} values than adults. Further PK-PD modelling analysis indicated that increasing doses on Day 2 and 3 in children under the age of 12 could increase concentrations to be more in the adult range; however available data are not sufficient to conclude that this would lead to clinically relevant improvements in outcomes. Therefore no change in dosing recommendations is requested.

Risks

Unfavourable effects

In the paediatric studies in CINV 208, 097 and Part IV of 134, a total of 308 paediatric patients have been exposed to aprepitant. During cycle 1, aprepitant was always combined with ondansetron and sometimes with dexamethasone. In study 208, AEs were recorded in 79 % and 77 % in the aprepitant and control arm, respectively. Serious AEs were observed in 30 % of subjects in the aprepitant arm and 27 % of subjects in the control arm.

No clear differences between the aprepitant and control arms are seen when AEs are summarised by system organ class. The most common reported adverse events from both treatment groups were within the blood and lymphatic system organ class, most notably anaemia (20.9%), febrile neutropenia (15.9%), and neutropenia (12.9%), as well as gastrointestinal disorder of vomiting (15.2%).

Anaemia occurred at a higher incidence in the control regimen (aprepitant regimen 27 (14.7%), control regimen 38 (22.6%)). Dizziness occurred more often in the aprepitant regimen 9 (4.9%) vs 1 (0.6%) in the standard regimen. But overall, the incidences of the adverse events mentioned above did not suggest significant differences between both treatment regimens. Findings were similar in the supportive studies 097 and 134. Also, the safety pattern observed in paediatric subjects does not suggest any clear differences to that already known for adults.

Listings of subjects with hypersensitivity Adverse Events from the paediatric trials have been provided by the Applicant following CHMP's request. This includes a variety of AEs (e.g. "dermatitis allergic", "rash", "urticaria") where only a single event is termed "anaphylactic shock". In study 208, 10/19

hypersensitivity AEs occurred in Cycle 1. In the listings of all AEs no clear difference is seen regarding hypersensitivity reactions between the 2 treatment arms and the causal relation to aprepitant remains uncertain. The current SmPC includes a precaution against hypersensitivity adverse events such as isolated reports of immediate hypersensitivity reactions including flushing, erythema, and dyspnoea have occurred during infusion of fosaprepitant.

In total, there were 2 patients in cycle 1 who discontinued study medication due to an AE in the aprepitant arm, whereas no subjects in the control regimen discontinued study medication due to an AE. Four subjects discontinued study treatment (i.e. aprepitant) in cycles 2-6 due to AEs. These discontinuations may be due to a reasonable precaution taken by investigators in a clinical trial and do not necessarily implicate intolerability of aprepitant in the respective subjects.

Transaminase increases in the aprepitant arm, >10X and >20X the upper limit of normal were slightly higher in the aprepitant group (7/151 [4.6%] and 3/151 [2.0%]) compared to the control group (3/149 [2.0%] and 1/149 [0.7%]) and liver enzyme increase is reflected in the SmPC. It is worthwhile to note that of those with an elevation >20 times the upper limit of normal, all 4 subjects were treated with methotrexate, which is known to cause hepatotoxicity.

Uncertainty in the knowledge about the unfavourable effects

There remains a possibility that the encountered safety issues represent mostly those seen during short-term exposure to aprepitant. Considering that aprepitant is for short term treatment this considered of minor importance.

Effects table

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
		%				
Complete response 1' endpoint	Proportion of patients with no vomiting, no retching, and no use of rescue medication (ITT, delayed phase)		50.7	26.0	(p<0.0001) Robust and convincing according to sensitivity analyses, other study phases, subgroups.	Study 208
No vomiting	Proportion of patients with no vomiting, no retching (ITT, delayed phase)	%	55.3	28.0	(nominal p=<0.0001)	
Time to first vomiting	Time-to event, from start of chemotherapy (ITT)	hours	94.5	26.0	(nominal p<0.0001)	
Unfavourable Effects						
Total AEs in cycle 1		%	79	77	No significant differences in safety patterns seen between the treatment arms	Study 208
Total SAEs		%	30	27		Study 208
Total		%	1,3	0		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
drug-related SAEs						

Benefit-risk balance

Importance of favourable and unfavourable effects

The possibility of avoiding the very problematic adverse reactions of nausea and vomiting induced by moderately to very highly emetogenic anticancer agents is considered particularly valuable in children. As such, demonstrated improvement over standard antiemetic therapy is considered clinically relevant. The unfavourable effects were similar across treatment arms in Study 208, i.e. the addition of aprepitant to the ondansetron backbone did not add significantly to the toxicity profile of the anti-emetic regimen. The added aprepitant ADRs are therefore considered unlikely to be of significant clinical importance.

Benefit-risk balance

Overall and across age groups, the demonstrated add-on efficacy in terms of proportion of patients achieving Complete response compared with the control arm, at around 20% or above in the delayed and overall phases, is considered clinically relevant. Similarly, the difference in median time to first vomiting of 68 hours is also of clear clinical value.

In general, the ADRs of aprepitant appear minor, particularly in relation to the concomitant chemotherapy. Hypersensitivity reactions, although a concern, did not seem overrepresented in the aprepitant arm of study 208, and the observed reactions appear to have been generally manageable. Implemented routine risk minimisation measures are sufficient for informing the prescriber.

The benefits of add-on EMEND (aprepitant) to an antiemetic backbone of 5-HT3 blockade (ondansetron) with or without a corticosteroid (dexamethasone) for the prevention of chemotherapy-induced nausea and vomiting in paediatric patients are therefore considered to outweigh the risks.

Discussion on the benefit-risk assessment

Any reduction in chemotherapy-induced nausea and vomiting (CINV) is considered of clinical value, particularly in children and adolescents. The unfavourable effects were similar across treatment arms in Study 208 and are considered of marginal clinical significance especially in relation to those of the background of concomitant chemotherapy.

While PK modelling indicate that increasing the dose on Days 2 and 3 in children less than 12 years could increase C_{min} levels to be more in line with what was previously observed in adults, there are also other differences than pharmacokinetics between the studied paediatric and adult populations that could contribute to the differences in outcomes. It cannot therefore be unequivocally concluded that increasing the dose would lead to clinically relevantly better outcomes in children. As the B/R balance is clearly positive at the studied doses, no change of posology is required.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of

EMEND 125mg powder for oral suspension in the Prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in children, toddlers and infants from the age of 6 months to less than 12 years, EMEND powder for oral suspension is given as part of combination therapy (see section 4.2)

And

EMEND 80mg and 125mg hard capsules in the prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults and adolescents from the age of 12

is favourable and therefore recommends the granting of the marketing authorisation for the new pharmaceutical form and the extension of the indication for the 80mg and 125mg hard capsules.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0008/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan P/0008/2014 have been completed after the entry into force of that Regulation.