22 March 2018
EMA/219267/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ivemend

International non-proprietary name: fosaprepitant

Procedure No. EMEA/H/C/000743/II/0037

Note

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

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List of abbreviations

5-HT_3	5-hydroxytryptamine type 3
Acute	0 to 24 hours following initiation of chemotherapy
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine transaminase
ASaT	All Subjects as Treated
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
AUC_{0-24}	Area under the concentration-time curve from 0 to 24 hours
$AUC_{0-\infty}$	Area under the concentration-time curve from 0 to infinity
C_{24hr}, C_{48hr}, C_{72hr}	The lowest (trough) concentration that a drug reaches before the next dose is administered
CHMP	Committee for Human Medicinal Products
CI	Confidence interval
CINV	Chemotherapy-induced nausea and vomiting
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenzel
Complete Response	No vomiting, no retching, and no use of rescue medication
CRTZ	Chemoreceptor trigger zone
CSR	Clinical Study Report
DILI	Drug-induced liver injury
Delayed	>24 to 120 hours following initiation of chemotherapy
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EMR	Electronic medical record
EU	European Union
FDA	Food and Drug Administration
FAS	Full analysis set
HCP	Health Care Provider
HEC	Highly emetogenic chemotherapy
ITT	Intent-to-treat
IV	Intravenous
LEC	Low emetogenic chemotherapy
MARRS	Merck's Adverse Event Reporting and Review System
MEC	Moderately emetogenic chemotherapy
NCI	National Cancer Institute
NK1	Neurokinin 1
No Rescue Medication	Subject did not use medication to relieve symptoms of nausea or vomiting.
NOS	Not otherwise specified

No Vomiting	No emesis or retching or dry heaves (regardless of use of rescue medication)
PD	Pharmacodynamic
PDCO	Pediatric Committee
PFS	Powder for suspension
PIP	Pediatric Investigation Plan
PK	Pharmacokinetic(s)
PO	Orally, by mouth
PONV	Post-operative nausea and vomiting
Rescue Medication	Medication to relieve symptoms of established nausea or vomiting
RMP	Risk Management Plan
SAE	Serious Adverse Event
SD	Standard deviation
SOC	System Organ Class
ULN	Upper limit of normal
US	United States
Vomiting	When the contents of the stomach come up and out through the mouth (as defined in the Patient Diary)
WBC	White blood (cell) count

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme Limited submitted to the European Medicines Agency on 7 September 2017 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include adolescents, infants, toddlers and children aged 6 months and older for prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy.
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

The RMP version 5.0 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0010/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0010/2014 was completed. The PDCO issued an opinion on compliance for the PIP P/0010/2014.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

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: N/A

Timetable	Actual dates
Submission date	7 September 2017
Start of procedure:	28 October 2017
CHMP Rapporteur Assessment Report	21 December 2017
PRAC Rapporteur Assessment Report	21 December 2017
PRAC Outcome	11 January 2018
CHMP members comments	11 January 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 January 2018
Request for supplementary information (RSI)	25 January 2018
MAH's responses submitted to the CHMP on:	20 February 2018
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	8 March 2018
CHMP members comments	12 March 2018
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	16 March 2018
CHMP Opinion	22 March 2018

2. Scientific discussion

2.1. Introduction

Fosaprepitant is a selective, high-affinity antagonist of human substance P/neurokinin-1 (NK_1) receptors and is used in prevention of acute and delayed nausea and vomiting due to highly emetogenic and moderately emetogenic cancer chemotherapy (HEC and MEC, respectively) in adults. This application aims to expand the indication of fosaprepitant to paediatric patients 6 months to 17 years of age.

The difficulty of administering oral medications to children is often compounded by additional factors in paediatric cancer patients, such as anticipatory CINV and chemotherapy-related odynophagia and mucositis; thus the applicant sees a need to evaluate intravenously administered antiemetic agents that could circumvent some of the difficulties and provide more convenient dosing and potentially can improve patient adherence to prophylactic anti-emetic regimens.

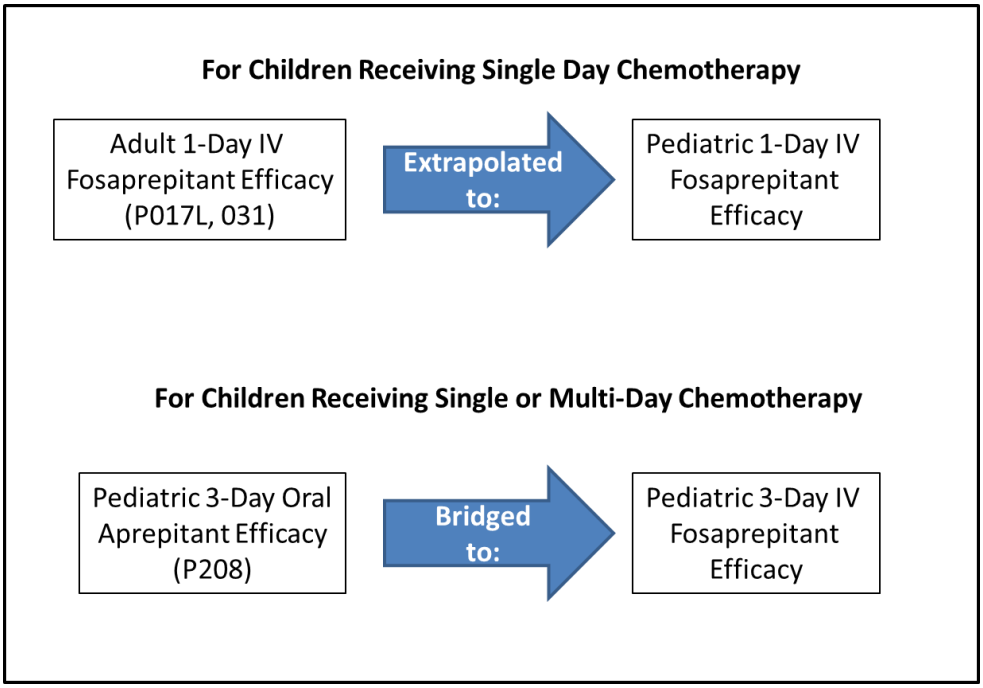
The submission is based on modelling and simulation, discussed in the frame of the PIP (EMEA-000406-PIP01-08-M04) initially approved on July 15, 2009 (full compliance check confirmed on October 10, 2014) and with the Rapporteurs during a pre-submission meeting on 19 December 2016. The paediatric clinical development for fosaprepitant consists of three paediatric clinical studies, Protocol P134, P029 and P044.

The pathophysiology of CINV is similar in adults and children, resulting from activation of neurotransmitter receptors in the chemoreceptor trigger zone (CRTZ) by chemotherapeutic agents. Both peripheral and central pathways can activate neuronal nuclei in this area and lead to vomiting. Serotonin (5-HT_3) receptor antagonists are widely used as antiemetic prophylaxis and are predominantly active on the peripheral terminals of vagal afferents in the gastrointestinal tract and CRTZ. NK_1-receptor antagonists, such as aprepitant and its prodrug fosaprepitant, act centrally by blocking substance P from binding to NK_1 receptors in the brain.

According to the applicant, efficacy of 1-day fosaprepitant treatment in children can be predicted from that demonstrated in adults based on similar chemotherapy-induced nausea and vomiting (CINV) pathophysiology and response to NK_1 receptor antagonists, given comparable fosaprepitant exposures and duration of emetogenic chemotherapy. Further, the applicant states that the conversion of fosaprepitant to aprepitant is rapid and occurs within the time of drug infusion (30 to 60 minutes); therefore, efficacy following fosaprepitant administration can be expected to be derived from exposure to aprepitant. Based on this rationale the applicant bridged the efficacy of 3-day fosaprepitant treatment in children from that demonstrated with the paediatric 3-day oral aprepitant regimen (aprepitant capsule is indicated in patients from the age of 12 years old, whereas aprepitant powder for oral suspension is indicated from the age of 6 months to less than 12 years).

Additionally, the MAH would like to use this opportunity to add hypersensitivity as an identified important risk in the RMP, as requested by the Agency following the outcome of MEA/H/C/PSUSA/00001471/201603 (CHMP Opinion dated 10 November 2016).

Figure 1: Efficacy Extrapolation/Bridging for 1-day and 3-day Pediatric Fosaprepitant Regimens



The recommended dose regimen of IVEMEND, to be administered with a 5-HT_3 antagonist, with or without a corticosteroid, for the prevention of nausea and vomiting associated with administration of single or multi-day chemotherapy regimens of Highly Emetogenic Chemotherapy (HEC) or Moderately Emetogenic Chemotherapy (MEC), is shown in Table 1. Single day chemotherapy regimens include those regimens in which HEC or MEC is administered for a single day only. Multi-day chemotherapy regimens include chemotherapy regimens in which HEC or MEC is administered for 2 or more days.

An alternative dose regimen that may be used with single-day chemotherapy regimens is shown in **Table 2**.

Dosing for Single or Multi-Day Chemotherapy Regimens

For paediatric patients receiving single or multi-day regimens of HEC or MEC, administer IVEMEND as an intravenous infusion through a central venous catheter on Days 1, 2, and 3. EMEND capsules or EMEND for oral suspension may be used on Days 2 and 3 instead of IVEMEND, as shown in **Table 1**.

Table 1: Recommended dosing for the prevention of nausea and vomiting associated with single or multi-day regimens of HEC or MEC

	Population	Day 1	Day 2	Day 3
IVEMEND*	Paediatric patients 12 years and older	115 mg intravenously	80 mg intravenously OR 80 mg orally (EMEND capsules)	80 mg intravenously OR 80 mg orally (EMEND capsules)
	Paediatric patients 6 months to less than 12 years and not less than 6 kg	3 mg/kg intravenously Maximum dose 115 mg	2 mg/kg intravenously OR 2 mg/kg orally (EMEND oral suspension) Maximum dose 80 mg	2 mg/kg intravenously OR 2 mg/kg orally (EMEND oral suspension) Maximum dose 80 mg
Dexamethasone**	All paediatric patients	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on days 1 through 4		
5-HT_3 antagonist	All paediatric patients	See selected 5-HT_3 antagonist prescribing information for the recommended dosage		

* For paediatric patients 12 years and older, administer IVEMEND intravenously over 30 minutes, completing the infusion approximately 30 minutes prior to chemotherapy. For paediatric patients less than 12 years, administer IVEMEND intravenously over 60 minutes, completing the infusion approximately 30 minutes prior to chemotherapy.
** **Dexamethasone** should be administered 30 minutes prior to chemotherapy treatment on Day 1.

Alternative Dosing for Single Day Chemotherapy Regimens

For paediatric patients receiving single day HEC or MEC, IVEMEND may be administered as an intravenous infusion through a central venous catheter on Day 1.

Table 2: Alternative dosing for the prevention of nausea and vomiting associated with single day regimens of HEC or MEC

	Population	Day 1
IVEMEND*	Paediatric patients 12 years and older	150 mg intravenously
	Paediatric patients 2 to less than 12 years	4 mg/kg intravenously Maximum dose 150mg
	Paediatric patients 6 months to less than 2 years and not less than 6 kg	5 mg/kg intravenously Maximum dose 150mg

Dexamethasone**	All paediatric patients	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on days 1 and 2.
5-HT_3 antagonist	All paediatric patients	See selected 5-HT_3 antagonist prescribing information for the recommended dosage

* For paediatric patients 12 years and older, administer IVEMEND intravenously over 30 minutes, completing the infusion approximately 30 minutes prior to chemotherapy. For paediatric patients less than 12 years, administer IVEMEND intravenously over 60 minutes, completing the infusion approximately 30 minutes prior to chemotherapy.
** **Dexamethasone** should be administered 30 minutes prior to chemotherapy treatment on Day 1.

The safety and efficacy of IVEMEND in infants below 6 months of age have not been established. No data are available.

2.2. Non-clinical aspects

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

There are no changes to section 5.3. of the SmPC as a consequence of this extension of indication, apart from an editorial change (deletion of the word "adults").

2.3. Clinical aspects

2.3.1. Introduction

The studies listed below have all been previously submitted and assessed within other procedures.

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

P029

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
2012-002340-24 [Ref. 5.3.3.2: P029 MK0517]	IIb	Worldwide (Europe, North and South America, Asia)	A Phase IIb, Partially-Blinded, Randomized, Active Comparator Controlled Study to Evaluate the Pharmacokinetics/ Pharmacodynamics, Safety, and Tolerability of Fosaprepitant in Pediatric Patients for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated with Emetogenic Chemotherapy. Open-Label Cohort to Further Evaluate the Pharmacokinetics/ Pharmacodynamics, Safety, and Tolerability of Fosaprepitant in Pediatric Patients Birth to <12 Years Old	A multicenter, partially-blinded, randomized, parallel-group, PK/PD, dose-ranging study with an open label substantial amendment that allowed for dose adjustment and further assessment of fosaprepitant in younger age cohorts (0 to <12 years old)	**Fosaprepitant regimen** Fosaprepitant 150 mg, 60 mg, 20 mg, or 5 mg/kg (or age/weight-adjusted dose) IV, single-dose + ondansetron IV ± dexamethasone IV **Control regimen** Placebo for fosaprepitant (normal saline) IV, single-dose + ondansetron IV ± dexamethasone IV	Eligible subjects were male or female, between the ages of birth and 17 years (inclusive) with a documented malignancy scheduled to receive chemotherapeutic agent(s) associated with moderate, high, or very high risk of emetogenicity	Fosaprepitant 150 mg: 42 Fosaprepitant 60 mg: 43 Fosaprepitant 20 mg: 40 Fosaprepitant 5 mg/kg: 74 Control: 35

P044

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
2014-001783-34 [Ref. 5.3.5.1: P044MK0517]	III	Worldwide (Europe, North and South America, Asia)	A Phase III, Randomized, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of MK-0517/Fosaprepitant and Ondansetron Versus Ondansetron for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Subjects Receiving Emetogenic Chemotherapy.	A randomized, placebo-controlled, parallel-group, multi-site, double-blind trial to evaluate the efficacy and safety of fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric patients receiving chemotherapeutic agent(s) associated with moderate or high risk of emetogenicity, or chemotherapy agent(s) not previously tolerated due to vomiting.	**Fosaprepitant regimen** Cycle 1: Day 1 Age 0 to < 12 years: Fosaprepitant 5 mg/kg (or age-specific adjustment not to exceed 150 mg) + ondansetron (Cycle 1) or any 5-HT3 antagonist (Cycles 2 to 6) ± dexamethasone IV 12 to 17 years: Fosaprepitant 150 mg + ondansetron (Cycle 1) or any 5-HT3 antagonist (Cycles 2 to 6) ± dexamethasone IV. **Control regimen** Cycle 1: Day 1 Age 0 to 17 years: Placebo for fosaprepitant (normal saline) + ondansetron (Cycle 1) or any 5-HT3 antagonist (Cycles 2 to 6) ± dexamethasone IV	Eligible patients were male or female, between the ages of birth and 17 years (inclusive) with a documented malignancy scheduled to receive chemotherapeutic agent(s) associated with moderate or high risk of emetogenicity	Fosaprepitant: 38 Control:37

P097

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
0869-097 [Ref. 5.3.5.1: P097]	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

P134

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
2006-005515-10 [Ref. 5.3.3.2: P134]	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

P148

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
2008-0031-78-17 [Ref. 5.3.3.2: P148]	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

P208

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
2011-000651-16 [Ref. 5.3.5.1: P208]	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

P017L1

Methodology	Study Population			Diagnosis/ Inclusion Criteria	Dosage/ Duration	Evaluation Criteria
	M	F	Age Range			
A worldwide, multicenter, randomized, double-blind, parallel-group trial with in- house blinding to assess the safety, tolerability, and efficacy of a single dose of intravenous fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving cisplatin chemotherapy	1470	852	19-83 20-86	Male and female patients ≥ 18 years of age, scheduled to receive their first course of cisplatin chemo-therapy for a documented solid malignancy at a dose of 70 mg/m^2 administered over a maximum of 3 hours.	Fosaprepitant Regimen: 4 days: fosaprepitant (150 mg IV on Day 1) in combination with ondansetron (32 mg IV Day 1) and dexa-methasone (12 mg on Day 1, 8 mg on Day 2, and 16 mg on Days 3 and 4). Aprepitant regimen: 4 days: aprepitant (125 mg PO on Day 1 and 80 mg on Days 2 and 3) in combination with ondansetron (32 mg IV on Day 1) and dexa-methasone (12 mg on Day 1, 8 mg on Days 2 and 3, and 8 mg on Day 4).	Efficacy: The primary endpoint assessed was the proportion of patients with Complete Response (no vomiting and no use of rescue therapy) overall (in the 120 hours following initiation of cisplatin). The secondary endpoints were the proportion of patients with Complete Response (no vomiting and no use of rescue therapy) in the delayed phase (25 to 120 hours following initiation of cisplatin), and the proportion of patients with no vomiting overall (in the 120 hours following initiation of cisplatin). Safety: Events related to the primary endpoint (vomiting, retching, nausea) were not defined as adverse experiences during Day 1 until the morning of Day 6, unless they met the definition of a serious adverse experience. Severe infusion site pain, severe infusion site erythema and/or severe infusion site induration, as well as any episode of infusion site thrombophlebitis were designated Events of Clinical Interest (ECI).

P031

Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
A Phase III Randomized Double Blind Active Comparator Controlled Parallel Group Study Conducted Under In House Blinding Conditions to Examine the Efficacy and Safety of a Single 150 mg Dose of Intravenous Fosaprepitant Dimeglumine for the Prevention of Chemotherapy Induced Nausea and Vomiting CINV Associated With Moderately Emetogenic Chemotherapy	A worldwide multi center phase III, randomized double blind active comparator controlled parallel group study with in house blinding to assess the safety tolerability and efficacy of a single IV dose of 150 mg fosaprepitant for the prevention of CINV in subjects treated with MEC	Fosaprepitant regimen: Day 1: 150 mg fosaprepitant IV initiated ~30 minutes prior to chemotherapy and infused over 20-30 minutes; 8 mg ondansetron PO ~30-60 minutes prior to chemotherapy plus 8 mg ondansetron PO ~8 hours after first dose of ondansetron; 12 mg dexamethasone PO plus 2 placebo dexamethasone capsules ~30 minutes prior to chemotherapy. Days 2-3: placebo for ondansetron every 12 hours. Control regimen: Day 1: 150 mg fosaprepitant placebo IV ~30 minutes prior to chemotherapy; 8 mg ondansetron PO ~30-60 minutes prior to chemotherapy plus 8 mg ondansetron PO ~8 hours after first dose of ondansetron; 20 mg dexamethasone PO ~30 minutes prior to chemotherapy. Days 2-3: 8 mg ondansetron PO every 12 hours.	Males females Age ≥ 18 years of age Naïve to moderately or highly emetogenic chemotherapy and scheduled to be treated with a single IV dose of one or more MEC agents	Fosaprepitant regimen 504 subjects Control regimen 497 subjects

2.3.2. Pharmacokinetics

The plasma exposure to aprepitant following IV administration of fosaprepitant has been characterized previously in adults. The plasma exposure to aprepitant following per oral (PO) administration of aprepitant (Emend) oral solution or capsules has been previously characterized in children from 6 months of age to 18 years of age and in adults.

The current variation concerns the extension of use of IV fosaprepitant in children 6 months of age to 18 years of age. Therefore, this section will mainly focus on the pharmacokinetics (PK) of aprepitant in this population following IV administration of fosaprepitant.

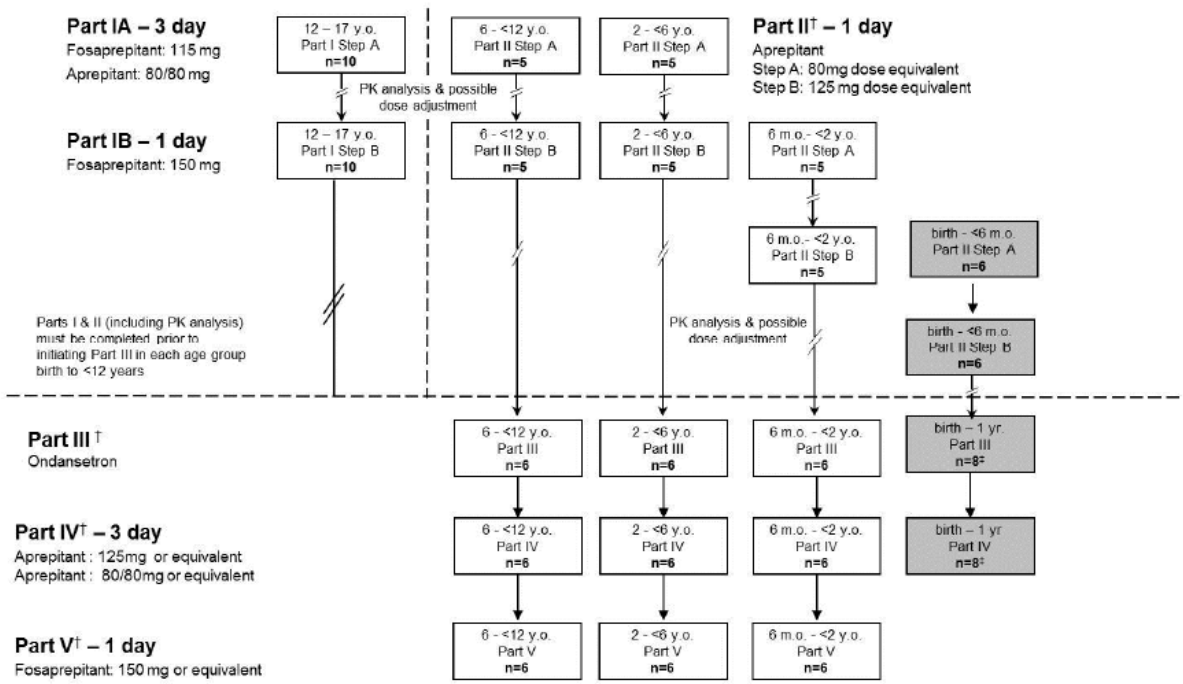
Study 134

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

A study schematic is shown in the

Figure 2 below.

Figure 2: Schematic of the design of study 134 (grey boxes indicate cohorts that were originally planned but later not included)



Patients were enrolled in age descending cohorts. The design of the study allowed evaluation of PK in older children before commencing treatment in younger patients in order to be able to adjust the dose between cohorts.

Both 1 day and 3 day regimens were evaluated. For children >= 12 years of age a fixed dosing regimen was used while for children < 12 years of age the dose was adjusted according to body size, either weight or body surface area. The different dose levels are listed below:

Part I (12 to 17 years of age)

Step A

Day 1: Fosaprepitant 115 mg IV + ondansetron IV

Days 2-3: Aprepitant 80 mg by mouth (PO) + ondansetron IV

Step B

Day 1: Fosaprepitant 150 mg IV + ondansetron IV

Part II (Birth to <12 years of age)

Step A

Day 1: Equivalent to aprepitant 80 mg PO + ondansetron IV

- 6 months to <12 years of age: Aprepitant 47 mg/m2 PO

Step B

Day 1: Equivalent to aprepitant 125 mg PO + ondansetron IV

- 2 years to <12 years of age: Aprepitant 74 mg/m2 PO
- 6 months to <2 years of age: Aprepitant 1.3mg/kg PO

Part III (Birth to <12 years)

Days 1 to 3: Ondansetron IV

Part IV (Birth to <12 years)

Day 1: Equivalent to aprepitant 125 mg + ondansetron IV

- 4 months to <12 years of age: Aprepitant 3.0 mg/kg PO

Days 2 to 3: Equivalent to aprepitant 80 mg + ondansetron IV

- 4 months to <12 years of age: Aprepitant 2.0 mg/kg PO

Part V (6 months to <12 years)

Day 1: Fosaprepitant 3.0 mg/kg IV + ondansetron IV

The 6, 7, 9, and 13 time point plasma profiles were utilized. The 6-point sampling schedule was to be utilized to evaluate the PK of IV dexamethasone in patients birth to one year of age. The 7-point sampling schedule was to be utilized to evaluate the PK of oral aprepitant in patients birth to one year of age. The 9-point sampling schedule included 9 draw times over 72 hours and was utilized to evaluate the PK of oral aprepitant in Parts II and IV. For Parts I and V, a 13-point sampling schedule included 13 draw times over 72 hours and was utilized to evaluate the PK of both aprepitant and fosaprepitant.

Validated bioanalysis methods were used for determination of aprepitant and fosaprepitant (only Part I and part V) and pertinent pharmacokinetic parameters (e.g. AUC0-∞, AUC0-24hr, Cmax, Tmax, CL/F, t1/2 and C24hr) were calculated based on non-compartmental analysis.

Pharmacokinetic parameters are summarized in **Table 3** for 12 to 17 year old patients receiving the 3 day regimen (fosaprepitant 115 mg IV on day 1 followed by aprepitant 80 mg PO on day 2 and day 3).

Table 3: Descriptive Statistics of Aprepitant Plasma Pharmacokinetic Parameters Following Administration of 115 mg IV Fosaprepitant on Day 1 Followed by 80 mg Oral Aprepitant on Days 2 and 3 in 12 - 17 Year Old Patients Undergoing Chemotherapy (Protocol 134, Part I Step A)

12 to 17 Years	C_{max} (ng/mL)	T_{max} (hr)	C_{24hr} (ng/mL)	$AUC_{0-24\ hr}$ (hr*ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)
N	12	12	8	8	10	11
AM	3240	0.41	433	19500	310	199
SD	1280	0.27	318	8010	288	281
Median	3080	0.25	407	19300	171	84.9
Min	1650	0.25	133	9940	66.2	BLQ
Max	6210	1	1120	33100	904	796

Table 4: Descriptive Statistics of Aprepitant Plasma Pharmacokinetic Parameters Following Administration of 150 mg IV Fosaprepitant in 12 - 17 Year Old Patients Undergoing Chemotherapy (Part I Step B)

12 to 17 Years	C_{max} (ng/mL)	T_{max} (hr)	C_{24hr} (ng/mL)	$AUC_{0-24\ hr}$ (hr*ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)
N	11	11	11	11	10	11
AM	5870	0.64	825	30800	230	114
SD	2770	0.3	321	7020	324	186
Median	4960	0.5	742	31000	112	14.5
Min	2880	0.5	413	17800	BLQ	BLQ
Max	12300	1.5	1360	42200	1080	498
Adult (P165)						
N	41	-	41	41	-	-
GM (95% CI)	4010 (3680, 4370)	N/A	577 (510, 654)	24500 (22700, 26300)	N/A	N/A

Table 5: Descriptive Statistics of Aprepitant Plasma Pharmacokinetic Parameters Following Administration of 3 mg/kg IV Fosaprepitant in 6 - <12 Year Old, 2 - <6 Year Old, 0.5 - <2 Year Old Patients Undergoing Chemotherapy (Protocol 134, Part V)

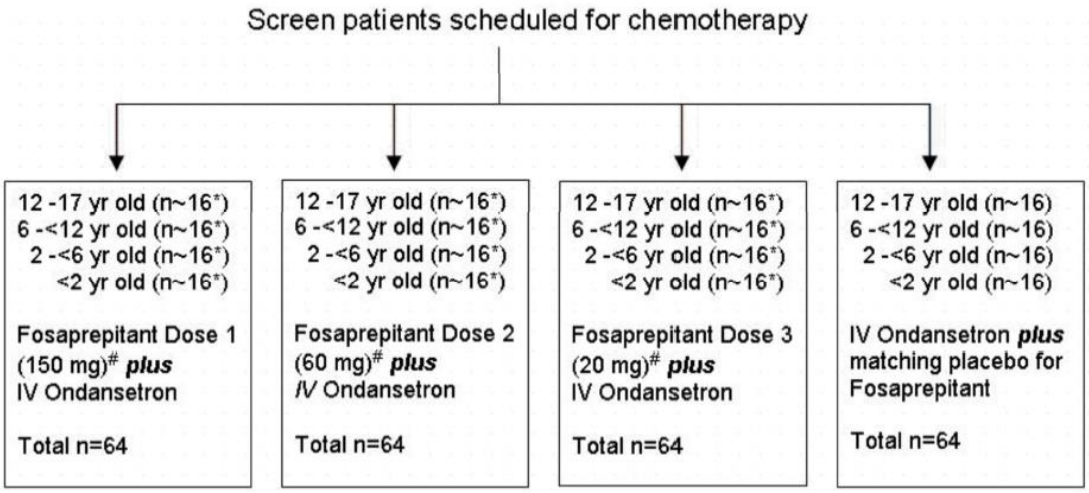
6 - <12 years	C_{max} (ng/mL)	T_{max} (hr)	C_{24hr} (ng/mL)	$AUC_{0-24\ hr}$ (hr*ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)
N	8	8	8	8	8	8
AM	2850	1.07	308	19500	37.5	NR
SD	641	0.11	240	6720	56.5	NR
Median	2830	1	210	16300	16.2	BLQ
Min	1800	1	100	14000	BLQ	BLQ
Max	3630	1.25	751	34000	159	92.5
2 - <6 years						
N	7	7	7	7	7	7
AM	2430	1.41	184	18300	NR	NR
SD	1100	0.83	189	11100	NR	NR
Median	2570	1.03	182	20600	BLQ	BLQ
Min	1260	1	BLQ	6190	BLQ	BLQ
Max	3880	3.27	462	36000	114	22.1
0.5 - < 2 years						
N	7	7	6	6	6	6
AM	1700	1.13	150	11700	NR	NR
SD	636	0.17	103	6980	NR	NR
Median	1730	1	169	11300	BLQ	BLQ
Min	838	1	BLQ	1810	BLQ	BLQ
Max	2470	1.42	282	19800	50.8	19.8
Adult (P165)						
N	41	-	41	41	-	-
GM (95% CI)	4010 (3680, 4370)	N/A	577 (510, 654)	24500 (22700, 26300)	N/A	N/A

Study 029

A Phase IIb, Partially-Blinded, Randomized, Active Comparator-Controlled Study to Evaluate the Pharmacokinetics/Pharmacodynamics, Safety, and Tolerability of Fosaprepitant in Pediatric Patients for the Prevention of Chemotherapy- Induced Nausea and Vomiting (CINV) Associated with Emetogenic Chemotherapy

The study design, per Amendment 01 and the revised study design, implemented with Amendment 04, are described below.

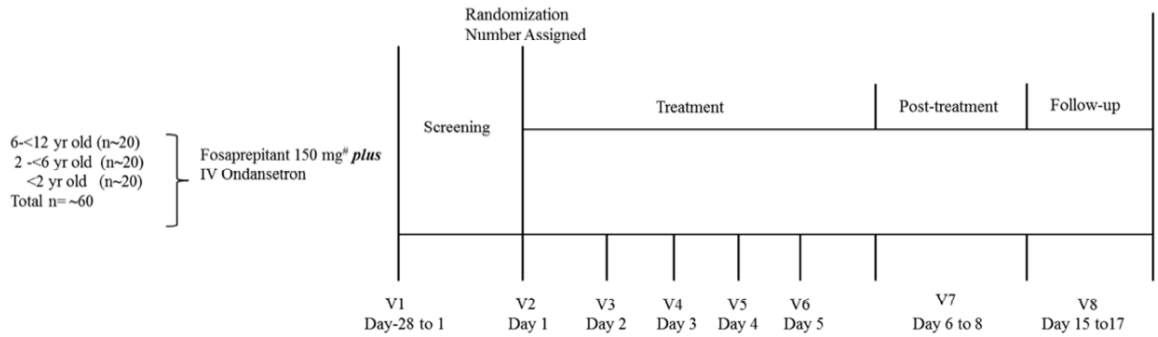
Figure 3: Amendment 01 Study Schematic



* Note: PK only drawn on 12 patients/age group (fosaprepitant dose groups only)
# Dose used for adolescents; children below 12 years of age received a corresponding weight-adjusted dose, described in Section 1.6 of the protocol [16.1.1]

Amendment 01 was designed as a partially-blinded, randomized, parallel-group, doseranging study designed to assess the PK, PD, safety and tolerability of aprepitant after administration of a single dose of fosaprepitant concomitant with IV ondansetron with or without dexamethasone. The study planned to enroll 256 pediatric cancer subjects from birth to 17 years old into 1 of 4 treatment groups; however, subjects <2 years of age were not permitted to enroll until PK and safety data became available from the older age cohorts.

Figure 4: Amendment 04 Study Schematic



Note: PK samples drawn from all subjects.
#All subjects received a corresponding age-specific weight-adjusted dose.

Amendment 04 added an open-label, single treatment arm designed to assess the PK, PD, safety and tolerability of aprepitant in subjects <12 years old after administration of a single 5 mg/kg dose of fosaprepitant with concomitant IV ondansetron with or without dexamethasone. In addition to the 166 subjects already enrolled, the revised study planned to enroll approximately 60 subjects from birth to <12 years old.

All treatment regimens were administered concomitantly with ondansetron, with or without dexamethasone at the discretion of the investigator. The fosaprepitant dosing regimens were designed to achieve aprepitant PK exposures (AUC) similar to those in adults. For subjects <12 years old, the doses were 3 mg/kg, 1.2 mg/kg, and 0.4 mg/kg. For subjects 12 to 17 years old, the doses were 150 mg, 60 mg, and 20 mg. Subjects in the control regimen received placebo for fosaprepitant.

Among subjects randomized/allocated to the fosaprepitant Dose 1 treatment group, plasma concentrations were available for a total of 34 subjects who received a single IV dose of fosaprepitant (150 mg for 12 to 17 year olds and 3 mg/kg for 2 to <12 year olds). Pharmacokinetic parameter values for each of the age groups (AUC0-24, AUC0-inf, Cmax, Tmax, C24, CL/F and t1/2) for this dose group across all age groups are summarised in **Table 6**.

Table 6: Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 150 mg Single Dose IV Fosaprepitant Regimen in Subjects Aged 12 to 17 Years and 3 mg/kg (up to 150 mg) in Pediatric Subjects 2 to <12 Years Old (LOQ Values – 10.0 ng/mL)

	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
12 to 17 Year-Olds	AUC0-∞ (hr*ng/mL)	AUC_{0-24hr} (hr*ng/mL)	C_{max} (ng/mL)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	T_{max} (hr)	Apparent Terminal $t_{1/2}$ (hr)	CL/F (mL/min)
N	3	12	12	12	0	12	3	3
AM	33800	30400	3500	735	NR	0.546	10.5	76.2
SD	7180	8290	972	310	NR	0.144	1.0	16.2
ACV (%)	21.3	27.3	27.7	42.2	NR	26.3	9.6	21.2
Med	33200	29400	3730	714	NR	0.500	10.7	75.2
Min	26900	21300	1800	343	NR	0.500	9.39	60.6
Max	41200	48100	4600	1240	NR	1.00	11.4	92.9
GM	33300	29400	3360	675	NR	0.534	10.5	75.1
GCV (%)	21.6	26.1	32.7	46.0	NR	20.1	9.8	21.6
6 to <12 Year-Olds[†]								
N	8	14	14	14	0	14	8	8
AM	34300	29200	3550	589	NR	1.99	7.69	69.2
SD	20300	14300	2460	433	NR	1.62	2.09	66.4
ACV (%)	59.1	48.8	69.2	73.5	NR	81.6	27.2	95.9
Med	28400	29500	2700	550	NR	1.14	7.64	46.6
Min	10900	9650	1210	81.0	NR	0.533	4.39	34.0
Max	69000	60700	9190	1260	NR	6.00	11.9	231
GM	29200	26000	2930	419	NR	1.55	7.45	55.0
GCV (%)	69.0	54.9	69.5	119.9	NR	79.6	28.1	68.8
2 to <6 Year-Olds								
N	5	6	6	6	0	6	5	5
AM	15300	21800	2320	278	NR	2.29	6.55	66.2
SD	11100	22200	1540	398	NR	2.14	3.62	25.5
ACV (%)	72.9	101.8	66.1	142.9	NR	93.5	55.3	38.5
Med	9830	10600	1590	63.2	NR	1.00	4.96	63.6
Min	9530	9140	1020	33.5	NR	1.00	4.29	31.9
Max	35100	65100	4550	1020	NR	6.08	12.9	101
GM	13100	15900	1960	115	NR	1.68	5.95	61.8
GCV (%)	60.6	94.7	69.8	255.1	NR	97.5	48.2	45.0
Adult (P165)								
N	41	41	41	41	-	-	-	-
GM (95% CI)	35100 (31500, 39200)	24500 (22700, 26300)	4010 (3680, 4370)	577 (510, 654)	N/A	N/A	N/A	N/A

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NR: Not Reportable

[†]AN# [redacted] was excluded from summary statistics due to dosing deviation.

Exposures in adolescent subjects receiving 150 mg closely matched the exposures observed in adults while pediatric subjects 2 to <12 years old, all together, had exposures less than those observed adults. Thus a higher dose of 5 mg/kg (Dose 4) was tested in subjects 0.5 to < 12 years old.

Among subjects randomized to fosaprepitant Dose 4 treatment group, plasma concentrations were available for a total of 72 subjects who received a single IV dose of fosaprepitant (5 mg/kg up to 150 mg for birth to <12 year olds). Pharmacokinetic parameter values for each of the age groups (AUC0-24, AUC0-inf, Cmax, Tmax, C24, C48, CL/F, and t1/2) for this dose group across all age groups are summarized below.

Table 7: Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 5 mg/kg (up to 150 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged 6 - < 12 Years (LOQ Values – 10.0 ng/mL)

6 to <12 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
	AUC0-∞‡ (hr*ng/mL)	AUC0-24hr† (hr*ng/mL)	Cmax (ng/mL)	C24hr (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2‡ (hr)	CL/F‡ (mL/min)
N	13	23	24	24	11	24	13	13
AM	55300	47400	4400	1210	164	2.92	9.77	42.1
SD	11900	17300	1910	1000	124	5.09	2.49	12.7
ACV (%)	21.5	36.5	43.5	83.0	75.9	174.7	25.5	30.3
Med	54000	45200	4390	867	99.6	1.00	9.33	38.0
Min	36200	21800	1960	452	18.5	0.917	5.99	22.4
Max	73200	89300	10500	4950	391	24.5	14.5	62.8
GM	54100	44700	4090	992	120	1.57	9.47	40.3
GCV (%)	22.6	36.2	39.8	61.9	112.7	114.7	26.4	31.7

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale;

†For AN # [redacted] the 0hr (End of Infusion) and 48hr samples were missing and AUC0-24hr parameter value was excluded from summary statistics.

‡Thirteen out of 24 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 13 subjects.

Table 8: Plasma Pharmacokinetic Parameters With Descriptive Statistics for Aprepitant Following Administration of 5 mg/kg (up to 150 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged 2 to <6 Years (LOQ Values – 10.0 ng/mL)

2 to <6 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
	AUC0-∞† (hr*ng/mL)	AUC0-24hr (hr*ng/mL)	Cmax (ng/mL)	C24hr (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2† (hr)	CL/F† (mL/min)
N	20	25	25	25	20	25	20	20
AM	46400	45000	4270	1060	232	1.90	9.27	31.8
SD	18600	23800	2370	1020	471	2.16	4.17	13.8
ACV (%)	40.1	52.9	55.4	96.3	202.6	114.1	45.0	43.5
Med	42800	36100	3950	577	50.8	1.00	8.21	27.7
Min	18600	16300	1500	194	0.00	0.917	5.61	12.8
Max	100000	131000	11300	4040	1970	9.33	22.9	72.0
GM	43300	40500	3800	738	NC	1.39	8.64	29.3
GCV (%)	39.0	47.2	51.0	99.9	NC	75.3	37.2	42.6

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NC: Not Calculated;

†Twenty out of 25 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 20 subjects.

Table 9: Plasma Pharmacokinetic Parameters With Descriptive Statistics for Aprepitant Following Administration of 5 mg/kg (up to 150 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged Birth to <2 Years (LOQ Values – 10.0 ng/mL)

Birth to <2 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
	AUC0-∞† (hr*ng/mL)	AUC0-24hr‡ (hr*ng/mL)	Cmax (ng/mL)	C24hr‡ (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2† (hr)	CL/F† (mL/min)
N	16	21	22	21	10	22	16	16
AM	37200	36800	3550	691	352	2.01	7.94	24.2
SD	15800	21800	1500	852	929	2.10	2.86	11.9
ACV (%)	42.5	59.2	42.2	123.3	264.1	104.3	36.0	49.3
Med	35700	32500	3260	535	30.8	1.08	7.02	21.6
Min	12500	10200	1340	78.0	0.00	1.00	4.16	7.81
Max	81100	118000	7040	3970	2990	9.00	12.4	50.4
GM	34200	32700	3280	436	NC	1.50	7.46	21.6
GCV (%)	45.8	50.9	43.0	123.7	NC	76.5	38.0	53.8

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NC: Not Calculated;

† Sixteen out of 22 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 16 subjects.

‡ For AN # [redacted] only 0hr (End of Infusion) sample is available and for this subject only Cmax and Tmax were reported with an assumption that Cmax was reached at the end of infusion.

Pharmacokinetic parameters obtained in adult patients after IV administration of 150 mg ivemend are presented in

Table 10 for purpose of comparison.

Table 10: Pharmacokinetic parameters obtained in adult patients after IV administration of 150 mg ivemend

Adult (P165)								
N	41	41	41	41	-	-	-	-
GM (95% CI)	35100 (31500, 39200)	24500 (22700, 26300)	4010 (3680, 4370)	577 (510, 654)	N/A	N/A	N/A	N/A

N: Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.

Pediatric subjects 6 months to <12 years old receiving 5 mg/kg, as a group, had higher exposures than those observed in adults.

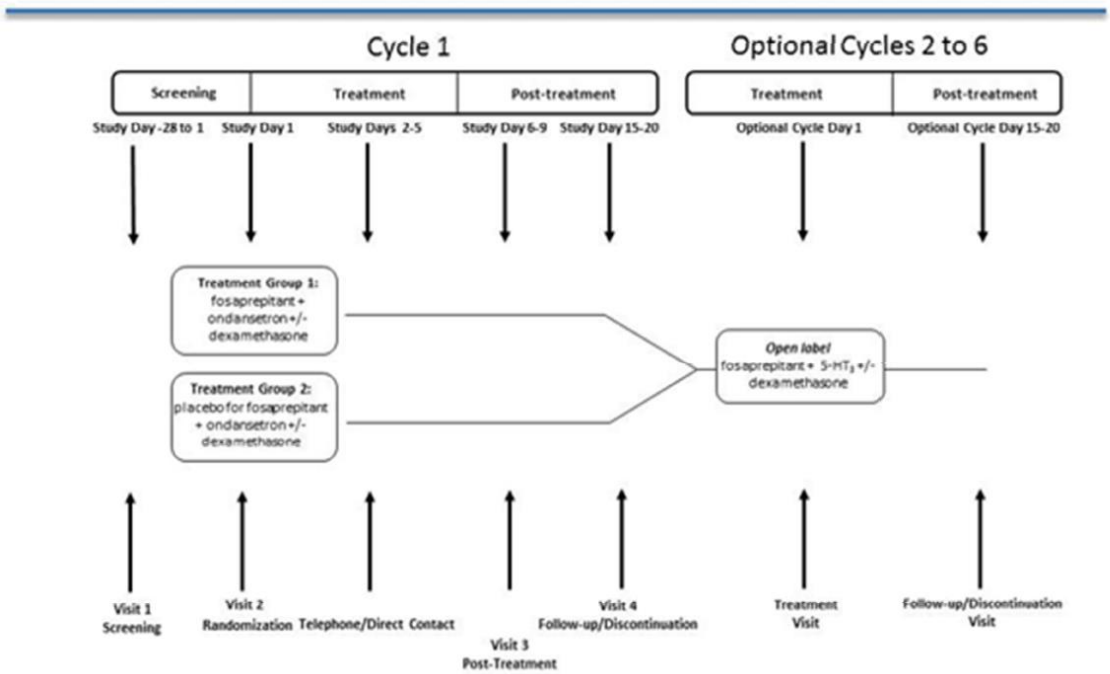
Study 044

A Phase III, Randomized, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of MK-0517/Fosaprepitant and Ondansetron Versus Ondansetron for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Subjects Receiving Emetogenic Chemotherapy

The main objectives of this study were assessed during a single chemotherapy cycle (Cycle 1), where 150 mg fosaprepitant as a single-dose IV administration in subjects 12 – 17 years old and 5 mg/kg (up to 150 mg) in subjects 2 to <12 were administered in a double-blind manner. Upon completion of Cycle 1, eligible subjects were invited to participate in an open-label fosaprepitant treatment period for up to 5 more cycles of chemotherapy.

A study schematic is presented in **Figure 5**.

Figure 5: A study schematic



A decision was made to terminate enrolment in the clinical trial early as the Sponsor determined, in consultation with relevant regulatory authorities, that data from this study were not necessary to support a marketing application for use in paediatric patients.

A total of 55 paediatric subjects aged 2 to 17 years old who received fosaprepitant had evaluable aprepitant plasma concentrations. Pharmacokinetic parameters (e.g. AUC0-24hr, Cmax, C24hr and Tmax) after single-dose IV administration of 150 mg fosaprepitant in subjects 12 to 17 years old and of 5 mg/kg (up to 150 mg) fosaprepitant in subjects 2 to <12 years old were evaluated with a non-compartmental analysis (NCA) for each age cohort.

Table 11: Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 150 mg Single Dose IV Fosaprepitant Regimen in Subjects Aged 12 to 17 Years (LOQ Values - 10.0 ng/mL)

12 to 17 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
	$AUC_{0-\infty}$ (hr*ng/mL)	AUC_{0-24hr} (hr*ng/mL)	C_{max} (ng/mL)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	T_{max} (hr)	Apparent Terminal $t_{1/2}$ (hr)	CL (mL/min)
N	8	23	26	23	15	26	8	8
AM	56800	34100	3560	856	236	1.65	15.5	59.3
SD	28600	12700	1580	612	185	4.69	6.19	43.8
ACV (%)	50.4	37.4	44.4	71.5	78.2	284.3	39.9	73.8
Med	54200	31600	3170	704	211	0.57	17.7	46.2
Min	15400	13600	1660	167	0.00	0.50	7.23	22.2
Max	112000	62800	8400	3010	509	24.5	24.6	162
GM	50000	31900	3290	703	NC	0.736	14.3	50.0
GCV (%)	63.5	39.0	40.1	71.4	NC	101.5	47.4	63.5

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where
ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NC: Not Calculated

Table 12: Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 5 mg/kg (up to 150 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged 2 to 12 Years (LOQ Values - 10.0 ng/mL)

	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
6 to <12 Year-Olds	**$AUC_{0-\infty}$ (hr*ng/mL)**	**AUC_{0-24hr} † (hr*ng/mL)**	**C_{max} (ng/mL)**	**C_{24hr} (ng/mL)**	**C_{48hr} (ng/mL)**	**T_{max} (hr)**	**Apparent Terminal $t_{1/2}$ (hr)**	**CL/F (mL/min)**
N	10	14	18	14	14	18	10	10
AM	60500	43700	4230	878	108	1.31	10.2	41.9
SD	23300	15700	1330	483	93.8	0.888	3.00	12.8
ACV (%)	38.6	35.9	31.6	55.0	87.1	68.0	29.5	30.7
Med	53500	41200	4180	740	93.5	1.00	10.5	42.3
Min	37900	27900	2020	307	0.00	0.50	6.13	21.7
Max	115000	83400	7560	1970	265	4.23	14.8	66.0
GM	57300	41500	4030	764	NC	1.15	9.76	40.1
GCV (%)	33.7	32.9	33.0	60.2	NC	49.0	31.9	33.0
2 to <6 Year-Olds								
N	6	9	11	9	9	11	6	6
AM	62500	48900	4170	1100	255	1.23	9.71	30.1
SD	55600	34200	2160	843	282	0.673	4.01	10.7
ACV (%)	88.9	70.0	51.7	76.8	110.7	54.9	41.3	35.6
Med	38600	33700	3610	715	271	1.00	8.75	28.0
Min	34800	26600	2390	483	11.3	0.98	5.87	14.3
Max	175000	133000	8490	2950	922	3.25	16.2	45.0
GM	50600	42100	3790	886	118	1.14	9.07	28.4
GCV (%)	69.7	56.5	45.5	74.1	325.4	36.2	41.6	41.4

N: Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.

In general, the dosing regimens across each of the age cohorts resulted in similar exposures. The observed exposure data in adolescents and pediatric subjects are consistent with those data observed in Protocol 029 for subjects administered with the same dose. Because of early termination of enrollment, the total number of randomized and evaluable subjects was substantially less than planned; therefore, these additional PK data were not included in the population PK model.

Population pharmacokinetics

The PK of aprepitant was evaluated in paediatric patients by a population modelling approach. Concentration-time data from four studies (Protocols 029, 097, 134, and 148) with moderately dense to dense PK sampling were combined to compile an analysis PK dataset following doses of aprepitant and fosaprepitant. The current population PK model (04LVBW) supporting this application is an update to the model previously submitted for 3-day oral pediatric regimens with the addition of plasma concentration data from 169 pediatric subjects in Protocol 029 to provide dosing recommendations for 1-day and 3-day fosaprepitant regimens. This final analysis dataset includes additional PK, dosing and demographic data from 22 patients 6 months to <2 years, 46 patients 2 years to <6 years, 64 patients 6 years to <12 years and 37 patients 12 to 17 years, all receiving a single IV dose of fosaprepitant. The original analysis (02Y0Y0) included a total of 1326 measurable concentrations from 147 pediatric patients aged 6 months to 19 years.

The aims of the current PopPK analysis were to:

- Update the existing population PK model of aprepitant after aprepitant/fosaprepitant administration using final clinical data from studies P097, P134, P148 and P029 and assess the impact of key covariates (including demographics, oral and IV formulations) in CINV / PONV patients;
- Evaluate / validate the updated population PK model to insure its accuracy, precision and robustness;
- Perform a model-based simulations and determine the appropriate single-(1) day and 3-day dosing regimens of fosaprepitant by assessing PK exposure of aprepitant in targeted age groups of pediatric patients (i.e., <2 years old, 2 to <6 years old, 6 to <12 years old, 12 to <18 years old).

Modeling followed a conventional approach starting with structural model development followed by evaluation of covariates and model qualification. Simulations of the therapeutic dosing regimen were based on the final model.

All PK data were evaluated using nonlinear mixed-effects modeling implemented in NONMEN v7.3 with first order conditional estimation (FOCE).

The previous structural population PK model4 included an allometric component accounting for body size (i.e., parameters were scaled to WT/70 using a power of 0.75 for clearances and a power of 1 for volumes). However, the effects of WT on all parameters were also fitted on the pediatric data and compared with the theoretical values.

The previous structural model also included the effect of age (i.e., post-natal age) on CYP3A4-mediated clearance. The age effect was re-evaluated in the current analysis and thus not included in the structural model.

In NONMEM control files, the doses of fosaprepitant were scaled using a conversion factor of 534.44 / 614.4 assuming that fosaprepitant with molecular weight of 614.4 g/mol, is rapidly converted to the active drug, aprepitant (molecular weight of 534.44 g/mol).

Conversion of fosaprepitant to aprepitant in children

The topic of conversion of fosaprepitant to aprepitant in children with comparison to that in adults was addressed and resolved under the scope of Article 46 of Regulation 1901/2006, procedure number EMEA/H/C/743/P46/024.1.

Following IV infusions of fosaprepitant in paediatric patients from 6 months to 12 years (3 mg/kg) and adolescents 12 through 17 years of age (150 mg), fosaprepitant is rapidly converted to aprepitant, typically within 30 minutes from the end of the infusion and consistent with that observed in adults (150 mg). Some (9/23) fosaprepitant plasma concentration values were observed for a longer duration (i.e., beyond 30 minutes after the end of the infusion time) in patients 6 months to <12 years (Figures 4, 5, 6 and 7). After the 2.25-hour PK sampling time point, all fosaprepitant plasma concentrations in paediatric patients 6 months to <12 years old were reported as below the limit of quantitation (BLQ). Whilst these findings could be suggestive of a slower conversion to aprepitant in younger children, given the difference in length of infusion duration for fosaprepitant and the significant variability in the fosaprepitant plasma concentrations observed among the patients 6 months to <12 years of age, it is unlikely that these observations are clinically relevant and therefore, not expected to influence the current (2017) population PK model or the underlying assumptions. Additionally, conversion of fosaprepitant to aprepitant involves hydrolysis of the phosphoramide moiety by phosphatases in a

variety of mammalian tissues and is unlikely to differ significantly between adult and paediatric subpopulations. Furthermore, the variability in time to non-quantifiable concentrations of fosaprepitant did not impact the Tmax of aprepitant in the paediatric subjects, with measurable aprepitant concentrations appearing rapidly, from the first samples collected; therefore, the assumption of instantaneous conversion of fosaprepitant to aprepitant appears to be conserved across adult and paediatric populations.

Figure 6: Individual Fosaprepitant (MK-0517) Plasma-Time Profiles Following Administration of 150 mg IV Fosaprepitant in 12-17 year Old Patients Undergoing Chemotherapy (N=11; LLQQ=10 ng/mL)

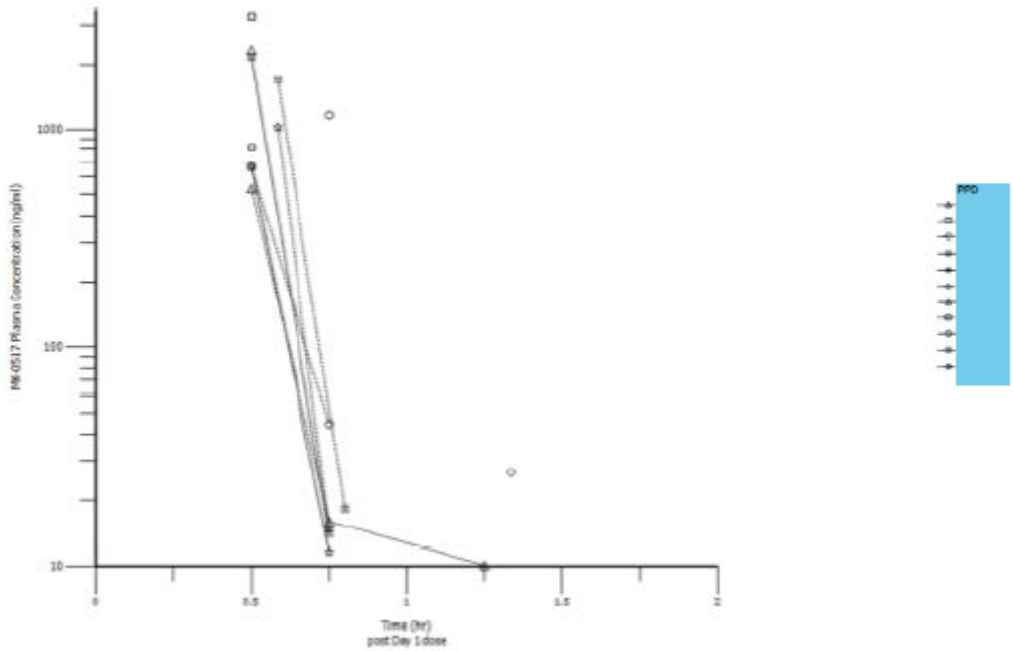


Figure 7: Individual Fosaprepitant (MK-0517) Plasma-Time Profiles in Log Scale Following Administration of 3mg/kg IV Fosaprepitant in 6-12 Years Old (N=8; LLQQ=10 ng/mL)

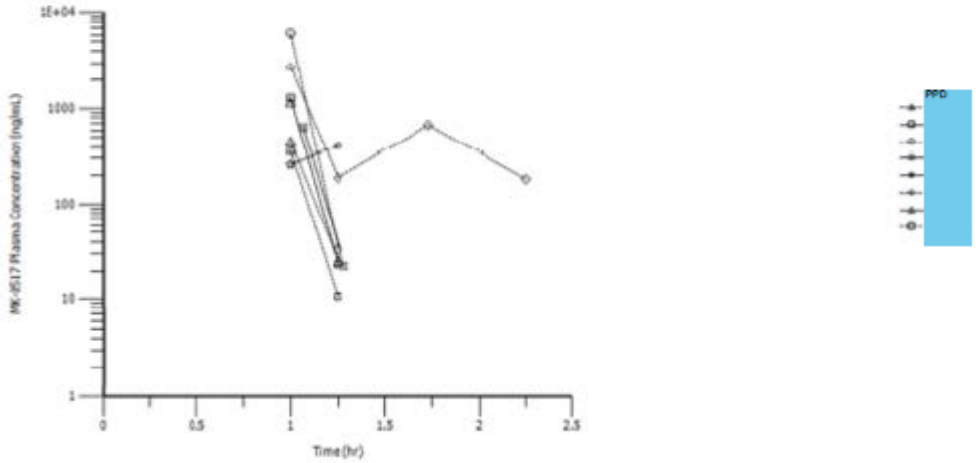


Figure 8: Individual Fosaprepitant (MK-0517) Plasma-Time Profiles in Log Scale Following Administration of 3mg/kg IV Fosaprepitant in 2-6 Years Old (N=8; LLQQ=10 ng/mL)

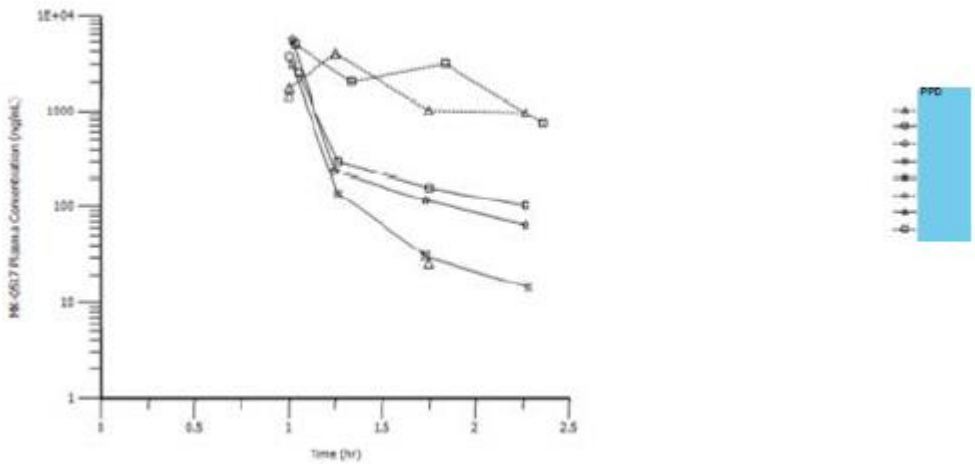
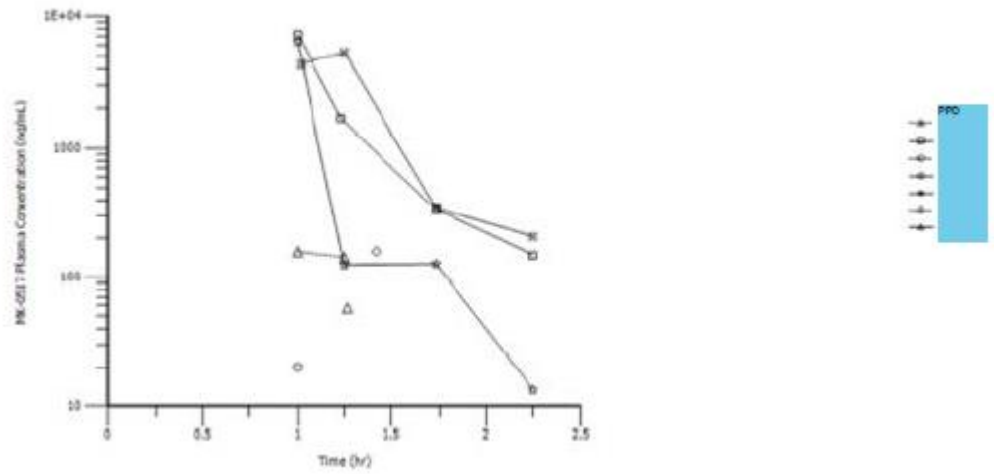


Figure 9: Individual Fosaprepitant (MK-0517) Plasma-Time Profiles in Log Scale Following Administration of 3mg/kg IV Fosaprepitant in 0.5-2 Years Old (N=7; LLQQ=10 ng/mL)



Covariates and PK parameters

The relationships between covariates and PK parameters were explored graphically to obtain information of covariates likely to affect the PK of aprepitant. Scatter matrix plots presenting the relationships between the inter-individual variability of PK parameters and the continuous variables included LOESS lines, Pearson correlation coefficients, and the corresponding p-value for each relationship. Box plots were used to describe the relationship for categorical covariates.

The following covariates were firstly tested:

- Intrinsic factors: age, sex, race
- Extrinsic factors: aprepitant formulations (capsule and suspension), dose levels, ethylenediaminetetraacetic acid level (original and reduced)

Evaluation of fosaprepitant formulation on systemic PK parameters was also performed to detect potential effect of ethylenediaminetraacetic acid (EDTA) in fosaprepitant, which was at reduced level for fosaprepitant in Study P029 and original level for fosaprepitant in Study P134.

The covariates with relevant trends were formally evaluated within the population PK model using a full model approach. Full model parameter estimates and 95% confidence interval (CIs) were derived with the standard error generated with NONMEM ($COV). Statistically significant covariates were retained in the reduced final model if the 95%CI excluded the null value relative to the reference population.

Model validation and qualification of population PK models for fosaprepitant/aprepitant was based on numerical criteria (eg. parameter precision and number of significant digits of the final estimate) and diagnostic plots (eg. conditional weighted residuals vs time after dose) common to pharmacometric model development. Internal model validation with the final model was conducted by performing visual predictive check (VPC).

Sensitivity analysis was performed to evaluate the impact BLQ concentration on the model output. The final population PK model was re-run using M3 approach described by Beal10 and the estimated typical

values and VPC plots were compared with those derived with the final model, which excluded all BLQ concentrations.

The final population PK model of aprepitant/fosaprepitant in pediatric population was used to simulate the PK of aprepitant to support single dose of fosaprepitant and 3-day dosing regimens fosaprepitant and aprepitant in CINV/PONC pediatric patients. The simulation data set included demographic data from studies P097, P134, P148 and P029. Monte-Carlo simulations were performed in NONMEM ($SIM) based on the dosing regimens. Simulations were generated using a total of 100 replicates. Individual PK parameters (Cmax, concentration at 24 h [C24], concentration at 48 h [C48], and concentration at 72 h [C72]) were computed using NCA based on rich concentration profiles of aprepitant. Partial areas under the concentration-time curve from 0 to 24 hours post-dose (AUC0-24h) and AUCinf were computed using the linear trapezoidal rule.

Modeling results

Dosing history and demographic data provided for a total of 316 paediatric subjects, administrated by aprepitant/fosaprepitant for the prevention of CINV/PONC were included in the population PK analysis. Descriptive statistics of continuous and categorical demographic data from subjects in studies P134, P148, P097 and P029 are respectively summarised in **Table 13**:

Table 13: Descriptive Statistics of Continuous Covariates of Paediatric Subjects Included in the Population PK Analysis (Summarized by Clinical Studies)

Continuous Covariates	Continuous Covariates Mean (CV%) Median [Minimum-Maximum]				
	P134 N=85	P097 N=18	P148 N=44	P029 N=169	Overall N=316
Age (years)	7.36 (72.8) [redacted]	15.0 (11.9)	6.83 (76.0)	7.98 (58.6)	8.06 (63.6) 7.92 [0.500-19.0]
Body mass index (kg/m^2)	17.4 (19.1) [redacted]	20.0 (19.1)	17.5 (23.1)	17.2 (21.8)	17.5 (21.3) 16.6 [11.6-34.3]
Height (cm)	119 (28.8) [redacted]	169 (4.6)	117 (28.4)	126 (24.5)	125 (26.5) 126 [63.5-185]
Weight (kg)	28.0 (67.8) [redacted]	56.9 (23.8)	27.7 (76.6)	29.9 (61.1)	30.6 (64.4) 25.4 [6.80-104]

CV= Coefficient of variation; N= Number of subjects
Note 1: Interim data of Study P029 was used to derive the descriptive statistics.
Note 2: SUBJID=# [redacted] (Study P029, [redacted]) was included in the interim data but was excluded from the final data since the dose was not adequately captured. The patient characteristics of this subject are included in the descriptive statistics.

Table 14: Descriptive Statistics of Categorical Covariates of Paediatric Subjects Included in the Population PK Analysis (Summarized by Clinical Studies)

Categorical Covariates		Count (%) of Subjects in Sub-Population				
		P134 N=85	P097 N=18	P148 N=44	P029 N=169	Overall N=316
Age Group	<2 years	18(21.2%)	0	12(27.3%)	22(13.0%)	52(16.5%)
	2 to < 6 years	24(28.2%)	0	11(25.0%)	46(27.2%)	81(25.6%)
	6 to <12 years	20(23.5%)	0	12(27.3%)	64(37.9%)	96(30.4%)
	12 to ≤19 years	23(27.1%)	18(100%)	9(20.5%)	37(21.9%)	87(27.5%)
Race	White	PPD				252(79.7%)
	Black					12(3.80%)
	Asian					18(5.70%)
	American Indian/native					2(0.633%)
	Multi/Other					32(10.1%)
Sex	Male	29(34.1%)	15(83.3%)	31(70.5%)	91(53.8%)	166(52.5%)
	Female	56(65.9%)	3(16.7%)	13(29.5%)	78(46.2%)	150(47.5%)

N= Number of subjects
Note 1: Interim data of Study P029 was used to derive the descriptive statistics.
Note 2: SUBJID=#PPD (Study P029, PPD was included in the interim data but was excluded from the final data since the dose was not adequately captured. The patient characteristics of this subject are included in the descriptive statistics.

Table 15: Summary of Continuous Demographic Data at Baseline (Summarized by Age Groups)

Continuous Covariates	Continuous Covariates Mean (CV%) Median [Minimum-Maximum]			
	<2 years N=52	2 to <6 years N=81	6 to <12 years N=96	12 to ≤19 years N=87
Age (years)	1.20 (35.7)	4.05 (29.0)	9.17 (18.4)	14.7 (11.4)
Body mass index (kg/m^2)	16.9 (11.3)	15.4 (12.9)	17.0 (20.3)	20.2 (22.0)
Height (cm)	76.4 (8.7)	101 (9.5)	136 (8.9)	165 (5.3)
Weight (kg)	9.94 (18.1)	15.8 (23.0)	32.0 (31.8)	55.3 (26.4)

CV= Coefficient of variation; N= Number of subjects
Note 1: Interim data of Study P029 was used to derive the descriptive statistics. Note 2: SUBJID=#PPD (Study P029, PPD was included in the interim data but was excluded from the final data since the dose was not adequately captured. The patient characteristics of this subject are included in the descriptive statistics.

Table 16: Summary of Categorical Demographic Data (Summarized by Age Groups)

Categorical Covariates		Count (%) of Subjects in Sub-Population			
		<2 years N=52	2 to <6 years N=81	6 to <12 years N=96	12 to ≤19 years N=87
Race	White	[redacted]			
	Black				
	Asian				
	American Indian/native				
	Multi/Other				
Sex	Male	28(53.8%)	36(44.4%)	49(51.0%)	53(60.9%)
	Female	24(46.2%)	45(55.6%)	47(49.0%)	34(39.1%)

N= Number of subjects
Note 1: Interim data of Study P029 was used to derive the descriptive statistics. Note 2: SUBJID=# [redacted] (Study P029, [redacted]) was included in the interim data but was excluded from the final data since the dose was not adequately captured. The patient characteristics of this subject are included in the descriptive statistics.

The total number of aprepitant concentrations available for the development of the population PK model of aprepitant/fosaprepitant is presented in **Table 17**:

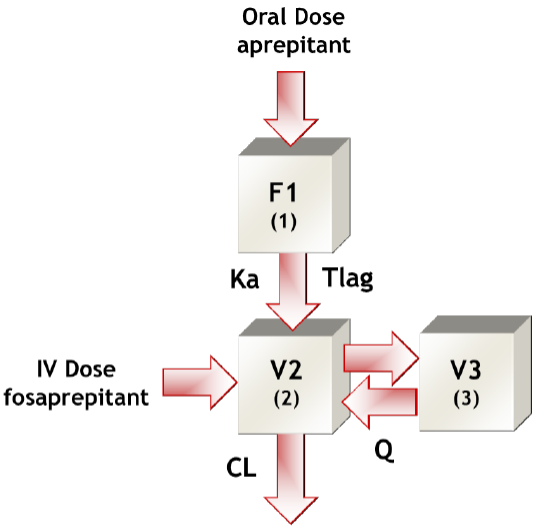
Table 17: Number of Aprepitant Concentrations Available for the Population PK Modelling (Summarized by Clinical Studies)

PK Samples	Number of PK Samples (% of Total within Study) (% of the Overall)				
	P134 N=85	P097 N=18	P148 N=44	P029 N=169	Overall N=316
BLQ	189 (17.8%)	35 (19.0%)	83 (21.3%)	18 (2.05%)	325 (12.9%)
Non-BLQ	871 (82.2%)	149 (81.0%)	306 (78.7%)	862 (98.0%)	2188 (87.1%)

BLQ= Below the limit of quantification; N= Number of subjects; PK= Pharmacokinetic
Note 1: Interim data of Study P029 was used to derive the descriptive statistics.
Note 2: SUBJID=# [redacted] (Study P029, [redacted]) was included in the interim data but was excluded from the final data since the dose was not adequately captured. The 5 PK samples collected patient characteristics in this subject are included in the counts.

A two-compartment pharmacokinetic model with first-order absorption, lag-time and relative bioavailability was used as the structural model of aprepitant. The schematic of this structural population PK model is shown below:

Figure 10: Schematic Representation of the Population Pharmacokinetic Model of prepitant in Pediatric Population



CL = Systemic clearance; F1 = Relative bioavailability for oral administration; Ka = First-order constant of absorption; Tlag = Lag-time of absorption; Q = Inter-compartmental clearance; V2 = Central volume of distribution; V3 = Peripheral volume of distribution
Note: Compartment (1) represents the depot compartment (2) represents central compartment and compartment (3) – peripheral compartment.

The concentration data were analyzed on the log10 scale, which allowed description of assay error with a single-parameter log-normal distribution.

The base population PK model included the following covariate effects:

- effect of WT on clearance (CL and Q) normalized to 70 kg to a power of 0.75: $\times(\text{Weight}/70)^{0.75}$
- effect of WT on volumes (V2 and V3) normalized to 70 kg: $\times(\text{Weight}/70)$

Typical values of CL and V2 of aprepitant in CINV / PONV patients computed from the base structural model were 5.25 L/h and 46.3 L, respectively. The relative standard error (RSE) for CL and V2 were 4.4% and 12.9%, respectively. The capsule formulation was associated to a lag time of absorption (Tlag) of 0.95 h. The relative bioavailability for oral absorption (F1) of aprepitant was 83.9%. All model parameters were estimated with a RSE <40%.

Exploratory analyses were first performed to visually assess the effect of key covariates (i.e., age, sex, race, reduced vs. original EDTA content, formulation, study, WT, dose levels) on PK parameters of aprepitant derived with the structural model.

According to scatter matrix plot, negative trend was observed between individual random effect of V2 and baseline age which was statistically significant (p=0.0015) and similar trend was observed using categorical age group based on boxplot. This covariate was added to the structural model (run015) using multiplicative function (i.e., $V2 = tvV2 \times (Age/8)^{Age\_V}$).

According to the covariate box plot of the structural model (run015) a negative trend also was observed between Ka and formulation. Thus, the formulation effect was induced in the model using exponential function (i.e., Ka = tvKa × exp(Form_Ka)), with one specific value for each suspension formulation (i.e., one for Study P134 and another for Study P148).

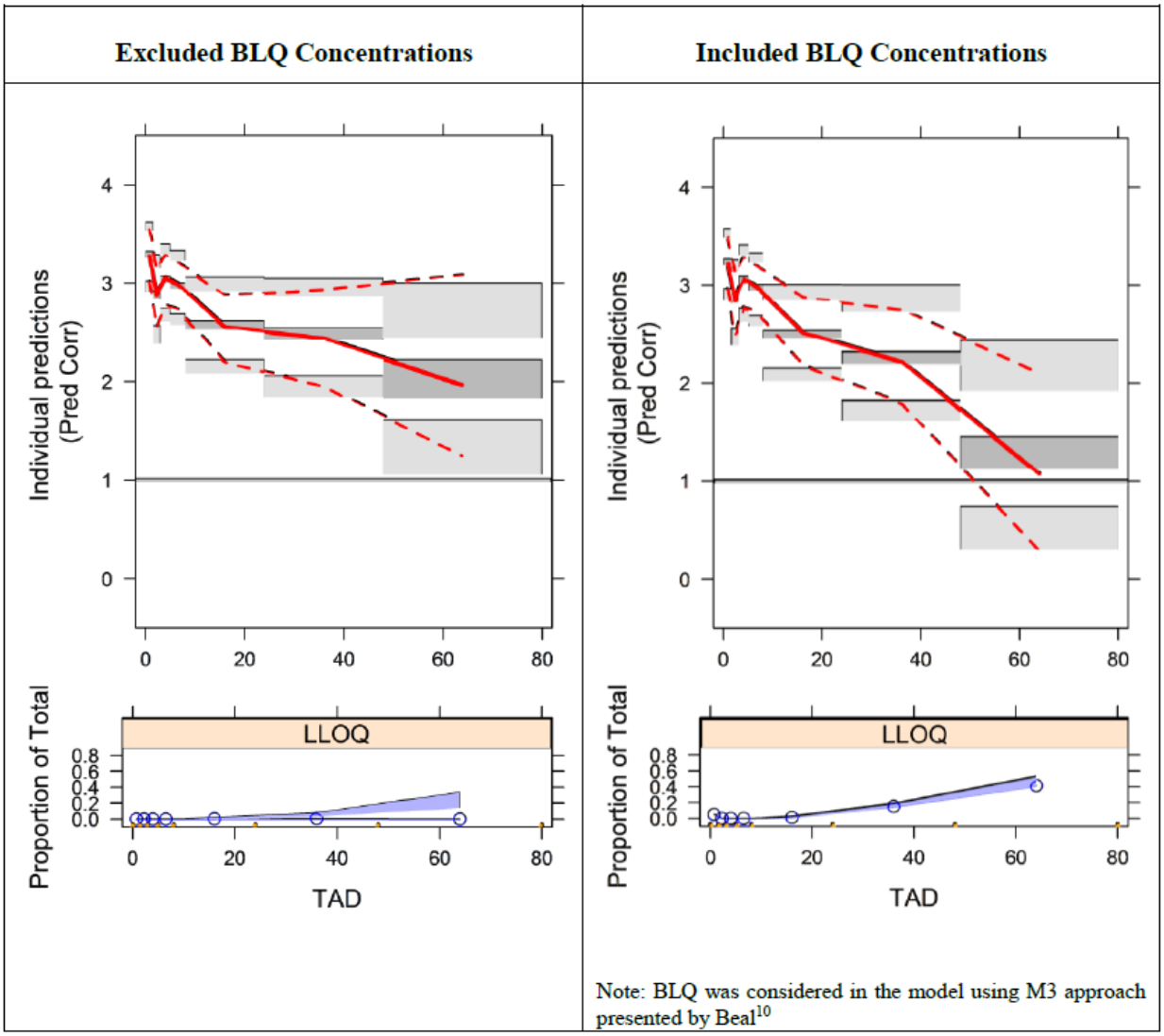
A small negative trend was observed between individual random effect of CL and total dose. Since in the previous analysis the inclusion of dose on CL significantly improved the overall model fit, this effect was re-evaluated with the current dataset using a power function (i.e., CL = tvCL × $(Dose/80)^{Dose\_CL}$).

After including the above covariates (i.e., age on V2, formulation on Ka and dose on CL), exponents of WT/70 on the PK parameters were fitted with the current dataset with same fitted value for clearances (i.e., CL and Q) and same fitted value for volumes (i.e., V2 and V3). The fitted exponents were almost the same as the fixed exponents (i.e., 0.79 for clearances and 1.03 for volumes) and the estimation of WT effects does not significantly improved the overall model fit (i.e., OFV decreasing of -0.5). Thus the model with fixed exponents was kept for the next step.

The inclusion of EDTA on CL significantly decreased the OFV by 23.51 ($p<0.001$) and at the second step EDTA on V3 decreased the OFV by 15.16 ($p<0.001$). No covariate was significant at the 3rd step and no covariate was removed in the backward elimination with $p<0.001$. However, based on the 95%CI derived for the effects of EDTA on CL and V3, only the effect of reduced EDTA on CL was statistically significant and thus was retained in the final model.

The impact of BLQ concentrations on the estimation of the PK parameters of aprepitant was evaluated using the M3 method. VPC plots for the model estimated with and without considering the BLQ concentrations are shown in **Figure 11**.

Figure 11: Visual Predictive Check – Final Population PK Model (Interim Data P029) With and Without BLQ Concentrations (Overall Population)



BLQ= Below limit of quantification; LLOQ= Lower limit of quantification; TAD= Time after dose

Note: 6 bins were generated with the following boundaries for TAD: 1.5,3,5,8,24,48,80 h

The final population PK model developed with the PK dataset with interim data of Study P029 was updated with the final dataset with locked data from all studies. Typical population PK values of aprepitant derived with the final dataset are presented in **Table 18**:

Table 18: Typical Values of the Final Population PK Model of Aprepitant/Foraprepitant (Locked Data P029)

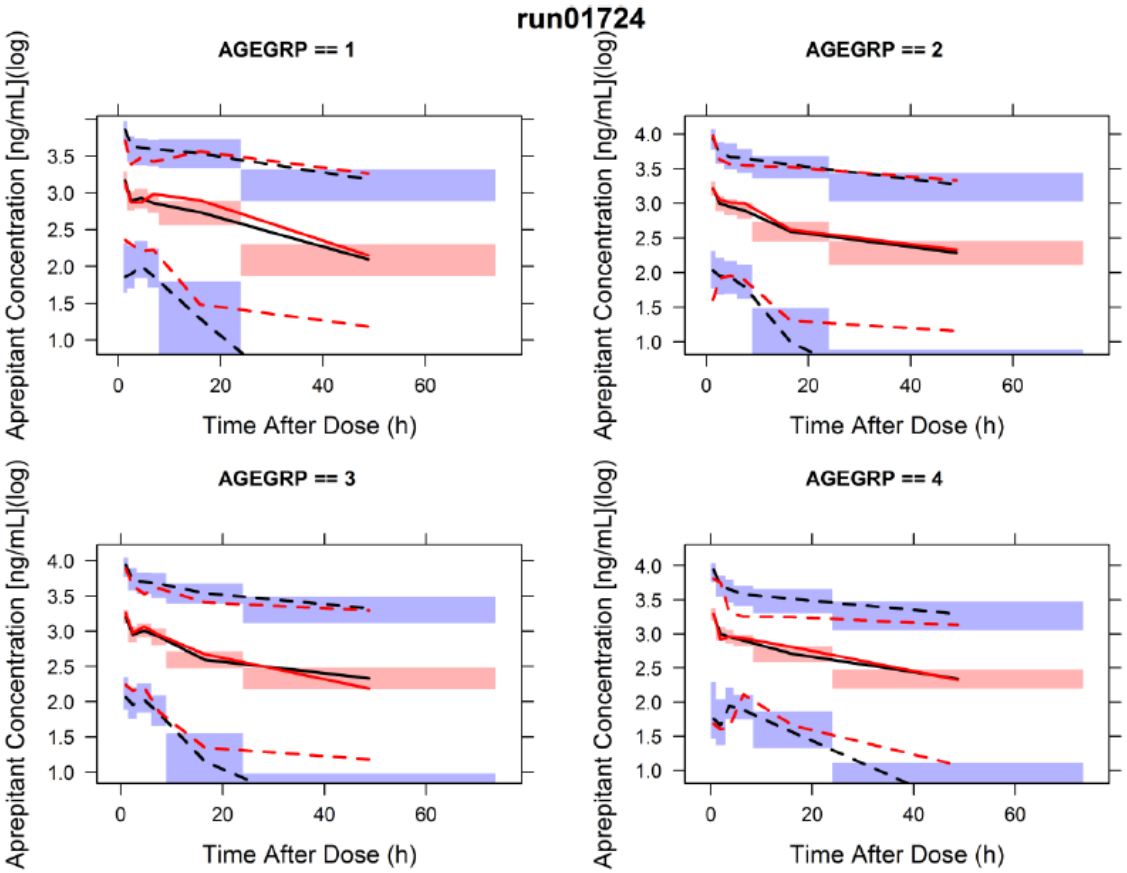
Parameter	Units	Estimate	SE	RSE	Shrinkage	Equations
OFV		-4123.2978				
CL	L/h	5.38	0.363	6.7%		$CL = tvCL \times (WT/70)^{0.75} \times Effect_{Dose} \times \exp(\eta CL)$
V2	L	47.8	4.94	10.3%		$V2 = tvV2 \times (WT/70) \times Effect_{AGE} \times \exp(\eta V2)$
Q	L/h	35.6	8.52	23.9%		$Q = tvQ \times (WT/70)^{0.75} \times \exp(\eta Q)$
V3	L	37.9	4.48	11.8%		$V3 = tvV3 \times (WT/70) \times \exp(\eta V3)$
Ka	1/h	0.319	0.118	37.2%		$Ka = tvKa \times Effect_{Form} \times \exp(\eta Ka)$
Tlag - capsule	h	0.938	0.0272	2.9%		Tlag = Caps_Tlag
Tlag - suspension	h	0 fix				
F1		0.918	0.0803	8.7%		$F1 = tvF1 \times \exp(\eta F1)$
Dose_CL		-0.253	0.0410	16.2%		$Effect_{Dose} = (Dose/80)^{Dose\_CL}$
AGE_V2		-0.205	0.0424	20.7%		$Effect_{AGE} = (Age/8)^{AGE\_V2}$
Form_Ka (suspension, P134)		0.369	0.374	101.3%		$Effect_{Form}$ (suspension) = exp(Form_Ka)
Form_Ka (excipients, P148)		0.821	0.407	49.6%		$Effect_{Form}$ (excipients) = exp(Form_Ka)
EDTA_CL (reduced level in P029)		-0.295	0.0645	21.9%		$Effect_{EDTA}$ reduced level = exp(EDTA_CL)×
IIV CL		60.7%	0.0564	15.3%	11.0%	ω^2_{CL}
IIV V2		58.8%	0.0641	18.5%	21.4%	ω^2_{V2}
IIV Q		72.2%	0.257	49.4%	64.5%	ω^2_{Q}
IIV V3		61.6%	0.0934	24.6%	34.1%	ω^2_{V3}
IIV Ka		103.6%	0.231	21.6%	50.2%	ω^2_{Ka}
IIV F1		55.1%	0.0969	31.9%	51.3%	ω^2_{F1}
Log10ResErr		0.159		.	17.2%	log10(Cobs) = log10(Cpred)+Log10ResErr

AGE_V2 = Effect of age on population V2; CL = Systemic clearance; Dose_CL = Effect of dose on CL; EDTA_CL = Effect of EDTA on CL; F1 = Relative bioavailability for oral administration; Ka = First-order rate constant of absorption; IIV = Inter-individual variability; OFV = Objective function value; Q = Inter-compartmental clearance; RSE= Relative standard error; SE= Standard error; Tlag = Lag-time of absorption; tvF1 = Typical value of relative bioavailability for oral administration; tvCL = Typical value of systemic clearance; tvQ = Typical value of inter-compartmental clearance; tvV2= Typical value of central volume of distribution; tvV3= Typical value of peripheral volume of distribution; V2 = Central volume of distribution; V3 = Peripheral volume of distribution

Note: IIV CV% were calculated as $100\% \times (\omega^2)^{0.5}$

A visual predictive check by Age group for the final model is shown in **Figure 12**:

Figure 12: A visual predictive check by Age group for the final model



AGEGRP = Age group.
Note 1: AGEGRP=1: subjects with <2 years; AGEGRP=2: subjects with 2 to <6 years; AGEGRP=3: subjects with 6 to <12 years; AGEGRP=4: subjects with 12 to ≤19 years.
Note 2: Full and dashed red lines represent 2.5th, 50th and 95th percentiles of observed aprepitant concentrations within each bin; shaded area represent 95% percentile interval of percentiles of predicted concentrations (50th percentiles are in red and 2.5th and 97.5th percentiles in blue).
Note 3: 6 bins were generated with equal counts of observation per bin

2.3.3. Pharmacodynamics

Mechanism of action

No new data on the mechanism of action were submitted.

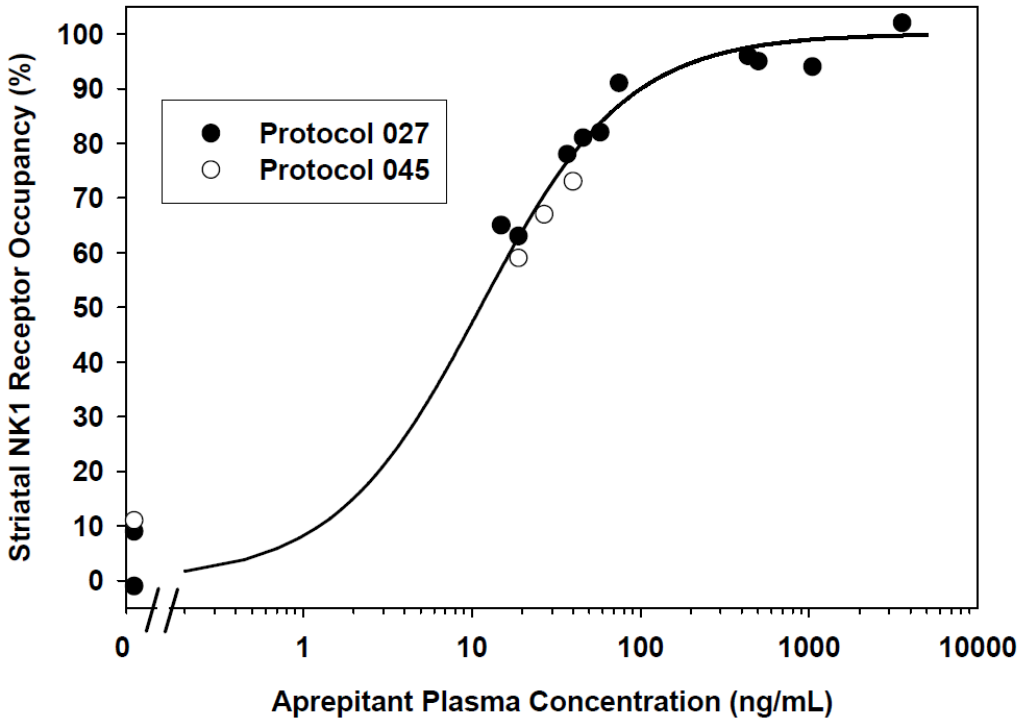
Primary and secondary pharmacology

No new information on primary and secondary pharmacology was submitted.

2.3.4. PK/PD modelling

The correlation of plasma aprepitant concentrations with the binding of aprepitant to brain NK1 receptors was assessed in two Phase I studies (Protocol 027) and (Protocol 045) in healthy young men. Data from both studies were combined in an exploratory post-hoc analysis, which revealed that the relationship between plasma aprepitant concentration and NK1 receptor occupancy was well correlated with a curve described by the Hill equation (see figure below). Based on this curve, aprepitant plasma concentrations of ~10 ng/mL and ~100 ng/mL are associated with brain NK1 receptor occupancies of ~50 and 90%, respectively.

Figure 13: Correlation of Plasma Aprepitant Concentration with Binding of Aprepitant to Striatal NK1 Receptors in Adults



Extrapolation

The MAA for a paediatric indication of fosaprepitant is based on extrapolation of data from an adult population treated with fosaprepitant (1-day regimen) and a paediatric population treated with aprepitant (3-day regimen).

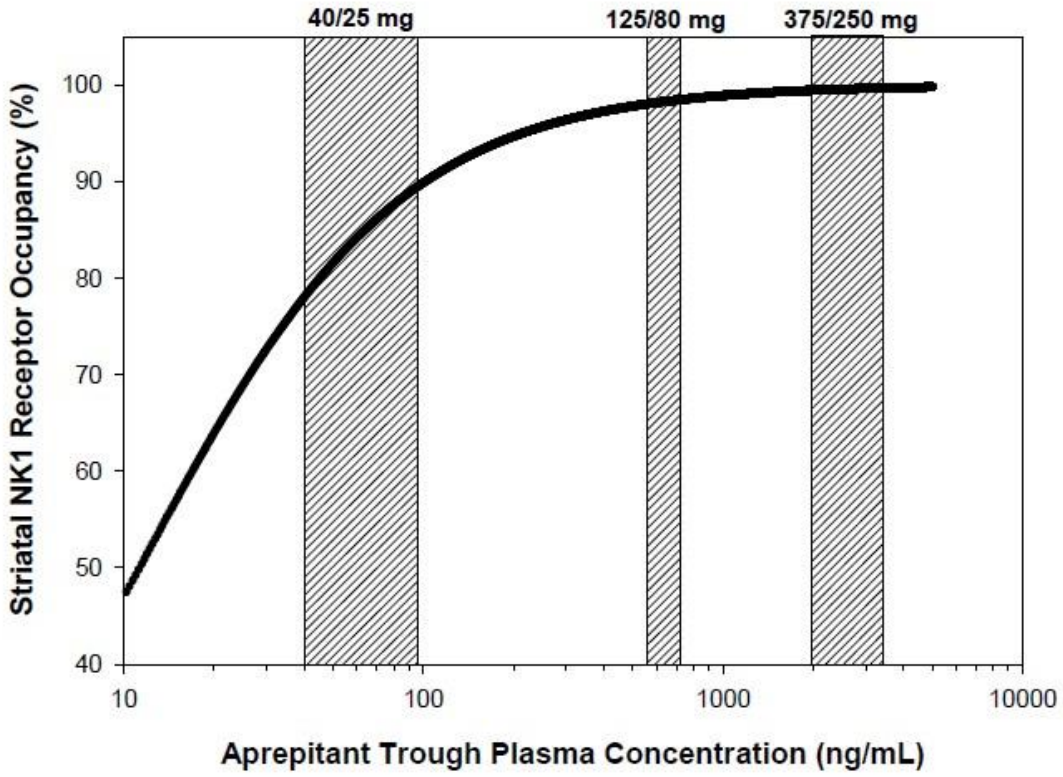
The steps taken to determine an appropriate aprepitant dose in a paediatric population was assessed within procedure EMEA/H/C/527/X/49/G. Aprepitant dose selection in the paediatric population was based on an approach to match the drug exposure to those previously demonstrated to be safe and efficacious in adults. In adults, plasma exposures of the approved aprepitant 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% (see figure above). Higher doses were not associated with greater efficacy, whereas doses associated with CNS NK1 receptor occupancy <80 to 85% were submaximally efficacious. Pharmacokinetic data from aprepitant study P097, P134 as well as PK data from a separate PONV-study (P148) were used to develop a population PK-model for aprepitant which

was used to conduct dose adjustments for subjects 6 months to <12 years of age that would approximate PK parameters associated with safe and efficacious exposures in adults. The efficacy and safety of this aprepitant dose regimen was further evaluated within Protocol 134 (Part IV) as well as Protocol 208.

The Applicant has in a previous application presented an analysis where the upper part of the established PKPD curve on receptor occupancy vs. concentration is super-imposed with the observed trough concentration ranges in adults at different dosing regimens.

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.

Figure 14: Aprepitant Trough Plasma Concentration (ng/mL)



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.

However, based on simulated data regarding aprepitant dosing, the group 6-<12 years had the lowest mean AUC among the paediatric groups. Cmin levels were lower than in adults in all paediatric patients < 12 years, while Cmin levels in adolescents were relatively similar as in adult cancer patients. It was noted that trough concentrations of around 100-150 ng/ml, obtained at the proposed doses for children < 12 years, were 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 375/259 mg). From pharmacokinetic data it was therefore not evident that paediatric patients would obtain >95% receptor occupancy and maximum efficacy. However, since the

proposed dose regimen led to clinically relevant response rates in all age groups, it was considered acceptable for the aprepitant paediatric indication.

Thus, with a rapid and high conversion rate to aprepitant after intravenous fosaprepitant administration, the expected NK1 receptor occupancy would be similar in a paediatric aprepitant or fosaprepitant treated population. Even without exactly the same levels of aprepitant Cmin levels in an adult and paediatric population, the effect size is determined clinically relevant in the paediatric population.

2.3.5. Discussion on clinical pharmacology

Fosapripetant is a prodrug which is converted rapidly in the body to apripetant following IV injection. Apripetant in its turn works as an antagonist on NK_1-receptors thereby reducing nausea and vomiting following administration of highly and moderately emetogenic cancer chemotherapy (abbreviated HEC and MEC, respectively).

Intravenous fosaprepitant is already approved as a one day (single dose) regimen for treatment of chemotherapy-induced nausea and vomiting (CINV) as well as for the prevention of postoperative nausea and vomiting (PONV) in adults. The current recommended dose is 150 mg as a 20 min to 30 min infusion. It should be coadminstered with p.o. corticosteroids and 5-HT_3 antagonist.

Oral aprepitant (Emend) is approved for use in children from 6 months to 18 years of age as a 3 day regimen for the treatment of prevention of chemotherapy-induced nausea and vomiting (CINV) when used in combination with other antiemetic agents.

In this application the MAH seeks to bridge the efficacy of the 3-day oral aprepitant dose in children to a 3-day iv fosaprepitant dose in the same age categories. The applicant also seeks to extrapolate the efficacy of 1-day fosaprepitant dose in adults to a 1-day dose in children. Therefore clinical pharmacology data need to support the extension of the approved adult one day IV fosaprepitant regimen to children from 6 months of age to 17 years of age and the extension of the 3 day PO aprepitant regimen to a 3 day IV or PO fosaprepitant or aprepitant regimen bassed on similarity in exposure regardless of IV or PO adminiatration.

The PK of aprepitant in children following IV administration of fosaprepitant has been studied. The complexity due to different dosing regimens for different age groups and studies makes interpretation of observed PK data and exposure metrics difficult. Population PK modeling is therefore necessary in order to integrate the complete body of data and draw conclusions regarding the adequacy of the proposed dosing regimens.

A thorough population PK analysis using the data from studies Protocols 029, 097, 134, and 148 was carried out by the applicant and the methods used were appropriate. The current analysis was based on a previous popPK model that was used to support the extension of the indication for Emend to children down to 6 months of age (see European Public Assessment Report for Emend EMEA/H/C/527/X/0049/G). The model was adequate to describe the PK data in the entire paediatric population and is considered qualified for simulation of the proposed dosing regimens in children from 2 years to 18 years of age. Conclusion regarding the influence of body weight on the drug disposition is supported.

The PopPK model was sufficient for the purpose of describing the exposure in the pediatric population at hand (6 months to 18 years of age). The current model does not take maturation of eliminating systems into account; but due to the lack of a maturation function on clearance, the difference in exposure comparing models with and without maturation function does not translate to large

differences in receptor occupancy and expected efficacy. Similarly, although the model does not take account to the PK data that were below the lower limit of quantification, this is not expected to translate into large differences in receptor occupancy and clinical efficacy.

Aprepitant is likely metabolised by cytochrome P450 enzymes. These enzymes are known to mature during at least the first year after birth. The Applicant provided simulations of exposure using a model where the previous maturation function is included. The impact on different exposure metrics, eg. Cmax, C24, C48, C72, AUC, was illustrated using simulations and thoroughly discussed. The applicant was asked to illustrate the impact of maturation on secondary PK parameters (AUC, Cmax, half-life and Cmin) using the previously postulated maturation function for children of various age groups with a special focus on the children between 6 months and 2 years.

In order to further address this issue and illustrate the impact of maturation on secondary PK parameters (AUC, Cmax, half-life and Cmin), the Applicant has performed additional assessments by applying three different maturation functions in the current structural base PK model. Based upon model diagnostics, a maturation function, describing the ontogeny of CYP3A4, was not included in the current (2017) population PK model for aprepitant, the addition of a maturation function(s) did not further improve model predictive performance. Taken together, the approach adopted in the 2017 model development is reasonably robust across assumptions and available data and continues to support the dosing recommendations and resultant estimates of aprepitant exposure metrics provided in the original application. The discussion and extended analysis provided supports the dosing of Ivemend in children above 6 months of age. The current model is considered to be sufficient for describing the observed data although the impact of organ maturation is not included.

The Applicant also presented data on conversion of fosaprepitant to aprepitant in children and also discussed the consequences of a potential difference in the rate of conversion comparing adults and children. It is agreed that the conversion is likely to be sufficiently rapid in children.

Since the bioavailability of aprepitant is high the assumption that IV and PO administration can be used interchangeably can be supported.

Fosaprepitant is recommended to be administered as an IV infusion on Day 1. For patients receiving multi-day chemotherapy, administration should continue on Day 2 and Day3. It is also recommended that identical doses of IV fosaprepitant or PO *aprepitant* can be administered interchangeably on Day 2 and Day3.

2.3.6. Conclusions on clinical pharmacology

Modelling and simulation of paediatric pharmacokinetic (PK) data were used to identify fosaprepitant dosing regimens that would match aprepitant exposures previously demonstrated to be efficacious in adults and children.

Taken together, the presented data supports the 3-day regimen extrapolation from aprepitant to fosaprepitant in a paediatric population and the 1-day regimen extrapolation of fosaprepitant efficacy from adults to a paediatric population.

2.4. Clinical efficacy

2.4.1. Dose response studies

Two supportive studies were referenced for the extrapolation of the 1-day dosing regimen (Protocol 017L1 and Protocol 031).

Both trials were worldwide, multi-center, Phase III, randomized, double blind trials designed to assess the safety, tolerability and efficacy of a single 150 mg IV fosaprepitant dose in combination with ondansetron and dexamethasone for the prevention of CINV in adult subjects naïve to HEC and MEC chemotherapy.

Three studies were referenced (one pivotal study (Protocol 208) and two supportive Phase I studies (Protocols 097 and 134)) for the bridging of the paediatric 3-day regimen from aprepitant to fosaprepitant.

P208 was a randomized, double blind, Phase III study to evaluate the efficacy and safety of the 3-day oral aprepitant regimen when administered concomitantly with ondansetron, with or without dexamethasone, in paediatric subjects from 6 months to 17 years of age. The aprepitant dose chosen for Protocol 208 was supported by 2 Phase I studies (P097 and P134).

Study	treatment	Target population	Regimen
P017L1	fosaprepitant	adult	1-day
P031	fosaprepitant	adult	1-day
P208	aprepitant	paediatric	3-day
P097	aprepitant	paediatric	3-day
P134	Fosaprepitant + aprepitant	paediatric	3-day

Two additional studies are referenced to for the safety evaluation. They are further described at the beginning of the safety-part below.

All studies but one have previously been assessed in other procedures. A tabulation of studies and main procedures where the studies have been assessed is presented below:

Study	Assessed in procedure	Referenced for
P017L1	EMEA/H/C/743/X/006 ; EMEA/H/C/743/II/07	1-day regimen
P031	EMEA/H/C/000743/II/0031	1-day regimen
P208	EMEA/H/C/527/X/49/G	3-day regimen + safety
P097	EMEA/H/C/527/X/49/G	3-day regimen + safety
P134	EMEA/H/C/527/X/49/G ; EMA/H/C/743/P46 024 ; EMA/H/C/527/P46 040 ; EMEA/H/C/000743/II/0034/G	3-day regimen + safety

P029	EMA/H/C/743/P46 025 ; EMA/H/C/743/P46 026	safety
ONO-7436-03	EMEA/H/C/527	safety
P044		safety

Study P017L1

P017L1: Randomized, Double-Blind, Active-Controlled, Parallel-Group Study for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated with Cisplatin Chemotherapy.

Protocol 017L1 was the pivotal non-inferiority study that compared a single dose IV (SDIV) fosaprepitant regimen to the approved 3-day oral aprepitant regimen in adult subjects receiving initial treatment with a cisplatin-based HEC.

Methods

Based on observed plasma aprepitant levels obtained on Days 2-4 following a single 15 or 30 minute infusion of fosaprepitant, CNS NK_1 receptor occupancy levels were predicted to remain greater than 90% through at least Day 3 following a single 150 mg IV fosaprepitant dimeglumine dose administered over 20-30 minutes, and greater than or equal to approximately 80% through at least Day 4. Protocol 017L1 was, therefore, designed to test the hypothesis that receptor occupancy levels of this degree would be sufficient to confer similar (i.e., non-inferior) clinical efficacy compared to the approved 3-day oral regimen. Study participants were randomized to 1 of 2 treatment groups.

Treatments

Treatment	Day 1	Days 2-4
Protocol 017L1 - HEC		
Fosaprepitant Regimen	Fosaprepitant 150mg IV Ondansetron 32 mg IV Dexamethasone 12 mg PO	**Day 2** Dexamethasone 8mg PO **Days 3-4** Dexamethasone 16mg PO
Aprepitant Regimen	Aprepitant 125mg PO Ondansetron 32 mg IV Dexamethasone 12 mg PO	**Day 2-3** Aprepitant 80 mg PO Dexamethasone 8mg PO **Day 4** Dexamethasone 8mg PO

The fosaprepitant dose chosen for this regimen was supported by Phase I studies that investigated pharmacokinetics of various doses and administration regimens for IV fosaprepitant, MK-0517 Protocol 009L1 and Protocol 012L1 and MK-0869 Protocol 165.

Outcomes/endpoints

Complete Response was defined as no vomiting and no use of rescue medication. No Vomiting was defined as no emesis, retching or dry heaves, regardless of whether or not the subject took rescue therapy to treat established nausea or vomiting.

Complete Response in the overall phase was selected for evaluation of the primary efficacy endpoint.

Numbers analysed

A total of 2,247 patients were included in the Full Analysis Set (FAS) patient population.

Outcomes and estimation

All efficacy analyses were based on the FAS patient population. The FAS population included patients who received at least one dose of study therapy, received cisplatin chemotherapy, and had at least one post-treatment efficacy assessment.

Table 19: Number (%) of Patients with Complete Response by Phase and Treatment Group with the Difference between Treatment Groups Full Analysis Set Patient Population

	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference(A-B)
Phase	n/m	% (95% CI)	n/m	% (95% CI)	% (95% CI)[†]
Overall Phase	795/1106	71.9 (69.1, 74.5)	820/1134	72.3 (69.6, 74.9)	-0.4 (-4.1, 3.3)
Acute Phase	963/1082	89.0 (87.0, 90.8)	974/1107	88.0 (85.9, 89.8)	1.1 (-1.6, 3.8)
Delayed Phase	822/1106	74.3 (71.6, 76.9)	841/1133	74.2 (71.6, 76.8)	0.1 (-3.5, 3.7)

[†] The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.

Complete response = no vomiting and no use of rescue therapy.

Overall phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.

Acute phase = 0 to 24 hours post-initiation of cisplatin chemotherapy.

Delayed phase = 25 to 120 hours post-initiation of cisplatin chemotherapy.

n/m = Number of patients with Complete response/number of patients included in the analysis.

Figure 15: Kaplan-Meier Curves for Time to First Vomiting Episode from Start of Chemotherapy Administration in the Overall Phase (Full Analysis Set Patient Population)

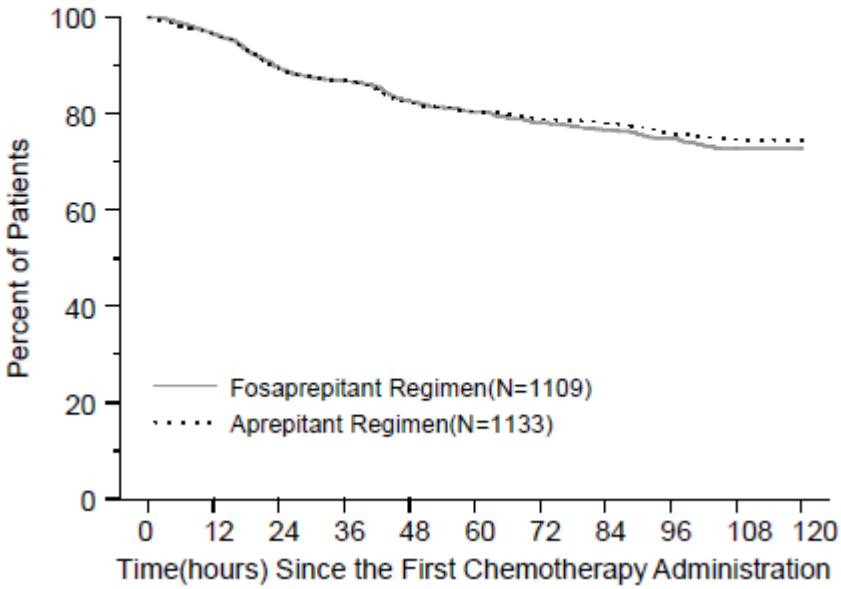


Table 20: Percent of Patients with "No Impact of CINV on Daily Life" by Treatment Group – Overall Phase Full Analysis Set Patient Population

	FLIE Domain or Item Number	Fosaprepitant Regimen (A) n/m (%)	Aprepitant Regimen (B) n/m (%)	Difference‡ (A-B)	95% CI‡ Difference
Total Score					
Nausea and Vomiting Specific	Total Score	748/1083 (69.1)	776/1108 (70.0)	-1.0	(-4.8, 2.9)
Domain and Item Scores					
Nausea-specific	Nausea Domain	710/1084 (65.5)	708/1108 (63.9)	1.6	(-2.4, 5.6)
Nausea-specific 'ability to enjoy daily meal'	Item 4	731/1084 (67.4)	738/1107 (66.7)	0.8	(-3.2, 4.7)
Nausea-specific 'daily functioning'	Item 7	773/1084 (71.3)	771/1108 (69.6)	1.7	(-2.1, 5.5)
Nausea-specific 'personal hardship'	Item 8	742/1084 (68.5)	747/1107 (67.5)	1.0	(-2.9, 4.9)
Vomiting-specific	Vomiting Domain	852/1084 (78.6)	904/1108 (81.6)	-3.0	(-6.3, 0.4)
Vomiting-specific 'ability to enjoy daily meal'	Item 13	889/1084 (82.0)	941/1107 (85.0)	-3.0	(-6.1, 0.1)
Vomiting-specific 'daily functioning'	Item 16	898/1081 (83.1)	961/1105 (87.0)	-3.9	(-6.9, -0.9)
Vomiting-specific 'hardship on other people'	Item 18	899/1081 (83.2)	951/1105 (86.1)	-2.9	(-5.9, 0.1)

† No Impact of CINV on Daily Life is defined as an average item score of >6 on the 7 point scale.

‡ The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.

Overall phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.

CINV = Chemotherapy-induced nausea and vomiting.

FLIE = Functional Living Index-Emesis.

n/m = Number of patients with No Impact of CINV on Daily Life/number of patients included in the analysis of the item.

Study P031

P031: A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Efficacy and Safety of a Single 150 mg Dose of Intravenous Fosaprepitant Dimeglumine for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated With Moderately Emetogenic Chemotherapy.

Protocol 031 was a worldwide, double-blind study assessing the efficacy, safety, and tolerability of a single IV dose of 150 mg fosaprepitant for the prevention of CINV in adult subjects treated with MEC.

Methods

The study randomized 1015 subjects in a 1:1 ratio to receive either a single dose of 150 mg IV fosaprepitant or placebo on Day 1 prior to the start of an initial cycle of MEC as add-on to concomitant oral administration of the 5-HT3 antagonist ondansetron, and the corticosteroid dexamethasone on Day 1; however, only subjects in the control regimen were to receive ondansetron on Days 2 and 3, subjects in the fosaprepitant regimen received placebo for ondansetron.

Outcomes/endpoints

Primary outcome measures: Complete response (CR) defined as no vomiting*, no use of rescue in the delayed phase (25 to 120 hours after first dose of MEC).

Secondary outcome measure: CR overall (0 – 120 hours), CR acute (0-24 hours), no vomiting overall (0-120 hours)

*vomiting: no emetic episode or dry heaves/retching.

Complete Response in the delayed phase was selected for evaluation of the primary efficacy endpoint based on guidance from regulatory agencies.

Outcomes and estimation

Table 21: Subjects with Complete Response[†] by Phase and Treatment Group (Intent to Treat)

Endpoint	Phase	Fosaprepitant Regimen n/m (%)	Control Regimen n/m (%)	Difference in % vs. Control Regimen %	P-Value[‡]
Complete Response[†]	Acute Phase	468 / 502 (93.2)	453 / 498 (91.0)	2.3	0.184
	Delayed Phase	396 / 502 (78.9)	341 / 498 (68.5)	10.4	<0.001
	Overall Phase	387 / 502 (77.1)	333 / 498 (66.9)	10.2	<0.001

[†] Complete Response = No vomiting and no use of rescue therapy.
[‡] Based on CMH (Cochran-Mantel-Haenszel) method with stratification of gender.
Acute Phase: 0 to 24 hours following initiation of first dose of moderately emetogenic chemotherapy (MEC).
Delayed Phase: 25 to 120 hours following initiation of first dose of moderately emetogenic chemotherapy (MEC).
Overall Phase: 0 to 120 hours following initiation of first dose of moderately emetogenic chemotherapy (MEC).
n/m = Number of subjects with Complete Response/number of subjects included in time period.

Table 22: Subjects with No Vomiting[†] by Phase and Treatment Group (Intent to Treat)

Endpoint	Phase	Fosaprepitant Regimen n/m (%)	Control Regimen n/m (%)	Difference in % vs. Control Regimen %	P-Value[‡]
No Vomiting[†]	Acute Phase	476 / 502 (94.8)	458 / 498 (92.0)	2.9	0.069
	Delayed Phase	421 / 502 (83.9)	374 / 498 (75.1)	8.8	<0.001
	Overall Phase	415 / 502 (82.7)	363 / 498 (72.9)	9.8	<0.001

[†] No Vomiting=No emetic episodes, including no vomit (expulsion of stomach contents through the mouth) and no retching or dry heaves (an attempt to vomit that is not productive of stomach contents), regardless of use of rescue medication.
[‡] Based on CMH (Cochran-Mantel-Haenszel) method with stratification of gender.
Acute Phase: 0 to 24 hours following initiation of first dose of moderately emetogenic chemotherapy (MEC)
Delayed Phase: 25 to 120 hours following initiation of first dose of moderately emetogenic chemotherapy (MEC)
Overall Phase: 0 to 120 hours following initiation of first dose of moderately emetogenic chemotherapy (MEC)
n/m = Number of subjects with No Vomiting/number of subjects included in time period.

2.4.2. Main studies

Study P208**:** 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 Paediatric Patients.

Methods

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.

Treatments

Table 23: Treatments in study 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]		

Objectives

Primary objective: To compare the three-day oral aprepitant regimen (aprepitant plus ondansetron), to ondansetron alone.

Blinding

Cycle 1 of this study was conducted as a double-blind study under in-house blinding conditions. Cycles 2-6 were conducted as an open-label study.

Randomization

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).

Statistical Methods

The Intent-to-Treat (ITT) population which consists of all patients (in the group they were) randomized and who received study drug served as the primary population for the analysis of efficacy data in this study. A supportive analysis was performed for the primary and secondary efficacy endpoints using the Full Analysis Set (FAS) population. The FAS population is a subset of all randomized patients including all patients who have received chemotherapy, received a dose of study drug and have at least one post-treatment efficacy assessment.

The primary efficacy analysis compared the aprepitant regimen to the control regimen with respect to the proportion of patients reporting Complete Response in the 25 to 120 hours (delayed phase) following initiation of emetogenic chemotherapy.

The secondary efficacy analyses will compare the aprepitant regimen to the control regimen with respect to the proportion of patients reporting Complete Response (acute and overall) and the proportion of patients reporting No Vomiting overall.

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 was evaluated by comparing the 1-tailed p-value to 0.025 and significance declared if the p-value was ≤0.025.

Baseline data

More male than female patients were enrolled, 54 vs. 46%. With regard to age group, the youngest age group (6 month – 2 year) represented nearly 12% of study participants while the other three age groups (2-6 year; 6-12 year; 12-17 year) represented approximately 30% each.

Numbers analysed

In total 307 subjects were randomised 1:1 to aprepitant or control regimen. 5 patients did not receive study medication and were excluded from the ITT population.

The Full Analysis Set (FAS) patient population included 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. The five subjects excluded from the ITT population were also excluded from the FAS. An additional subject was excluded from the FAS population because this subject did not complete the post-treatment efficacy assessment; this subject was considered as having an unfavourable response in the ITT analysis.

A total of 63 subjects were excluded from the PP population due to protocol violations.

Table 24: Disposition of subjects – cycle 1.

	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.						

Data Source: [16.4]

Outcomes and estimation

Primary endpoint – Complete response

Table 25: 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.		

Source: Study P208 CSR, Table 11-1

Table 26: 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

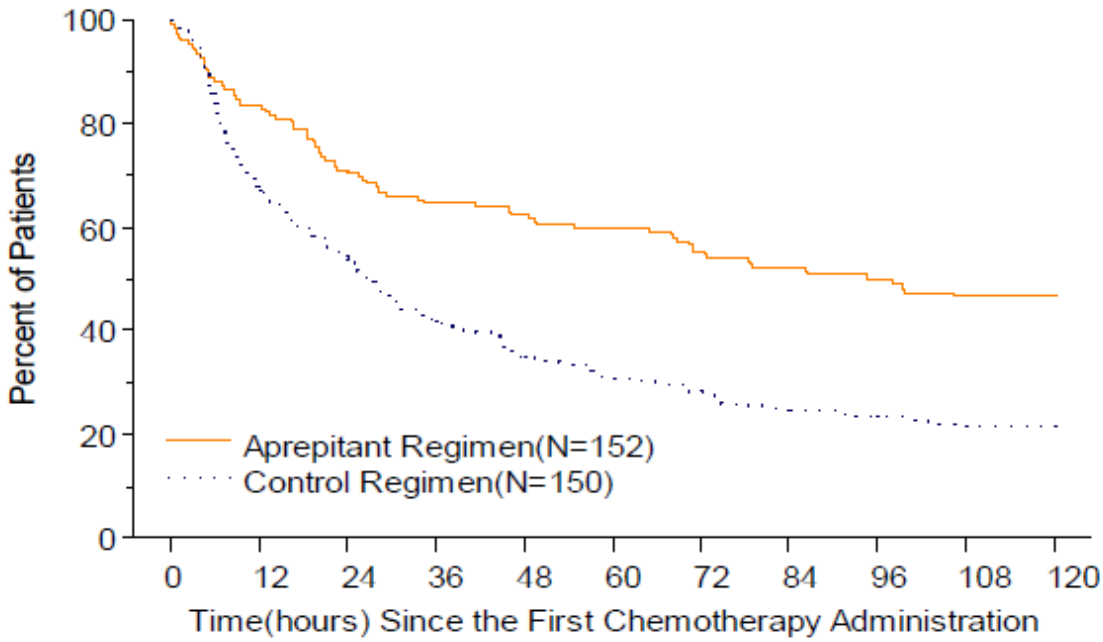
Acute Phase: 0 to 24 hours following initiation of chemotherapy.

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

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

Source: Study P208 CSR, Table 11-4

Figure 16: 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



Source: Study P208 CSR, Figure 11-1.

Table 27: Number of patients with complete response in the Overall Phase by age and treatment group – Cycle 1 (Intent to treat population)

	Aprepitant Regimen	Control Regimen
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)

Source: Study P208 CSR, Table 11-8.

Table 28: Number of patients with complete response in the Delayed Phase by age and treatment group – Cycle 1 (Intent to treat population)

	Aprepitant Regimen	Control Regimen
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)

Source: Study P208 CSR, Table 11-9

Table 29: Number of patients with complete response in the Acute Phase by age and treatment group – Cycle 1 (Intent to treat population)

	Aprepitant Regimen	Control Regimen
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)

Source: Study P208 CSR, Table 11-10

Study P097

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.

Methods

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 focused on Cycle 1 of chemotherapy. The second component consisted of an optional open-label 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.

Objectives

Primary objective was safety. Efficacy and PK were secondary objectives.

Baseline data

Baseline and disease characteristics were balanced between study groups but bone sarcoma was more frequent in the standard therapy group compared to the aprepitant treatment group (83.3% and 53.1%, respectively).

Numbers analysed

Fifty (50) patients were randomised, 32 to the aprepitant arm, 18 to standard therapy. Four subjects in aprepitant arm were not included in the final analyses.

Outcomes and estimation

Table 30: Number (%) of Patients With Complete Response†by Treatment and Phase (Modified-Intention-to-Treat Population) - Cycle 1 Part 1

	Aprepitant Triple Therapy Regimen n/m (%) (95% CI)	Standard Therapy 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** 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** 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** Aprepitant 80 mg P.O., dexamethasone 4 mg P.O.; **Day** Dexamethasone 4 mg P.O.
Standard Therapy = **Day** 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** 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** Placebo for aprepitant 80 mg P.O., dexamethasone 8 mg P.O.; **Day** 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.

Source: CSR P097, Table 11-3

Study P134

This is 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.

Methods

This Phase I study evaluated PK, safety and tolerability in patients 6 months to 17 years of age. Efficacy was an exploratory evaluation. The study consisted of five parts, described below, evaluating oral aprepitant in either a powder for solution (PFS) or capsule formulation and intravenous (iv) fosaprepitant dimeglumine.

PK data from P097 and P134, as well as from a separate paediatric PONV trial of single low dose of aprepitant, Protocol 148 (P148), were used to construct a population PK-model. The model was used for simulations of dose adjustments for subjects 6 months to <12 years. Based on these results, further evaluation of safety and efficacy was conducted within Part IV of Protocol 134 as well as Protocol 208.

Objectives

Primary objective: To estimate PK of aprepitant in patients, birth to 17 years of age, scheduled for MEC or HEC or chemotherapy not previously tolerated due to CINV, and to evaluate safety and tolerability of aprepitant.

Efficacy was an exploratory objective.

Conduct of the study

All enrolled patients were subjects to HEC or MEC. Patients in Part III could continue to Part IV and Part V but patients could also enrol in Part IV and V without participating in previous Part.

Table 31: 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.
15/19 in Part III continued to Part IV and 12 of those continued to Part V.

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. 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 Part III as "control" is limited due to the different HEC/MEC chemotherapy, among other heterogeneities across study parts.

Numbers analysed

A total of 91 paediatric patients 6 months to 17 years old were enrolled across 5 parts of the study.

Outcomes and estimation

Exploratory efficacy results

Table 32: Number (%) of Subjects with Complete Response by Phase, P134

Part I	Phase	Fosaprepitant (115 mg) Regimen (Step A)		Fosaprepitant (150 mg) Regimen (Step B)	
		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	Phase	Aprepitant (80 mg eq.) Regimen (Step A)		Aprepitant (125 mg eq.) Regimen (Step B)	
		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-V	Phase	Ondansetron (Part III)		Aprepitant Regimen (Part IV)		Fosaprepitant Regimen (Part V)	
		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 P134, Table 11-25, Table 11-26, and Table 11-27.

Table 33: Number (%) of Subjects with Complete Response in the Overall Phase, P134

Part I	Subgroup	Fosaprepitant (115 mg) Regimen (Step A)		Fosaprepitant (150 mg) Regimen (Step B)	
		n/m	% (CI)	n/m	% (CI)
	12 years to 17 years	2 / 11	18.2 (2.3, 51.8)	8 / 11	72.7 (39.0, 94.0)
Part II	Subgroup	Aprepitant (80 mg eq.) Regimen (Step A)		Aprepitant (125 mg eq.) Regimen (Step B)	
		n/m	% (CI)	n/m	% (CI)
	6 months to <2 years	2 / 5	40.0 (5.3, 85.3)	3 / 6	50.0 (11.8, 88.2)
	2 years to <6 years	8 / 8	100.0 (63.1, 100.0)	5 / 6	83.3 (35.9, 99.6)
	6 years to <12 years	5 / 6	83.3 (35.9, 99.6)	3 / 6	50.0 (11.8, 88.2)

Part III-V	Subgroup	Ondansetron (Part III)		Aprepitant Regimen (Part IV)		Fosaprepitant Regimen (Part V)	
		n/m	% (CI)	n/m	% (CI)	n/m	% (CI)
	6 months to <2 years	1 / 6	16.7 (0.4, 64.1)	3 / 7	42.9 (9.9, 81.6)	2 / 7	28.6 (3.7, 71.0)
	2 years to <6 years	1 / 6	16.7 (0.4, 64.1)	2 / 6	33.3 (4.3, 77.7)	2 / 7	28.6 (3.7, 71.0)
	6 years to <12 years	0 / 7	0.0 (0.0, 41.0)	4 / 7	57.1 (18.4, 90.1)	0 / 8	0.0 (0.0, 36.9)

The proportion of patients (aged 6 months to <12 years) experiencing vomiting in the acute phase was lower for the single-dose 80 mg-equivalent PO regimen compared with the single-dose 125 mg–equivalent PO regimen. These results are contra-intuitive, but likely a reflection of the small sample size, heterogeneity of the patient population and non-randomised nature of the study.

The proportions achieving complete response in the different phases are similar in study P134 and study P208 (pivotal for the application regarding aprepitant use in children 6 months to 17 years) regarding age groups 6 months to < 2 years and 2 years to <6 years whereas the proportion is higher in the 6 years to <12 years age group.

Ancillary analyses

Summary of main studies

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

Table 34: Summary of Efficacy

Title: Randomized, Double-Blind, Active Controlled, Parallel-Group Study for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated with Cisplatin Chemotherapy			
Study identifier	**Protocol 017L1 (P017L1)**		
Design	interventional		
Hypothesis	Non-inferiority		
Treatments groups	Fosaprepitant		Fosaprepitant 150 mg IV on Day 1, in combination with ondansetron 32 mg IV Day 1, and dexamethasone 12 mg on Day 1, 8 mg on Day 2, and 16 mg on Days 3 and 4 n=1143
	Aprepitant		aprepitant 125 mg PO on Day 1 and 80 mg on Days 2 and 3, in combination with ondansetron 32 mg IV on Day 1, and dexamethasone 12 mg on Day 1, 8 mg on Days 2 and 3, and 4. n=1169
Endpoints and definitions	Primary endpoint	Overall Complete Response	Complete Response (no vomiting and no use of rescue therapy) overall (in the 120 hours following initiation of cisplatin)
	Secondary: endpoint	Complete response in the Delayed phase	Complete Response (no vomiting and no use of rescue therapy) in the delayed phase (25 to 120 hours following initiation of cisplatin)
	Secondary: endpoint	No vomiting	proportion of patients with no vomiting overall (in the 120 hours following initiation of cisplatin)

Results and Analysis			
Analysis description			
Analysis population and time point description	Full analysis set (FAS) included patients who received at least one dose of study therapy, received cisplatin chemotherapy, and had at least one post-treatment efficacy assessment		
Effect estimate per comparison	Treatment group	Fosaprepitant	Aprepitant
	Primary endpoint		
	n/m (%)	795/1106 (71.9)	820/1134 (72.3)
	95% CI	69.1, 74.5	69.6, 74.9

Title: A Phase III Randomized Double Blind Active Comparator Controlled Parallel Group Study Conducted Under In House Blinding Conditions to Examine the Efficacy and Safety of a Single 150 mg Dose of Intravenous Fosaprepitant Dimeglumine for the Prevention of Chemotherapy Induced Nausea and Vomiting CINV Associated With Moderately Emetogenic Chemotherapy			
Study identifier	**Protocol 031 (P031)**		
Design	interventional		
Hypothesis	superiority		
Treatments groups	Fosaprepitant		single dose of 150 mg IV fosaprepitant Day 1 before the start of an initial cycle of MEC as add-on to concomitant oral administration of the 5-HT3 antagonist ondansetron, and the corticosteroid dexamethasone on Day 1
	Control		placebo on Day 1 prior to the start of an initial cycle of MEC as add-on to concomitant oral administration of the 5-HT3 antagonist ondansetron, and the corticosteroid dexamethasone on Day 1; and ondansetron on Days 2 and 3
Endpoints and definitions	Primary endpoint	Complete Response Delayed phase	Complete Response (no vomiting and no use of rescue therapy) in the delayed phase (25 to 120 hours after first dose of MEC)
	Secondary: endpoint	Complete response overall	Complete Response (no vomiting and no use of rescue therapy) overall
	Secondary: endpoint	No vomiting	proportion of patients with no vomiting overall (0-120 hours)

Results and Analysis			
Analysis description			
Analysis population and time point description	Intent to treat population		
Effect estimate per comparison	Treatment group	Fosaprepitant	Control
	Primary endpoint		
	n/m (%)	421/502 (83.9)	374/498 (75.1)
	p	<0.001	

Title: 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	
Study identifier	**Protocol 208 (P208)**
Design	interventional
Hypothesis	Superiority

Treatments groups	Aprepitant		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)
	Control		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)
Endpoints and definitions	Primary endpoint	Complete Response Delayed phase	Complete Response (no vomiting and no use of rescue therapy) in the delayed phase (25 to 120 hours initiation of emetogenic chemotherapy)
	Secondary: endpoint	Complete Response Acute phase	Complete Response (no vomiting and no use of rescue therapy) in the acute phase (0-24 hours)
	Secondary: endpoint	Complete response overall	Complete Response (no vomiting and no use of rescue therapy) overall (0-120 hours)
	Secondary: endpoint	No vomiting	proportion of patients with no vomiting (0-120 hours)

Results and Analysis

Analysis description			
Analysis population and time point description	Intent to treat population		
Effect estimate per comparison	Treatment group	Aprepitant	Control
	Primary endpoint		
	n/m (%)	77/152 (50.7)	39/150 (26.0)
	p	<0.0001	

Title: 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			
Study identifier	**Protocol 097 (P097)**		
Design	interventional		
Hypothesis	superiority		
Treatments groups	Aprepitant		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
	Control		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
Endpoints and definitions	Primary endpoint	Safety	
	Secondary: endpoint	Complete Response overall phase	Complete Response (no vomiting and no use of rescue therapy) overall (0-120 hours)

Results and Analysis			
Analysis description			
Analysis population and time point description	Modified Intent to treat		
Effect estimate per comparison	Treatment group	Aprepitant	Control
	Secondary endpoint		
	n/m (%)	8/28 (28.6)	1/18 (5.6)
	95% CI	13.2, 48.7	0.1, 27.3

Title: 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			
Study identifier	**Protocol 134 (P134)**		
Design	interventional		
Hypothesis	superiority		
Treatments groups	IA		Fosaprepitant 115 mg IV (Day 1) + Aprepitant 80 mg PO (Day 2 + 3)
	IB		Fosaprepitant 150 mg IV (Day 1)
	IIA		Aprepitant 47 mg/m^2 PO (Day 1)
	IIB		Aprepitant 74 mg/m^2 alt. 1.3 mg/kg PO (Day 1)
	III		Ondansetron IV (Day 1-3)
	IV		Aprepitant 3 mg/kg PO (Day 1) + Aprepitant 2 mg/kg PO (Day 2 + 3;)
	V		Fosaprepitant 3 mg/kg IV (Day 1)
Endpoints and definitions	Primary endpoint	Pharmacokinetics	

	Exploratory endpoint	Efficacy	Complete Response (no vomiting and no use of rescue therapy) overall
Results and Analysis			
Analysis description	Subjects with complete response in the overall phase		

Part I	Subgroup	Fosaprepitant (115 mg) Regimen (Step A)		Fosaprepitant (150 mg) Regimen (Step B)	
		n/m	% (CI)	n/m	% (CI)
	12 years to 17 years	2 / 11	18.2 (2.3, 51.8)	8 / 11	72.7 (39.0, 94.0)
Part II	Subgroup	Aprepitant (80 mg eq.) Regimen (Step A)		Aprepitant (125 mg eq.) Regimen (Step B)	
		n/m	% (CI)	n/m	% (CI)
	6 months to <2 years	2 / 5	40.0 (5.3, 85.3)	3 / 6	50.0 (11.8, 88.2)
	2 years to <6 years	8 / 8	100.0 (63.1, 100.0)	5 / 6	83.3 (35.9, 99.6)
	6 years to <12 years	5 / 6	83.3 (35.9, 99.6)	3 / 6	50.0 (11.8, 88.2)

Part III-V	Subgroup	Ondansetron (Part III)		Aprepitant Regimen (Part IV)		Fosaprepitant Regimen (Part V)	
		n/m	% (CI)	n/m	% (CI)	n/m	% (CI)
	6 months to <2 years	1 / 6	16.7 (0.4, 64.1)	3 / 7	42.9 (9.9, 81.6)	2 / 7	28.6 (3.7, 71.0)
	2 years to <6 years	1 / 6	16.7 (0.4, 64.1)	2 / 6	33.3 (4.3, 77.7)	2 / 7	28.6 (3.7, 71.0)
	6 years to <12 years	0 / 7	0.0 (0.0, 41.0)	4 / 7	57.1 (18.4, 90.1)	0 / 8	0.0 (0.0, 36.9)

2.4.3. Discussion on clinical efficacy

This extension of indication is based on a number of studies, all which have previously been submitted and assessed within other procedures, and modelling and simulations, the applicant seeks to bridge the efficacy of the 3-day oral aprepitant dose in children to a 3-day iv fosaprepitant dose in the same age categories. The applicant also seeks to extrapolate the efficacy of 1-day fosaprepitant dose in adults to a 1-day dose in children. SmPC is also aligned with SmPC for aprepitant (removal of "cisplatin based cancer chemotherapy" from indication.

Two studies are included to support the applied 1-day dose regimen, study P017L1 and study P031. Three studies are included to support the applied 3-day dose regimen, study P208, study P097 and study P134.

There is support for fosaprepitant as a single iv dose of 150 mg in adults and the applicant does not invoke (in this MAA) any new efficacy data regarding the 1-day fosaprepitant regimen in children. Hence, if the 1-day regimen in adults is pharmacologically possible to extrapolate to a paediatric population, the efficacy endpoints would be supported.

The applicant includes three studies in this MAA to support the 3-day dose regimen, study P208, study P097 and study P134.

Design and conduct of clinical studies

Study P017L1 was designed as a non-inferiority study to compare one single dose of fosaprepitant 150 mg iv to a 3 day regimen of aprepitant in adults. Complete response in the overall phase was used as primary efficacy measure. The study has previously been assessed within procedures EMEA/H/C/743/X/006 and EMEA/H/C/743/II/07 and was found supportive for the 1 day fosaprepitant regimen.

Study P031 was designed to explore the add-on efficacy of a single iv dose of 150 mg fosaprepitant for prevention of CINV in adults treated with MEC. Complete response in the delayed phase (25-120 hours

after first dose MEC) was primary endpoint. The study has previously been assessed within procedure EMEA/H/C/0007/43/II/031 and was found to confirm prior findings conducted with (fos)aprepitant: fosaprepitant has a moderate add-on effect on CINV to a background of steroids and a 5-HT_3-antagonist.

Study P208 investigated the efficacy of a 3-day aprepitant regimen compared to ondansetron alone in a paediatric population (6 months to 17 years old). Primary endpoint was complete response in the delayed phase (25-125 hours after first dose of chemotherapy). The study has previously been assessed within procedure EMEA/H/C/527/X/49/G and efficacy data was found supportive to the 3-day aprepitant regimen. Overall, complete response in the delayed phase doubled in the aprepitant group compared to the control group.

Study P097 was a smaller study with primary objectives of safety while efficacy endpoints were secondary or exploratory. The study compared standard therapy with aprepitant triple therapy and was assessed in the same procedure X/49/G as P208. Study P097 was assessed as supportive to study P208 for efficacy.

Study P134 was also small and thus precludes any firm conclusions based on comparison between different study groups, with regard to efficacy endpoints. However, weighted together with study P097, study P134 is considered supportive to the efficacy endpoints of study P208.

Efficacy data and additional analyses

The clinical aetiology, pathophysiology and manifestation of CINV do not differ between a paediatric and adult population, and age is no covariate for CINV severity.

The company extrapolated the efficacy of the proposed paediatric 1-day fosaprepitant regimen from that demonstrated in the adult fosaprepitant program. The efficacy of the proposed paediatric 3-day fosaprepitant regimen was bridged from that demonstrated in paediatric subjects receiving the 3-day oral aprepitant regimen. As efficacy is extrapolated and bridged from previously completed studies, pivotal studies designed to demonstrate the efficacy of fosaprepitant in children were not performed. As such, efficacy data from the adult fosaprepitant program and the paediatric aprepitant program are presented.

The recommended dose regimen of IVEMEND, to be administered with a 5-HT3 antagonist, with or without a corticosteroid, for the prevention of nausea and vomiting associated with administration of single or multi-day chemotherapy regimens of Highly Emetogenic Chemotherapy (HEC) or Moderately Emetogenic Chemotherapy (MEC), was 115 mg on day 1 to be followed by 80 mg iv or orally (EMEND capsules) on days 2 and 3 for patients above 12 years old and 3 mg/kg on day 1 to be followed by 2 mg/kg either iv or orally on days 2 and 3 for patients above 6 months and less than 12 years of age for paediatric patients receiving single or multi-day regimens of HEC or MEC.

For paediatric patients receiving single day HEC or MEC, IVEMEND may be administered as an intravenous infusion through a central venous catheter on Day 1 as 150 mg iv for patients 12 years and older, 4 mg/kg for patients 2 to less than 12 years and 5 mg/kg for patients 6 months to less than 2 years and not less than 6 kg. The safety and efficacy of IVEMEND in infants below 6 months of age have not been established. No data are available.

It is recommended that instead of iv fosaprepitant on Day 2 and 3 in the 3-day fosaprepitant regimen, it should be possible to use oral aprepitant (equal dose). However a change between iv fosaprepitant and oral aprepitant is not suggested for Day 1 in the 3-day fosaprepitant regimen. Based on routine practices of chemotherapy administration in children, the combination aprepitant/fosaprepitant

antiemetic regimen suggested above (oral on Day 1 followed by IV on Days 2 and 3) is not anticipated to be used. On Day 1, most paediatric patients receive intravenous chemotherapy in a hospital or outpatient setting, where IV anti-emetics, such as fosaprepitant, can be easily administered. This is supported by data from both the oral aprepitant and IV fosaprepitant paediatric clinical development programs in which relatively few subjects received only oral chemotherapy on Day 1. The proposed alternative oral aprepitant dosing on Day 2 and 3 of the 3-day fosaprepitant regimen was added to offer flexibility for patients who are receiving 1 or 2 days of IV chemotherapy. The flexibility of using oral aprepitant on Days 2 and 3 allows health care providers to prescribe a regimen that would not require patients to return to the hospital/outpatient clinic for the sole purpose of receiving an IV dose of fosaprepitant. Furthermore, for the minority of patients not receiving IV chemotherapy on Day 1, the 3-day oral aprepitant regimen is available and offers additional dosing flexibility.

Therefore although interchangeability between fosaprepitant and aprepitant in 3-day regimen is supported, the clinical use of a combination containing the discussed sequence is not foreseen.

Emend (oral aprepitant) 80 and 125 mg is indicated for "Prevention nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults and adolescents from the age of 12." and the powder for oral suspension is approved for "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."

Further, section 4.1 of Ivemend is also aligned with SmPC for aprepitant in terms of removing reference to "cisplatin based cancer chemotherapy". This is acceptable as fosaprepitant is a prodrug of aprepitant rapidly converting to it following administration , therefore data available on highly non-cisplatin based emetogenic chemotherapies with Emend are applicable to Ivemend too.

2.4.4. Conclusions on the clinical efficacy

The applied indication is based on extrapolation and bridging of previously submitted (in other procedures) and assessed data. The present assessment is in consistency with previous assessments for the supportive studies in the studied populations. Clinical efficacy in the "Prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults and paediatric patients aged 6 months and older" can be derived from these studies.

2.5. Clinical safety

Introduction

The safety profile of fosaprepitant IV administered to paediatric patients 6 months to 17 years of age is based on information from studies "Protocol 134", "Protocol 029" and "Protocol 044" with safety data collected from 331 paediatric oncology patients exposed to any dose of fosaprepitant. The applicant also refers to supportive data in studies "Protocol 208" and "Protocol 097" (3-day oral aprepitant regimen) for safety in paediatric patients. The applicant has also provided results from a search within its "Adverse Event Reporting and Review System database" containing reports of serious adverse experiences and adverse experiences of special interest from clinical trials, including expanded access programs, reports from the medical literature, and all adverse experiences from marketed use that are reported to the MAH. The applicant also provide information about a literature search of all published clinical literature referencing aprepitant and fosaprepitant, which the applicant reviewed for consistency with the safety findings reported in this marketing application.

The applicant states that fosaprepitant is rapidly and completely converted to aprepitant within 30 minutes of intravenous administration and therefore the safety and tolerability of the currently approved 3-day oral aprepitant regimen (study P208, P097 and P134), established in paediatric patients receiving emetogenic chemotherapy, should support the safety profile of the proposed 3-day IV fosaprepitant regimen.

This application also includes exposure data (study P134) for fosaprepitant following administration as part of a 1-day IV regimen (all age groups) and a 3-day IV/oral regimen (115 mg IV fosaprepitant given on day 1, followed by 80 mg oral aprepitant on days 2 and 3 in adolescent subjects).

Study	Treatment	Target population
P029	fosaprepitant	Paediatric
P044	fosaprepitant	Paediatric
P134	fosaprepitant + aprepitant	Paediatric
P208	aprepitant	Paediatric
P097	aprepitant	Paediatric

The applicant propose the dose for the 1-day regimen to be 150 mg for adolescents 12 to 17 years, 4 mg/kg (up to 150 mg) for children 2 to <12 years and 5 mg/kg (up to 150 mg) for 6 month to <2 year olds. The proposed dose for the 3-day regimen is 115 mg on Day 1 followed by 80 mg on Days 2 and 3 for 12 to 17 year olds and 3 mg/kg (up to 115 mg) on Day 1 followed by 2 mg/kg (up to 80 mg) on Days 2 and 3 for 6 month to <12 year olds.

Patient exposure

A total of 361 unique subjects were randomised in Protocol 029, 044 and 134 (Parts I and V which included fosaprepitant to a paediatric population). Of those, 331 received fosaprepitant either in Cycle 1 and/or optional in Cycles 2 to 6 (Protocol 029 and 044 only).

Table 35: Number of Subjects Exposed to any dose of Fosaprepitant by Age Category (overall exposure) in Cycles 1-6; All Subjects as Treated; Protocols 134, 029 and 044 Combined

	12 to 17 years	6 to <12 years	2 to <6 years	birth to <2 years	Total
134 Part I	23	0	0	0	23
134 Part V	0	8	8	7	23
029 Cycles 1-6	61	76	60	23	220
044 Cycles 1-6	33	21	11	0	65

Source: Summary clinical safety, Table 2.7.4:2

The applicant pooled supportive safety data for the 1-day regimen from subjects who received 150 mg and 5 mg/kg in Protocols 134, 029 and 044 (1-Day supportive pool), see table below.

The applicant derived the proposed 3-day paediatric IV fosaprepitant regimen through population PK model-based analysis and achieved similar exposures (AUC0-24, Cmax, C24hr, C48hr and C72hr) as the approved paediatric 3-day oral aprepitant regimen associated with efficacy, safety and tolerability

in children 6 months to 17 years of age. The applicant states that following administration of a single 3 mg/kg IV fosaprepitant dose, aprepitant is cleared rapidly in children with negligible C24 values. The applicant further states that given low daily through levels and negligible accumulation, administration of fosaprepitant for 3 consecutive days is not predicted to result in daily exposures outside the range associated with safety following administration of higher fosaprepitant doses (150 mg and 5 mg/kg). As such, the safety and tolerability of a 3-day IV fosaprepitant regimen is supported by pooled safety data from paediatric subjects receiving a single IV dose of fosaprepitant at or above the highest proposed daily doses in the 3-day regimen of 115 mg for adolescents and 3 mg/kg for 6 month to <12 year olds. Supportive safety data were pooled by the applicant from subjects in Protocols 134, 029 and 044 who received 3 mg/kg, 5mg/kg and 150 mg as part of 1-day regimens and 115 mg IV on Day 1 as part of a 3-day IV/PO regimen (3-Day supportive pool). The applicant notifies that all subjects in the 1-day supportive pool are also included in the 3-day supportive pool. The 1-day and 3-day supportive pool also includes 148 and 208 paediatric patients respectively, who received fosaprepitant 150 mg, 5 mg/kg, or 3 mg/kg in Cycles 2 to 6 of Protocols 029 and 044.

Table 36: Pooled Dataset for Pivotal Safety Analysis Protocols 134 Parts I and V, Protocol 029 (Cycle 1) and Protocol 044 (Cycle 1)

Integrated Dataset Treatment Groups	Age Subgroup and Protocol Numbers		Total
	12 to 17 years of age	<12 years of age	
1-Day Supportive Pool Includes: Fosaprepitant 150 mg + 5mg/kg doses to support 1-day dosing regimen	**150 mg** Includes data from Protocols: 134 Part IB (N=11) 029 (N=17) 044 (N=18)	**5mg/kg** Includes data from Protocols: 029 (N=74) 044 (N=19)	**N= 139**
3-Day Supportive Pool Includes: Fosaprepitant 150 mg + 5mg/kg + 3 mg/kg and a 3-day regimen of fosaprepitant 115 mg on Day 1 and aprepitant 80 mg on Days 2 and 3 to support 3-day dosing regimen	**150 mg** Includes data from Protocols: 134 Part IB (N=11) 029 (N=17) 044 (N=18) **115mg** Includes data from Protocol 134 Part IA (N=12)	**5mg/kg** Includes data from Protocols: 029 (N=74) 044 (N=19) **3mg/kg** Includes data from Protocols: 134 Part V (N=23) 029 (N=25)	**N=199**

Source: Summary clinical safety, Table 2.7.4:3

A total of 199 subjects from the integrated datasets received at least a partial dose of fosaprepitant in Cycle 1 and were, by the applicant, included in the pivotal analysis of safety.

Table 37: Extent of Exposure to Fosaprepitant by Dose in Cycle 1 All Subjects as Treated Protocols 134, 029 and 044 Combined

	12 to 17 years	6 to <12 years	2 to <6 years	birth to <2 years	Total
Any Dose	58	63	48	30	199
0-10 mg	1	1	1	0	3
20-30 mg	0	0	0	2	2
30-40 mg	0	0	3	12	15
40-50 mg	0	1	8	7	16
50-75 mg	0	9	17	9	35
75-100 mg	0	12	14	0	26
100-125 mg	14	9	4	0	27
125-150 mg	43	30	1	0	74
>150 mg	0	1	0	0	1
Each subject could be counted for different dosage categories row.					

Source: Summary clinical safety, Table 2.7.4:5

The extent to which subjects were exposed to fosaprepitant in the optional Cycles 2 to 6 is reported in table below.

Table 38: Extent of Exposure to Fosaprepitant by Dose in Cycles 2-6 All Subjects as Treated Protocols 029 and 044 Combined

	12 to 17 years	6 to <12 years	2 to <6 years	birth to <2 years	Total
Any Dose	72	75	43	18	208
0-10 mg	0	2	1	0	3
10-20 mg	0	2	2	0	4
20-30 mg	0	0	1	0	1
30-40 mg	0	0	4	6	10
40-50 mg	0	0	9	7	16
50-75 mg	0	11	14	10	35
75-100 mg	0	16	13	0	29
100-125 mg	0	20	5	0	25
125-150 mg	72	40	3	0	115
>150 mg	0	0	0	0	0
Each subject could be counted for different dosage categories row.					

Source: Summary clinical safety, Table 2.7.4:5

The applicant also, due to the statement of rapid and complete conversion of fosaprepitant to aprepitant, provide safety data of the 3-day oral aprepitant regimen demonstrated in Protocols 097 and 208 as supportive data for safety of a 3-day fosaprepitant regimen.

In addition to the studies conducted by the Applicant, a small (n=27), prospective, open label study of fosaprepitant in paediatric subjects 6 months to 18 years of age was conducted by Ono Pharmaceutical Co., Ltd and used to support approval of fosaprepitant in Japan for the prevention of CINV in this age group (Study ONO-7847-03). In this study, subjects 12 to 18 years of age received a single 150 mg dose of fosaprepitant; subjects 6 months to 11 years of age received a single 3 mg/kg (up to 150 mg) dose of fosaprepitant.

Ondansetron was required as part of the antiemetic regimen for Protocol 134 and Cycle 1 of Protocols 029 and 044.

In all three studies (P134, P029 and P044), IV dexamethasone was permitted for subjects as an optional component of the antiemetic regimen at the discretion of the investigator according to the product label for paediatric usage or local standard of care. Because of the known drug-drug interaction profile between aprepitant and dexamethasone in adults, dexamethasone was administered at 50% of the otherwise intended dose to subjects receiving concomitant fosaprepitant.

Table 39: Exposure of Dexamethasone by Dose for Fosaprepitant Regimen in Cycle 1 All Subjects as Treated Protocols 134, 029 and 044 Combined

	1 Day	2 Days	3 Days	4 Days	5 Days	>5 Days	Total Subjects	Duration Range	Mean Duration
Any Dose	20	11	18	4	0	0	53	1 to 4 days	2.1 days
0-4 mg	30	12	9	0	0	0	51	1 to 3 days	1.6 days
4-10 mg	11	4	2	1	0	0	18	1 to 4 days	1.6 days
10-20 mg	2	0	0	0	0	0	2	1 to 1 days	1.0 days
Each subject could be counted for different dosage categories row.									

Source: Summary clinical safety, Table 2.7.4:8

Adverse events

The ASaT population was used for the analysis of safety data and included all randomized subjects (in study P134, P029 and P044) who received at least one dose of study medication. Events related to the efficacy endpoint (vomiting and dry heaves/retching) were not defined as AEs during the period of diary data collection (~120 hours following initiation of emetogenic chemotherapy in Cycle 1) unless they met the definition of a Serious Adverse Event (SAE). After completion of the diary reporting period (Day 5), vomiting and dry heaves/retching were considered AEs.

'In the optional Cycles 2 to 6 of Protocols 029 and 044, only SAEs and non-serious AEs determined by the investigator to be drug-related or events that led to discontinuation from the study were required to be reported.

Protocols 134, 029, and 044 Combined, Cycle 1

Table 40: Adverse Event Summary in Cycle 1 All Subjects as Treated Protocols 134, 029 and 044 Combined

	1-Day Supportive Pool		**3-Day Supportive Pool**		**Control Regimen** Pooled from P029 and P044)		**Total**	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	139		199		69		268	
with one or more adverse events	118	(84.9)	167	(83.9)	54	(78.3)	221	(82.5)
with no adverse event	21	(15.1)	32	(16.1)	15	(21.7)	47	(17.5)
with drug-related[†] adverse events	9	(6.5)	11	(5.5)	5	(7.2)	16	(6.0)
with serious adverse events	40	(28.8)	61	(30.7)	20	(29.0)	81	(30.2)
with serious drug-related adverse events	2	(1.4)	3	(1.5)	1	(1.4)	4	(1.5)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	3	(2.2)	4	(2.0)	0	(0.0)	4	(1.5)
discontinued due to a drug-related adverse	3	(2.2)	3	(1.5)	0	(0.0)	3	(1.1)
discontinued due to a serious adverse	2	(1.4)	2	(1.0)	0	(0.0)	2	(0.7)
discontinued due to a serious drug-related	2	(1.4)	2	(1.0)	0	(0.0)	2	(0.7)

† Determined by the investigator to be related to the drug.

‡ Study medication withdrawn.
The column "1-Day Supportive Pool" includes subjects receiving fosaprepitant in single-day doses of 150mg and 5mg/kg.
The column "3-Day Supportive Pool" includes subjects receiving fosaprepitant in single-day doses of 150mg, 5mg/kg and 3mg/kg and a 3-day regimen of fosaprepitant 115 mg on Day 1 and aprepitant 80 mg on Days 2 and 3.
The column "Total" includes subjects receiving fosaprepitant in single-day doses of 150mg, 5mg/kg and 3mg/kg and a 3-day regimen of fosaprepitant 115 mg on Day 1 and aprepitant 80 mg on Days 2 and 3, and control regimen.

Source: Summary clinical safety, Table 2.7.4:21

Table 41: Adverse Events Summary By Age Category in Cycle 1 All Subjects as Treated Protocols 134, 029 and 044 Combined

	Birth To < 2 Years						2 Years To < 6 Years					
	1-Day Supportive Pool		3-Day Supportive Pool		Control Regimen		1-Day Supportive Pool		3-Day Supportive Pool		Control Regimen	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	23		30		0		32		48		16	
with one or more adverse events	19	(82.6)	23	(76.7)	0	(0.0)	27	(84.4)	40	(83.3)	12	(75.0)
with no adverse event	4	(17.4)	7	(23.3)	0	(0.0)	5	(15.6)	8	(16.7)	4	(25.0)
with drug-related† adverse events	1	(4.3)	1	(3.3)	0	(0.0)	3	(9.4)	3	(6.3)	0	(0.0)
with serious adverse events	11	(47.8)	13	(43.3)	0	(0.0)	10	(31.3)	17	(35.4)	5	(31.3)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.1)	1	(2.1)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.1)	2	(4.2)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.1)	1	(2.1)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.1)	1	(2.1)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.1)	1	(2.1)	0	(0.0)

	6 Years To < 12 Years						12 Years To < 17 Years					
	1-Day Supportive Pool		3-Day Supportive Pool		Control Regimen		1-Day Supportive Pool		3-Day Supportive Pool		Control Regimen	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	38		63		20		46		58		33	
with one or more adverse events	35	(92.1)	56	(88.9)	16	(80.0)	37	(80.4)	48	(82.8)	26	(78.8)
with no adverse event	3	(7.9)	7	(11.1)	4	(20.0)	9	(19.6)	10	(17.2)	7	(21.2)
with drug-related† adverse events	2	(5.3)	4	(6.3)	3	(15.0)	3	(6.5)	3	(5.2)	2	(6.1)
with serious adverse events	9	(23.7)	17	(27.0)	7	(35.0)	10	(21.7)	14	(24.1)	8	(24.2)
with serious drug-related adverse events	0	(0.0)	1	(1.6)	0	(0.0)	1	(2.2)	1	(1.7)	1	(3.0)
discontinued‡ due to an adverse event	1	(2.6)	1	(1.6)	0	(0.0)	1	(2.2)	1	(1.7)	0	(0.0)
discontinued due to a drug-related adverse event	1	(2.6)	1	(1.6)	0	(0.0)	1	(2.2)	1	(1.7)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.7)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.7)	0	(0.0)

The column "1-Day Supportive Pool" includes subjects receiving fosaprepitant in single-day doses of 150mg and 5mg/kg.
The column "3-Day Supportive Pool" includes subjects receiving fosaprepitant in single-day doses of 150mg, 5mg/kg and 3mg/kg and a 3-day regimen of fosaprepitant 115 mg on Day 1 and aprepitant 80 mg on Days 2 and 3.

† Determined by the investigator to be related to the drug.

‡ Study medication withdrawn.

Source: Summary clinical safety, Table 2.7.4:22

The most frequently reported AEs were anaemia, neutropenia, thrombocytopenia, and febrile neutropenia within the blood and lymphatic SOC, followed by vomiting in the gastrointestinal disorder SOC (see **Table 42**).

Table 42: Subjects with Adverse Events (Incidence ≥ 2% in One or More Treatment Groups) in Cycle 1 All Subjects as Treated Protocols 134, 029 and 044 Combined

	1-Day Supportive Pool		3-Day Supportive Pool		Control Regimen		Difference (percentage)	
	n	%	n	%	n	%	1-Day	3-Day
Subjects in population	139		199		69			
with one or more adverse events	118	84,9	167	83,9	54	78,3	6,6	5,6
with no adverse events	21	15,1	32	16,1	15	21,7	-6,6	-5,6
Blood and lymphatic system disorders	**70**	**50,4**	**101**	**50,8**	**33**	**47,8**	**2,6**	**3**
Anaemia	43	30,9	57	28,6	15	21,7	9,2	6,9
Febrile neutropenia	22	15,8	34	17,1	11	15,9	-0,1	1,2
Leukopenia	15	10,8	20	10,1	5	7,2	3,6	2,9
Neutropenia	28	20,1	41	20,6	13	18,8	1,3	1,8
Thrombocytopenia	23	16,5	38	19,1	11	15,9	0,6	3,2
Cardiac disorders	**3**	**2,2**	**3**	**1,5**	**2**	**2,9**	**-0,7**	**-1,4**
Eye disorders	**3**	**2,2**	**4**	**2,0**	**0**	**0,**	**2,2**	**2**
Gastrointestinal disorders	**52**	**37,4**	**79**	**39,7**	**17**	**24,6**	**12,8**	**15,1**
Abdominal pain	11	7,9	19	9,5	5	7,2	0,7	2,3
Abdominal pain upper	2	1,4	2	1,0	2	2,9	-1,5	-1,9
Constipation	13	9,4	18	9,0	6	8,7	0,7	0,3
Diarrhoea	10	7,2	13	6,5	1	1,4	5,8	5,1
Dyspepsia	3	2,2	3	1,5	0	**0,**	2,2	1,5
Nausea	10	7,2	17	8,5	3	4,3	2,9	4,2
Proctalgia	1	**7,**	2	0,	2	2,9	4,1	-2,9
Stomatitis	5	3,6	7	3,5	3	4,3	-0,7	-0,8
Vomiting	23	16,5	37	18,6	4	5,8	10,7	12,8
Metabolism and nutrition disorders	**21**	**15,1**	**33**	**16,6**	**7**	**10,1**	**5**	**6,5**
Decreased appetite	9	6,5	12	6,0	4	5,8	0,7	0,2
Hypoalbuminaemia	2	1,4	5	2,5	0	0,	1,4	2,5
Hypokalaemia	4	2,9	7	3,5	3	4,3	-1,4	-0,8
Hypophosphataemia	6	4,3	9	4,5	1	1,4	2,9	3,1
Musculoskeletal and connective tissue disorders	**10**	**7,2**	**13**	**6,5**	**6**	**8,7**	**-1,5**	**-2,2**
Back pain	4	2,9	5	2,5	1	1,4	1,5	1,1
Bone pain	0	0,	1	,5	2	2,9	-2,9	-2,4
Nervous system disorders	**9**	**6,5**	**19**	**9,5**	**9**	**13,0**	**-6,5**	**-3,5**
Dizziness	2	1,4	6	3,0	1	1,4	0	1,6
Headache	3	2,2	9	4,5	3	4,3	-2,1	0,2
Seizure	2	1,4	2	1,0	2	2,9	-1,5	-1,9
Renal and urinary disorders	**2**	**1,4**	**5**	**2,5**	**1**	**1,4**	**0**	**1,1**
Respiratory, thoracic and mediastinal disorders	**17**	**1,22**	**24**	**12,1**	**4**	**5,8**	**-4,58**	**6,3**
Cough	6	4,3	9	4,5	1	1,4	2,9	3,1
Epistaxis	3	2,2	4	2,0	0	0,	2,2	2
Hiccups	4	2,9	5	2,5	2	2,9	0	-0,4

Skin and subcutaneous tissue disorders	**12**	**8,60**	**15**	**7,50**	**3**	**4,30**	**4,30**	**3,20**
Rash	6,00	4,30	6,00	3,00	1,00	1,40	2,9	1,6
Vascular disorders	3,00	2,20	5,00	2,50	2,00	2,90	-0,70	-0,40
General disorders and administration site conditions	**26**	**18,70**	**43**	**21,60**	**10**	**14,50**	**4,2**	**7,1**
Fatigue	3,00	2,20	6,00	3,00	3,00	4,30	-2,10	-1,30
Mucosal inflammation	8,00	5,80	10,00	5,00	0,00	0,00	5,8	5
Pyrexia	14,00	10,10	24,00	12,10	4,00	5,80	4,30	6,30
Hepatobiliary disorders	3,00	2,20	4,00	2,00	1,00	1,40	0,8	0,6
Infections and infestations	18,00	12,90	30,00	15,10	9,00	13,00	-0,10	2,10
Paronychia	0,00	0,00	0,00	0,00	2,00	2,90	-2,9	-2,9
Upper respiratory tract infection	4,00	2,90	5,00	2,50	1,00	1,40	1,50	1,10
Injury, poisoning and procedural complications	1,00	0,70	4,00	2,00	0,00	0,00	0,7	2
Investigations	48,00	34,50	58,00	29,10	19,00	27,50	7,00	1,60
Alanine aminotransferase increased	9,00	6,50	11,00	5,50	5,00	7,20	-0,7	-1,7
Aspartate aminotransferase increased	11,00	7,90	13,00	6,50	4,00	5,80	2,10	0,70
C-reactive protein increased	4,00	2,90	6,00	3,00	1,00	1,40	1,5	1,6
Haemoglobin decreased	3,00	2,20	4,00	2,00	1,00	1,40	0,80	0,60
Neutrophil count decreased	20,00	14,40	22,00	11,10	7,00	10,10	4,3	1
Platelet count decreased	22,00	15,80	25,00	12,60	6,00	8,70	7,10	3,90
Weight decreased	0,00	0,00	0,00	0,00	2,00	2,90	-2,9	-2,9
White blood cell count decreased	6,00	4,30	9,00	4,50	5,00	7,20	-2,90	-2,70

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.
The column "1-Day Supportive Pool" includes subjects receiving fosaprepitant in single-day doses of 150mg and 5mg/kg.
The column "3-Day Supportive Pool" includes subjects receiving fosaprepitant in single-day doses of 150mg, 5mg/kg and 3mg/kg and a 3-day regimen of fosaprepitant 115 mg on Day 1 and aprepitant 80 mg on Days 2 and 3.
The column "Difference" includes the different, in percentage) between the control regimen and the 1-Day and 3-Day regimen.

Source: Summary clinical safety, Table 2.7.4:24 Modified

The two most commonly reported Grade 3 AEs were febrile neutropenia and anemia with a similar incidence in both the fosaprepitant and control groups. The most commonly reported Grade 4 toxicities were neutropenia and thrombocytopenia, in which similar incidences were reported in both the fosaprepitant and control groups.

Table 43: Subjects With Adverse Events by Maximum Toxicity Grade (Incidence ≥5% in One or More Treatment Groups)in Cycle 1 All Subjects as Treated Protocols 134, 029 and 044 Combined

	1-Day Supportive Pool		**3-Day Supportive Pool**		**Control Regimen**	
	n	**%**	**n**	**%**	**n**	**%**
Subjects in population	139		199		69	
with one or more adverse events (any grade)	118	84.9	167	83.9	54	78.3
with no adverse events (any grade)	21	15.1	32	16.1	15	21.7
Blood and lymphatic system disorders (any grade)	**70**	**50.4**	**101**	**50.8**	**33**	**47.8**
Anaemia	43	30.9	57	28.6	15	21.7
Grade 3	19	13.7	26	13.1	11	15.9
Grade 4	3	2.2	4	2.0	0	0.0
Febrile neutropenia (any grade)	22	15.8	34	17.1	11	15.9

Grade 3	20	14.4	29	14.6	9	13.0
Grade 4	2	1.4	4	2.0	2	2.9
Leukopenia (any grade)	15	10.8	20	10.1	5	7.2
Grade 3	6	4.3	6	3.0	2	2.9
Grade 4	6	4.3	9	4.5	1	1.4
Neutropenia (any grade)	28	20.1	41	20.6	13	18.8
Grade 3	10	7.2	15	7.5	3	4.3
Grade 4	10	7.2	17	8.5	7	10.1
Thrombocytopenia (any grade)	23	16.5	38	19.1	11	15.9
Grade 3	7	5.0	13	6.5	5	7.2
Grade 4	8	5.8	16	8.0	4	5.8
Gastrointestinal disorders (any grade)	**52**	**37.4**	**79**	**39.7**	**17**	**24.6**
Constipation (any grade)	13	9.4	18	9	6	8.7
Grade 3	0	0.0	0	0.0	1	1.4
Nausea (any grade)	10	7.2	17	8.5	3	4.3
Grade 3	1	0.7	1	0.5	0	0.0
Vomiting (any grade)	23	16.5	37	18.6	4	5.8
Grade 3	3	2.2	4	2.0	0	0.0
General disorders and administration site conditions (any grade)	**26**	**18.7**	**43**	**21.6**	**10**	**14.5**
Mucosal inflammation (any grade)	8	5.8	10	5.0	0	0.0
Grade 3	2	1.4	3	1.5	0	0.0
Pyrexia (any grade)	14	10.1	24	12.1	4	5.8
Grade 3	1	0.7	1	0.5	0	0.0
Infections and infestations (any grade)	**19**	**13.7**	**31**	**15.6**	**9**	**13.0**
Investigations (any grade)	**48**	**34.5**	**58**	**29.1**	**19**	**27.5**
Alanine aminotransferase increased (any grade)	9	6.5	11	5.5	5	7.2
Grade 3	2	1.4	2	1.0	1	1.4
Aspartate aminotransferase increased (any grade)	11	7.9	13	6.5	4	5.8
Grade 3	1	.7	1	.5	0	0
Neutrophil count decreased (any grade)	20	14.4	22	11.1	7	10.1
Grade 3	8	5.8	8	4.0	1	1.4
Grade 4	10	7.2	11	5.5	5	7.2
Platelet count decreased (any grade)	22	15.8	25	12.6	6	8.7
Grade 3	6	4.3	6	3.0	2	2.9
Grade 4	6	4.3	8	4.0	3	4.3
White blood cell count decreased (any grade)	6	4.3	9	4.5	5	7.2
Grade 3	3	2.2	5	2.5	1	1.4
Grade 4	2	1.4	3	1.5	4	5.8
Metabolism and nutrition disorders (any grade)	**21**	**15.1**	**33**	**16.6**	**7**	**10.1**
Decreased appetite (any grade)	9	6.5	12	6.0	4	5.8
Grade 3	2	1.4	4	2.0	1	1.4
Musculoskeletal and connective tissue disorders (any grade)	**10**	**7.2**	**13**	**6.5**	**6**	**8.7**
Nervous system disorders (any grade)	**9**	**6.5**	**19**	**9.5**	**9**	**13.0**
Respiratory, thoracic and mediastinal disorders (any grade)	**17**	**12.2**	**24**	**12.1**	**4**	**5.8**
Skin and subcutaneous tissue disorders (any grade)	**12**	**8.6**	**1 5**	**7.5**	**3**	**4.3**

The only drug related AE that occurred in >1% was hiccups (1.9%). Four of all drug related AEs were SAE: hyponatraemia (Fosaprepitant 3 mg/kg regimen; Protocol 134 Part V); anaphylactic reaction (Fosaprepitant 5 mg/kg regimen; Protocol 029); hypersensitivity (Fosaprepitant 150 mg regimen; Protocol 044); and seizure (Control regimen; Protocol 044).

Table 44: Subjects with Drug-Related Adverse Events in Cycle 1 All Subjects as Treated, Protocols 134, 029 and 044 Combined

	1-Day Supportive Pool		3-Day Supportive Pool		Control Regimen	
	n	%	n	%	n	%
Subjects in population	139		199		69	
with one or more drug-related adverse events	9	6.5	11	5.5	5	7.2
with no drug-related adverse events	130	93.5	188	94.5	64	92.8
Bradycardia	1	0.7	1	0.5	0	0.0
Eye oedema	1	0.7	1	0.5	0	0.0
Gastrointestinal disorders	1	0.7	3	1.5	1	1.4
General disorders and administration site conditions	1	0.7	1	0.5	1	1.4
Discomfort	1	0.7	1	0.5	0	0.0
Anaphylactic reaction	1	0.7	1	0.5	0	0.0
Hypersensitivity	1	0.7	1	0.5	0	0.0
Hyperglycaemia	0	0	1	0.5	0	0
Hyponatraemia	0	0	1	0.5	0	0
Dizziness	1	0.7	1	0.5	0	0
Extrapyramidal disorder	1	0.7	1	0.5	0	0
Headache	1	0.7	1	0.5	0	0
Seizure	0	0	0	0	1	1.4
Syncope	0	0	1	0.5	0	0
Hiccups	3	2.2	3	1.5	2	2.9
Rash	1	0.7	1	0.5	0	0
Flushing	1	0.7	1	0.5	0	0
Hypotension	0	0	1	0.5	0	0

Every subject is counted a single time for each applicable row and column.

Protocols 029, and 044 Combined, Cycle 2-6

Table 45: Adverse Events Summary By Age Category in Cycles 2-6 All Subjects as Treated Protocols 029 and 044 Combined

	Birth To < 2 Years				2 Years To < 6 Years			
	1-Day Supportive Pool		3-Day Supportive Pool		1-Day Supportive Pool		3-Day Supportive Pool	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	18		18		23		43	
with one or more adverse events	17	(94.4)	17	(94.4)	18	(78.3)	33	(76.7)
with no adverse event	1	(5.6)	1	(5.6)	5	(21.7)	10	(23.3)
with drug-related[†] adverse events	0	(0.0)	0	(0.0)	1	(4.3)	1	(2.3)
with serious adverse events	10	(55.6)	10	(55.6)	9	(39.1)	19	(44.2)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	1	(4.3)	1	(2.3)

who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	6 Years To < 12 Years				12 Years To < 17 Years			
	1-Day Supportive Pool		3-Day Supportive Pool		1-Day Supportive Pool		3-Day Supportive Pool	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	35		75		72		72	
with one or more adverse events	30	(85.7)	63	(84.0)	54	(75.0)	54	(75.0)
with no adverse event	5	(14.3)	12	(16.0)	18	(25.0)	18	(25.0)
with drug-related† adverse events	0	(0.0)	3	(4.0)	2	(2.8)	2	(2.8)
with serious adverse events	21	(60.0)	42	(56.0)	27	(37.5)	27	(37.5)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	2	(2.8)	2	(2.8)

The column "1-Day Supportive Pool" includes subjects receiving fosaprepitant in doses of 150 mg and 5mg/kg.
The column "3-Day Supportive Pool" includes subjects receiving fosaprepitant in doses of 150 mg, 5 mg/kg and 3mg/kg.
† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.

The most frequently reported AEs in all treated subjects in the optional cycles 2 to 6 of P029 and P044, were similar to those observed in the integrated fosaprepitant and control datasets and included anaemia, febrile neutropenia, and thrombocytopenia within the blood and lymphatic SOC, followed by vomiting in the gastrointestinal disorder SOC.

Table 46: Subjects with Adverse Events by Maximum Toxicity Grade (Incidence ≥5% in One or More Treatment Groups) in Cycles 2-6 All Subjects as Treated Protocols 029 and 044 Combined

	1-Day Supportive Pool		3-Day Supportive Pool	
	n	%	n	%
Subjects in population (any grade)	148		208	
with one or more adverse events (any grade)	119	80.4	167	80.3
with no adverse events (any grade)	29	19.6	41	19.7
Blood and lymphatic system disorders (any grade)	**80**	**54.1**	**115**	**55.3**
Anaemia (any grade)	41	27.7	62	29.8
Grade 3	24	16.2	38	18.3
Grade 4	3	2.0	4	1.9
Febrile neutropenia (any grade)	53	35.8	70	33.7
Grade 3	40	27.0	49	23.6
Grade 4	12	8.1	20	9.6
Leukopenia (any grade)	17	11.5	28	13.5
Grade 3	4	2.7	4	1.9
Grade 4	9	6.1	16	7.7
Neutropenia (any grade)	17	11.5	28	13.5
Grade 3	8	5.4	14	6.7
Grade 4	7	4.7	10	4.8
Grade 5	1	0.7	1	0.5
Thrombocytopenia (any grade)	28	18.9	39	18.8
Grade 3	9	6.1	12	5.8
Grade 4	12	8.1	19	9.1
Gastrointestinal disorders (any grade)	**62**	**41.9**	**87**	**41.8**

Abdominal pain (any grade)	17	11.5	27	13.0
Grade 3	4	2.7	4	1.9
Constipation (any grade)	11	7.4	16	7.7
Diarrhoea (any grade)	11	7.4	16	7.7
Nausea (any grade)	25	16.9	38	18.3
Stomatitis (any grade)	14	9.5	16	7.7
Grade 3	2	1.4	3	1.4
Grade 4	0	0.0	1	0.5
Vomiting (any grade)	38	25.7	54	26.0
Grade 3	2	1.4	5	2.4
General disorders and administration site conditions (any grade)	**38**	**25.7**	**51**	**24.5**
Mucosal inflammation (any grade)	12	8.1	17	8.2
Grade 3	7	4.7	8	3.8
Pyrexia (any grade)	18	12.2	27	13.0
Infections and infestations (any grade)	**36**	**24.3**	**54**	**26.0**
Injury, poisoning and procedural complications (any grade)	**11**	**7.4**	**15**	**7.2**
Investigations (any grade)	**45**	**30.4**	**72**	**34.6**
Alanine aminotransferase increased (any grade)	11	7.4	20	9.6
Grade 3	4	2.7	6	2.9
Grade 4	1	0.7	3	1.4
Aspartate aminotransferase increased (any grade)	11	7.4	19	9.1
Grade 3	2	1.4	5	2.4
C-reactive protein increased (any grade)	5	3.4	11	5.3
Grade 3	1	0.7	1	0.5
Grade 4	2	1.4	5	2.4
Neutrophil count decreased (any grade)	22	14.9	29	13.9
Grade 3	6	4.1	9	4.3
Grade 4	11	7.4	15	7.2
Platelet count decreased (any grade)	18	12.2	25	12.0
Grade 3	3	2.0	6	2.9
Grade 4	6	4.1	8	3.8
White blood cell count decreased (any grade)	14	9.5	20	9.6
Grade 3	4	2.7	6	2.9
Grade 4	6	4.1	8	3.8
Metabolism and nutrition disorders (any grade)	**19**	**12.8**	**37**	**17.8**
Hypokalaemia (any grade)	7	4.7	18	8.7
Grade 3	2	1.4	8	3.8
Grade 4	0	0.0	1	0.5
Hypophosphataemia (any grade)	4	2.7	11	5.3
Grade 3	0	0.0	2	1.0
Grade 4	0	0.0	1	0.5
Musculoskeletal and connective tissue disorders (any grade)	**18**	**12.2**	**22**	**10.6**
Pain in extremity (any grade)	8	5.4	8	3.8
Pain in extremity (any grade)	8	5.4	8	3.8
Grade 3	1	0.7	1	0.5
Nervous system disorders (any grade)	**19**	**12.8**	**29**	**13.9**
Headache (any grade)	10	6.8	15	7.2

Grade 3	1	0.7	1	0.5
Respiratory, thoracic and mediastinal disorders (any grade)	**16**	**10.8**	**30**	**14.4**
Cough	8	5.4	15	7.2
Skin and subcutaneous tissue disorders (any grade)	**11**	**7.4**	**17**	**8.2**

There were 6 drug-related AEs in Cycle 2-6 of protocol 029 (2 cases of hiccups and one each of nausea, salivary hypersecretion, vomiting, extrapyramidale disorder, headache and seizure). There was no drug-related AE in cycle 2-6 of P044.

Protocols 208, and 097 Combined

The applicant also uses safety data from study P208 and P097 to support the 3-Day regimen.

Table 47: Subjects with Adverse Events (Incidence ≥ 2% in One or More Treatment Groups) <Cycle 1> All Subjects as Treated (ASaT) Population Protocols 208 and 097 Combined

	Aprepitant Regimen		Control Regimen		Difference
	n	%	n	%	(percentage)
Subjects in population	184		168		
with one or more adverse events	146	79,3	130	77,4	1,90
with no adverse events	38	20,7	38	22,6	-1,90
Blood and lymphatic system disorders	**71**	**38,6**	**67**	**39,9**	**-1,30**
Anaemia	27	14,7	38	22,6	-7,90
Febrile neutropenia	30	16,3	26	15,5	0,80
Leukopenia	8	4,3	10	6,0	-1,70
Neutropenia	24	13,0	18	10,7	2,30
Pancytopenia	4	2,2	6	3,6	-1,40
Thrombocytopenia	15	8,2	16	9,5	-1,30
Eye disorders	**7**	**3,8**	**2**	**1,2**	**2,60**
Gastrointestinal disorders	**69**	**37,5**	**59**	**35,1**	**2,40**
Abdominal pain	12	6,5	11	6,5	0,00
Abdominal pain upper	5	2,7	1	0,6	2,10
Constipation	5	2,7	6	3,6	-0,90
Diarrhoea	11	6,0	9	5,4	0,60
Nausea	20	10,9	20	11,9	-1,00
Stomatitis	6	3,3	5	3,0	0,30
Vomiting	30	16,3	26	15,5	0,80
General disorders and administration site conditions	**35**	**19,0**	**28**	**16,7**	**2,30**
Fatigue	9	4,9	3	1,8	3,10
Mucosal inflammation	7	3,8	7	4,2	-0,40
Pyrexia	12	6,5	13	7,7	-1,20
Infections and infestations	**26**	**14,1**	**26**	**15,5**	**-1,40**
Nasopharyngitis	3	1,6	4	2,4	-0,80
Rhinitis	1	0,5	4	2,4	-1,90
Urinary tract infection	5	2,7	5	3,0	-0,30
Injury, poisoning and procedural complications	**8**	**4,3**	**5**	**3,0**	**1,30**

Accidental overdose	1	0,5	4	2,4	-1,90
Investigations	**49**	**26,60**	**45**	**26,80**	**-0,20**
Alanine aminotransferase increased	6	3,3	8	4,8	-1,50
Aspartate aminotransferase increased	5	2,7	6	3,6	-0,90
Blood potassium decreased	4	2,2	2	1,2	1,00
Haemoglobin decreased	9	4,9	7	4,2	0,70
Neutrophil count decreased	16	8,7	23	13,7	-5,00
Platelet count decreased	14	7,6	16	9,5	-1,90
White blood cell count decreased	9	4,9	9	5,4	-0,50
Metabolism and nutrition disorders	20	10,9	21	12,5	-1,60
Decreased appetite	10	5,4	7	4,2	1,20
Dehydration	2	1,1	5	3	-1,90
Hypokalaemia	1	0,5	7	4,2	-3,70
Hypomagnesaemia	3	1,6	4	2,4	-0,80
Hypophosphataemia	2	1,1	4	2,4	-1,30
Musculoskeletal and connective tissue disorders	9	4,9	2	1,2	3,70
Nervous system disorders	27	14,7	14	8,3	6,40
Dizziness	9	4,9	1	0,6	4,30
Headache	17	9,2	8	4,8	4,40
Psychiatric disorders	4	2,2	2	1,2	1,00
Respiratory, thoracic and mediastinal disorders	27	14,7	13	7,7	7,00
Cough	10	5,4	5	3	2,40
Hiccups	8	4,3	1	0,6	3,70
Skin and subcutaneous tissue disorders	10	5,4	9	5,4	0,00
Vascular disorders	7	3,8	3	1,8	2,00

Source: Summary clinical safety, Table 2.7.4:27 Modified

Serious adverse event/deaths/other significant events

Table 48: Subjects with Serious Adverse Events in Cycle 1-6 All Subjects as Treated Protocols 134, 029 and 044 Combined

	Cycle 1						Cycle 2-6			
	1-Day Supportive Pool		**3-Day Supportive Pool**		**Control Regimen**		**1-Day Supportive Pool**		**3-Day Supportive Pool**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Subjects in population	139		199		69		148		208	
with one or more serious adverse events	40	28.8	61	30.7	20	29.0	67	45.3	98	47.1
with no serious adverse events	99	71.2	138	69.3	49	71.0	81	54.7	110	52.9
Blood and lymphatic system disorders	**22**	**15.8**	**38**	**19.1**	**13**	**18.8**	**52**	**35.1**	**74**	**35.6**
Anaemia	0	0	0	0	2	2.9	4	2.7	5	2.4
Bone marrow failure	1	0.7	1	0.5	1	1.4	3	2.0	3	1.4
Febrile neutropenia	19	13.7	30	15.1	9	13.0	46	31.1	63	30.3
Leukopenia	1	0.7	2	1.0	1	1.4	2	1.4	6	2.9
Neutropenia	0	0	3	1.5	2	2.9	4	2.7	8	3.8
Pancytopenia	1	0.7	1	0.5	0	0	0	0	1	0.5
Thrombocytopenia	0	0	1	0.5	0	0	4	2.7	4	1.9

Cardiac disorders	**1**	**0.7**	**1**	**0.5**	**0**	**0**	**0**	**0**	**0**	**0**
Tachycardia	1	0.7	1	0.5	0	0	0	0	0	0
Gastrointestinal disorders	**2**	**1.4**	**3**	**1.5**	**1**	**1.4**	**6**	**4.1**	**11**	**5.3**
Abdominal pain	0	0	0	0	0	0	1	0.7	1	0.5
Colitis	0	0	0	0	0	0	1	0.7	1	0.5
Diarrhoea	0	0	0	0	0	0	1	0.7	1	0.5
Proctalgia	0	0	0	0	0	0	2	1.4	2	1.0
Stomatitis	0	0	1	0.5	1	1.4	1	0.7	3	1.4
Vomiting	2	1.4	2	1.0	0	0	1	0.7	4	1.9
General disorders and administration site conditions	**4**	**2.9**	**5**	**2.5**	**1**	**1.4**	**9**	**6.1**	**10**	**4.8**
Complication associated with device	0	0	0	0	0	0	1	0.7	1	0.5
General physical health deterioration	1	0.7	1	0.5	0	0	0	0	0	0
Mucosal inflammation	2	1.4	3	1.5	0	0	4	2.7	5	2.4
Pyrexia	1	0.7	1	0.5	1	1.4	3	2.0	3	1.4
Soft tissue inflammation	0	0	0	0	0	0	1	0.7	1	0.5
Immune system disorders	**2**	**1.4**	**2**	**1.0**	**0**	**0**	**0**	**0**	**0**	**0**
Anaphylactic reaction	1	0.7	1	0.5	0	0	0	0	0	0
Hypersensitivity	1	0.7	1	0.5	0	0	0	0	0	0
Infections and infestations	**4**	**2.9**	**7**	**3.5**	**3**	**4.3**	**14**	**9.5**	**25**	**12.0**
Appendicitis	0	0	0	0	0	0	1	0.7	1	0.5
Bacteraemia	0	0	0	0	0	0	1	0.7	2	**1.0**
Catheter site infection	0	0	0	0	0	0	1	0.7	1	0.5
Cellulitis	0	0	0	0	0	0	0	0	1	0.5
Cytomegalovirus infection	0	0	0	0	0	0	1	0.7	1	0.5
Device related infection	0	0	0	0	0	0	2	**1.4**	4	**1.9**
Enterobacter bacteraemia	1	0.7	1	0.5	0	0	0	0	0	0
Febrile infection	0	0	0	0	0	0	0	0	1	0.5
Fungal sepsis	0	0	1	0.5	0	0	0	0	0	0
Gastroenteritis norovirus	1	0.7	1	0.5	0	0	1	0.7	2	**1.0**
Herpes virus infection	1	0.7	1	0.5	0	0	0	0	0	0
Herpes simplex	0	0	0	0	0	0	1	0.7	1	0.5
Herpes zoster	0	0	0	0	0	0	0	0	1	0.5
Infection	0	0	0	0	1	1.4	0	0	0	0
Influenza	0	0	0	0	0	0	1	0.7	1	0.5
Klebsiella bacteraemia	0	0	0	0	0	0	1	0.7	1	0.5
Neutropenic sepsis	0	0	2	1.0	0	0	0	0	0	0
Otitis media chronic	0	0	0	0	1	1.4	0	0	0	0
Postoperative wound infection	0	0	0	0	0	0	0	0	1	0.5
Pyelonephritis acute	0	0	0	0	0	0	1	0.7	1	0.5
Respiratory tract infection	0	0	0	0	0	0	0	0	1	0.5
Sepsis	0	0	0	0	0	0	2	**1.4**	3	**1.4**
Septic shock	0	0	1	0.5	0	0	0	0	0	0
Skin infection	0	0	0	0	1	1.4	0	0	0	0
Tooth infection	1	0.7	1	0.5	0	0	0	0	0	0
Tonsillitis	0	0	0	0	0	0	1	0.7	1	0.5
Urinary tract infection	0	0	0	0	0	0	0	0	1	0.5

Viral infection	0	0	0	0	0	0	2	**1.4**	2	**1.0**
Injury, poisoning and procedural complications	**0**	**0**	**1**	**0.5**	**0**	**0**	**0**	**0**	**0**	**0**
Wound dehiscence	0	0	1	0.5	0	0	0	0	0	0
Investigations	**4**	**2.9**	**4**	**2.0**	**2**	**2.9**	**2**	**1.4**	**3**	**1.4**
Amylase increased	1	0.7	1	0.5	0	0	0	0	0	0
C-reactive protein increased	1	0.7	1	0.5	0	0	0	0	1	0.5
Drug level increased	0	0	0	0	0	0	1	0.7	1	0.5
Neutrophil count decreased	2	1.4	2	1.0	2	2.9	1	0.7	1	0.5
White blood cell count decreased	0	0	0	0	1	1.4	0	0	0	0
Metabolism and nutrition disorders	**2**	**1.4**	**4**	**2.0**	**0**	**0**	**4**	**2.7**	**4**	**1.9**
Decreased appetite	2	1.4	2	1.0	0	0	1	0.7	1	0.5
Dehydration	0	0	1	0.5	0	0	2	**1.4**	2	**1.0**
Diet refusal	0	0	0	0	0	0	1	0.7	1	0.5
Hyponatraemia	0	0	1	0.5	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0.7**	**1**	**0.5**
Soft tissue mass	0	0	0	0	0	0	1	0.7	1	0.5
Nervous system disorders	**3**	**2.2**	**3**	**1.5**	**1**	**1.4**	**5**	**3.4**	**7**	**3.4**
Febrile convulsion	0	0	0	0	0	0	1	0.7	1	0.5
Hydrocephalus	1	0.7	1	0.5	0	0	1	0.7	1	0.5
Neuropathy peripheral	0	0	0	0	0	0	0	0	1	0.5
Neurotoxicity	0	0	0	0	0	0	1	0.7	1	0.5
Seizure	2	1.4	2	1.0	1	1.4	2	**1.4**	3	**1.4**
Product issues	**1**	**0.7**	**1**	**0.5**	**0**	**0**	**1**	**0.7**	**1**	**0.5**
Device breakage	0	0	0	0	0	0	1	0.7	1	0.5
Thrombosis in device	1	0.7	1	0.5	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	**1**	**0.7**	**1**	**0.5**	**0**	**0**	**0**	**0**	**1**	**0.5**
Asthma	1	0.7	1	0.5	0	0	0	0	0	0
Interstitial lung disease	0	0	0	0	0	0	0	0	1	0.5
Renal and urinary disorders	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0.7**	**1**	**0.5**
Cystitis haemorrhagic	0	0	0	0	0	0	1	0.7	1	0.5
Vascular disorders	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0.7**	**1**	**0.5**
Air embolism	0	0	0	0	0	0	1	0.7	1	0.5

Protocol 134, 029 and 044 combined, Cycle 1

Four of the considered drug-related AEs were SAEs: hyponatraemia (Fosaprepitant 3 mg/kg regimen; Protocol 134 Part V); anaphylactic reaction (Fosaprepitant 5 mg/kg regimen; Protocol 029); hypersensitivity (Fosaprepitant 150 mg regimen; Protocol 044); and seizure (Control regimen; Protocol 044).

Symptoms of hyponatremia presented in a patient 8 hours after fosaprepitant administration. At that time s-Na was 122 mEq/L (baseline 139 mEq/L; normal range 137-145 mEq/L). With treatment, the patient recovered to the next day.

Anaphylactic reaction occurred in one subject after administration of about 7 mg fosaprepitant. Fosaprepitant was discontinued (permanently), and with treatment the anaphylactic reaction resolved after about 10 minutes.

A severe hypersensitivity reaction occurred in one patient immediately after fosaprepitant infusion. Fosaprepitant was stopped (permanently) and with treatment against hypersensitivity reaction, the event resolved within 1 hour.

Seizure occurred in one patient about 45 minutes after completion of chemotherapy (cycle 1). The patient had received placebo fosaprepitant + ondansetron and dexamethasone prior to chemotherapy. The event resolved.

Protocols 029, and 044 Combined, Cycle 2-6

There was one drug-related SAE (seizure) in cycle 2-6 of protocol 029 and 044 combined. A subject who received fosaprepitant and experienced seizures in cycle 5. The patient had a history of brain sarcoma, tumour excision and previous seizure episodes.

Deaths

No subjects included in the Cycle 1 of Protocols 134, 029 and 044 died.

Two subjects in the optional cycles of Protocol 029 died, one due to progress of disease and the other due to neutropenia. A third subject who participated in the optional cycles died (due to tumour progression), approximately two months after discontinuation from the trial. Two of these three deaths are not reflected in the AE because the deaths occurred outside the reporting follow up period (ie, >14 days following the last dose of study medication). One subject in the optional cycles of Protocol 044 died due to sepsis.

Laboratory findings

After the approval and launch of the fosaprepitant formulations for use in adults, the US Food and Drug Administration requested that a separate fosaprepitant formulation with a reduced ethylenediaminetetraacetic acid (EDTA) content be developed for use in children. This request was in response to an upward trend in reported events of syncope in patients following launch of another product that had recently been reformulated to include EDTA. Although no fosaprepitant-related events of syncope had been reported in the adult clinical development program or during post marketing surveillance, a formulation with a reduced amount of EDTA was developed to support the paediatric development program.

Both the original and reduced EDTA formulations were used during the fosaprepitant paediatric clinical development program. The original formulation was used in the Phase I PK/safety study P134 and the reduced EDTA formulation was used in the Phase IIb study P029 and Phase III study P044.

In Protocol 134, the original fosaprepitant formulations (115 mg in Part IA and 150 mg in Part IB and V) were evaluated. To detect possible EDTA-related AEs, such as hypocalcaemia, hypomagnesemia, syncope and hypotension, the applicant included multiple measurements of heart rate and blood pressure as well as ionized calcium and magnesium monitoring before and after fosaprepitant infusion in Protocol 134. Across the study, no clinically meaningful AEs, changes in vital signs or electrolytes associated with EDTA were reported with the original fosaprepitant formulation. The drug-related AEs of syncope and hypotension reported in a single subject in Protocol 134 were associated with a normal ionized calcium level.

In Protocols 029 and 044, a reduced EDTA 150 mg fosaprepitant formulation was evaluated. Vital signs, including blood pressure and heart rate, and laboratory evaluations, including calcium and magnesium, were included in Protocol 029. Protocol 044 included additional measurements of blood pressure and heart rate pre- and post-fosaprepitant infusion as well as ionized calcium measurements,

15 minutes post fosaprepitant infusion. The applicant states that safety data collected with the reduced EDTA formulation in Protocols 044 and 029, demonstrated no drug-related events of hypocalcaemia, hypomagnesaemia, hypotension, or syncope.

For a few number of patients, laboratory values were collected at baseline and post fosaprepitant treatment (day 6 to 8) (around 33 patients in Protocol 134 and 132 patients in Protocol 029). Protocol 044 measured laboratory parameters at baseline and around 15 to 20 days post fosaprepitant treatment. There was an increase in NCI toxicity grade 3 and 4 for WBC, neutrophil and platelet count, as expected in a chemotherapy treated population. Even though there was a larger proportion of patients in the fosaprepitant treated group compared to the control group, who had decrease in WBC in study P029 and P044, no unexpected consistent deviations in laboratory parameters were noted. No consistent unexpected deviations were observed in vital signs or ECG-measurements.

Safety in special populations

There are no clinical data in subjects with severe hepatic insufficiency (Child-Pugh score >9).

There have not been any prospective studies evaluating aprepitant in pregnant or lactating women. Aprepitant may reduce the efficacy of hormonal contraceptives; therefore, women of childbearing potential participating in aprepitant/fosaprepitant clinical studies were advised to avoid pregnancy and were required to use two adequate barrier methods of contraception while participating in clinical studies.

Safety related to drug-drug interactions and other interactions

Interaction studies have only been performed in adults.

Discontinuation due to adverse events

Four subjects included in the Cycle 1 integrated dataset discontinued study medication due to an AE. The AEs were: anaphylactic reaction, discomfort/ flushing, hypersensitivity, and pyrexia. All but anaphylactic and hypersensitivity were moderate and all resolved on treatment after discontinuation of study drug.

No subjects in the optional Cycles 2 to 6 of Protocols 029 and 044 had an AE that resulted in discontinuation of study medication.

Post marketing experience

Fosaprepitant 115 mg was first approved 20-Aug-2007. As of 10-May-2017, fosaprepitant 150 mg (single dose regimen) is registered and approved in more than 75 countries. On 18-Mar-2016 fosaprepitant 150 mg single dose was approved in patients 12 to 17 years of age and 3 mg/kg in patients 6 months to <12 years of age, in Japan. Fosaprepitant has not been approved in paediatric patients outside Japan, but off-label use has occurred.

In total (as of 10-May-2017) an estimated 10,305,101 doses of fosaprepitant 150 mg or 115 mg constitutes the foundation of post-marketing experience. The applicant states that to date, the pattern of adverse experiences in the post-marketing environment remains generally consistent with the safety

data reported for fosaprepitant in clinical trials. An estimate of fosaprepitant use in the paediatric population cannot be determined from available data.

The applicant searched their internal database for fosaprepitant spontaneous and non-interventional study reports received from health care providers (HCPs) and consumers in patients less than 18 years of age (reported in the designated age field) from market introduction (20-Aug-2007) through 10-May-2017.

A total of 4,983 (1,328 [27%] serious) spontaneous and non-interventional study reports for fosaprepitant received from HCPs and consumers were identified. Of these, 69 reports (12 serious [17%]) involved AEs in paediatric patients (17 years of age and younger); 67 cases were received from HCPs. In 13 reports, the indication for use of fosaprepitant was not specified. The majority of the remaining reports involved treatment with fosaprepitant for post-operative nausea and vomiting (PONV) (40). The remaining 20 reports involved treatment with fosaprepitant for the following indications: vomiting (7), antiemetic supportive care (5), nausea (3), prophylaxis against chemotherapy-induced vomiting (2), product use issue (drug use in unapproved population) (1), off label use (1) and Ewing's sarcoma (1).

Table 49: Fosaprepitant Postmarketing Adverse Events in Pediatric Patients, 20-Aug-2007 to 10-May-2017

SOC	Preferred Term	Total # Serious Events	Total # Non-serious Events	Total # Events
Blood and lymphatic system disorders	Febrile neutropenia*	2	0	2
Cardiac disorders	Tachycardia	1	0	1
Eye disorders	Eyelid thickening	0	1	1
Gastrointestinal disorders	Diarrhoea	0	2	2
	Dysphagia	0	1	1
	Lip swelling*	0	1	1
	Nausea*	2	5	7
	Vomiting*	1	3	4
General disorders and administration site conditions	Adverse drug reaction	0	1	1
	Chills	0	1	1
	Drug ineffective	0	2	2
	Infusion site erythema*	0	1	1
	Infusion site pain*	0	1	1
	Infusion site phlebitis*	0	1	1
	Infusion site reaction*	0	1	1
	Injection site erythema*	0	2	2
	Injection site pain*	0	2	2
	Injection site urticaria*	0	1	1
	No adverse event*	0	3	3
	Pain	0	2	2
Immune system disorders	Anaphylactic reaction*	1	0	1
	Anaphylactic shock*	3	0	3
	Anaphylactoid reaction*	1	0	1
	Drug hypersensitivity*	0	2	2
	Hypersensitivity*	0	2	2
Injury, poisoning and procedural complications	Drug administered to patient of inappropriate age	0	8	8
	Inappropriate schedule of drug administration	1	1	2
	Incorrect drug administration rate	0	1	1
	Incorrect product storage	0	1	1
	Medication error	0	1	1
	Off label use	0	33	33
	Overdose	1	0	1
	Prescribed overdose	1	0	1
	Product use issue	0	3	3
Investigations	Alanine aminotransferase increased*	1	0	1
	Aspartate aminotransferase increased*	1	0	1
	pH urine decreased	0	1	1
	pH urine increased	0	1	1
	Weight decreased*	0	1	1

	White blood cell count decreased	1	0	1
Metabolism and nutrition disorders	Hypoalbuminaemia	0	1	1
Respiratory, thoracic and mediastinal disorders	Bronchospasm*	1	0	1
	Cough*	1	0	1
	Dyspnoea*	0	2	2
	Hiccups*	0	2	2
	Laryngeal oedema*	0	1	1
Skin and subcutaneous tissue disorders	Papule	0	1	1
	Petechiae	0	1	1
	Pruritus*	0	2	2
	Rash*	0	4	4
	Rash erythematous*	1	0	1
Social circumstances	Refusal of treatment by patient	0	1	1
Vascular disorders	Flushing*	1	0	1
Grand Total		21	103	124

The most frequently reported serious event was anaphylactic shock (3 events in 2 cases). In both cases, anaphylactic shock was reported as an AE; however, symptoms and/or vital signs indicative of anaphylactic shock were not provided to the applicant. The applicant informs that both patients recovered following treatment with corticosteroids or corticosteroid and an antihistamine.

The majority of reported events in paediatric patients involved non-serious events that were either described in the label or were preferred terms indicating off label use in paediatric patients. There is no pattern or trend presented in these reports to suggest a new safety concern not previously identified in adults for therapy with fosaprepitant.

2.5.1. Discussion on clinical safety

In total 331 paediatric patients were exposed to fosaprepitant in study P029, P044 and P134 (part I and V). The validity of safety information from study P208 and P097 (where a paediatric population received aprepitant) is in part determined by the possibility to bridge these results to the fosaprepitant regimen.

In a pooled analysis of 3 active-controlled clinical studies in paediatric patients (aged 6 months to 17 years) receiving either HEC or MEC and a single dose of IVEMEND at or above the recommended 1-day regimen dose, safety was evaluated for 139 patients receiving the 1-day regimen of IVEMEND. In the same analysis, safety was evaluated for 199 patients receiving either HEC or MEC and a single dose of IVEMEND at or above the recommended 3-day regimen of IVEMEND. Safety data following the administration of the 3-day IV/oral/oral regimen were also included.

In 3 active-controlled, open-label clinical studies, paediatric patients aged 6 months to 17 years received either highly or moderately emetogenic chemotherapy and a single dose of fosaprepitant at or above the recommended 1-day regimen dose (139 patients) or 3-day regimen (199 patients), in combination with ondansetron with or without dexamethasone.

ONO-7847-03 is a small (n=22) study in a paediatric age group in Japan. Adverse drug reactions assumed to be related to fosaprepitant was 1/22 (4.5%) and constituted of one case of mild abdominal pain. The safety results from the study do not contribute significantly to the overall safety analysis.

The different studies presented by the applicant include different inclusion and exclusion criteria. Baseline characteristics differ between studies, e.g. major malignancy type, as well as chemotherapy regimen and antiemetic therapy. This complicates the separation of the fosaprepitant specific safety profile.

When safety data from study P029, 044 and 134 were combined, AEs were observed in slightly more than 80% (i.e. 83.9-84.9%) of fosaprepitant exposed patients compared to 78% in control arm. Drug related AEs were considered to be similar in fosaprepitant exposed patients and patients in the control arm (around 6%). Few patients discontinued due to drug related adverse events (1.5-2.2% in fosaprepitant treated and 0 in control arm).

In age specific groups there was a slightly higher incidence of AEs among fosaprepitant treated patients 6 to <12 years old whereas there were no significant differences regarding AEs, drug related AEs, SAE, drug related SAE and discontinuation, between fosaprepitant treated patients and patients in the control group. Thus, the difference observed in the 6 to <12 years age group is considered to reflect the small sample.

No clear differences between fosaprepitant and control arm were seen when AEs were summarised by system organ class, except for a slightly higher proportion of gastrointestinal disorders and platelet count decrease in the fosaprepitant treated group. There were no differences when only grade 3 and 4 AEs were examined. Neither were there any clinically significant differences regarding drug related AEs and no consistent pattern of drug related AEs when the pooled data from study P029, 044 and 134 were examined.

There were no clinically significant differences between fosaprepitant 1-day regimen, 3-day regimen and controls in proportion of serious adverse events. The pattern of SAEs was a pattern expected in a population treated with chemotherapy. Five SAE were considered drug related, some previously known like hypersensitivity reactions, others not so well connected to the drug, like seizures. No drug-related SAE were fatal.

The safety profile of fosaprepitant in adult and paediatric patients was generally similar to that observed with aprepitant.

The most common adverse reactions reported at a greater incidence in paediatric patients treated with the aprepitant regimen than with the control regimen while receiving emetogenic cancer chemotherapy were hiccups (3.3 % versus 0.0 %) and flushing (1.1 % versus 0.0 %). Flushing or irritation at injection site is considered to be manageable as a fair number of patients in the targeted population will have a central venous access.

Interaction studies have only been performed in adults.

Interactions with other medicinal products following administration of intravenous fosaprepitant are likely to occur with active substances that interact with oral aprepitant. The potential for interactions with multi-day fosaprepitant regimens are anticipated to be no greater than those for oral aprepitant regimens. Therefore, the recommendations for use of IVEMEND with other medicinal products in paediatric patients are based upon adult data from fosaprepitant and aprepitant studies. When using combined IVEMEND and EMEND regimens, please refer to the Summary of Product Characteristics (SmPC) section 4.5 for EMEND capsules or EMEND for oral suspension.

No data are available following the administration of a 3-day IV fosaprepitant regimen in paediatric patients. The safety profile of the 3-day IV fosaprepitant regimen in paediatric patients is expected to be similar to that of the 1-day fosaprepitant regimen as the low daily trough levels do not significantly increase the exposures on subsequent days.

No dose adjustment is necessary for subjects with renal insufficiency or for mild to moderate hepatic insufficiency (Child-Pugh score 5 to 9). No new data regarding safety in special populations are from post-marketing experience, there were no reports that constitute a safety signal or grounds for a change in safety assessment at this point.

2.5.2. Conclusions on clinical safety

The safety profile (with regard to clinical AEs and SAE) in the paediatric population corresponds to the known safety profile of aprepitant, and fosaprepitant in an adult population.

2.5.3. PSUR cycle

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

2.6. 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 5.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 5.0 with the following content:

Safety concerns

Table 50: Safety specifications

Important identified risks	• Local tolerability • Hypersensitivity (including anaphylactic reactions and anaphylactic shock) • Drug interaction: hormonal contraceptives
Important potential risks	• Potential for medication errors
Missing information	• Use in pregnancy • Use in patients < 6 months of age or weighing <6kg • Use in patients with moderate or severe hepatic impairment

Pharmacovigilance plan

Routine pharmacovigilance activities are considered sufficient to identify and characterise the risks of the product and monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 51: Summary of safety concerns and risk minimisation activities

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Local tolerability	SmPC Sections 4.2, 4.4 and 5.3.	None
Hypersensitivity (including Anaphylactic reactions and Anaphylactic shock)	SmPC Sections 4.3, 4.4 and 4.8.	None
Drug interaction: Hormonal contraceptives	SmPC Sections 4.4 and 4.5	None
Important potential risks		
Potential for medication error	SmPC Sections 4.2 and 6.6	None
Missing information		
Use in pregnancy	SmPC Sections 4.6 and 5.3.	None
Use in patients < 6 months of age or weighing <6 kg	SmPC Sections 4.2.	None
Use in patients with moderate or severe hepatic impairment	SmPC Sections 4.2, 4.4 and 5.2.	None

2.7. Update of the Product information

As a consequence of this new indication, sections, 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the Applicant states that the proposed changes made in the PL do not require a new user consultation, neither the key safety information or the layout, format and design have been changed.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication applied for is: "Prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults and paediatric patients aged 6 months and older."

3.1.2. Available therapies and unmet medical need

Aprepitant - a selective, high-affinity antagonist of human substance P/neurokinin-1 (NK_1) receptors - is indicated for the same population and fosaprepitant is indicated in adults. Other available therapies include 5-HT_3-antagonists and corticosteroids.

3.1.3. Main clinical studies

The studies included to support fosaprepitant 1-day regimen in a paediatric population were performed with fosaprepitant in an adult population. The studies included to support fosaprepitant 3-day regimen in a paediatric population were performed with aprepitant in a paediatric population. All studies of efficacy have previously been assessed in other procedures, and have been found to support efficacy in the studied populations.

3.2. Favourable effects

The 1-day regimen of fosaprepitant was, in study P017L1, found to achieve similar response in terms of overall complete response, as 1-day aprepitant regimen. The fosaprepitant treated arm in study P031 achieved 83.9% complete response in the delayed phase, compared to 75.1% in the placebo arm.

The main supportive study for the 3-day regimen, P208, described a complete response in the delayed phase of 50.7% in the aprepitant arm compared to 26% in the control arm.

Fosaprepitant is rapidly converted in the body to its active form aprepitant following intravenous (IV) administration (see EPAR Ivemend).

3.3. Uncertainties and limitations about favourable effects

As the clinical efficacy of fosaprepitant is based on extrapolations, the precise magnitude of effect is uncertain.

3.4. Unfavourable effects

Unfavourable effects are in line with known, and previously assessed, unfavourable effects of aprepitant in a paediatric population and fosaprepitant in an adult population. No new, clinically significant, unfavourable effects have been noted in the pooled data analysis from the applicant.

3.5. Uncertainties and limitations about unfavourable effects

Few individuals in certain age groups hamper interpretation of unfavourable effects. However, no new uncertainties besides already known for an adult population have been noted.

3.6. Effects Table

Table 52: Effects Table for Ivemend in paediatric patients.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Overall CR	The efficacy of a 1-day fosaprepitant regimen in paediatric patients is expected to be similar to that of the 1-day adult fosaprepitant regimen	fosaprepitant	aprepitant	efficacy of the 1-day fosaprepitant regimen in paediatric patients was extrapolated from that demonstrated in adults receiving the 1-day fosaprepitant regimen		Study 017L1
Overall CR delayed phase			Placebo + ondasetron			Study 031 --- And CHMP AR for Ivemend in adults
Overall CR	The efficacy of a 3-day fosaprepitant regimen in paediatric patients is expected to be similar to that of the 3-day oral aprepitant regimen.	aprepitant	Placebo+ ondasetron	The efficacy of the 3-day fosaprepitant regimen in paediatric patients was based on that demonstrated in paediatric patients receiving the 3-day oral aprepitant regimen.		Study 208
		aprepitant	ondasetron			Study 097
		fosaprepitant	aprepitant			Study 134 And CHMP AR for Emend in paediatric patients
Unfavourable Effects						
In line with unfavourable effects of aprepitant, fosaprepitant in adults.						CHMP AR Emend CHMP AR Ivemend

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy of 1-day fosaprepitant treatment in children can be predicted from that demonstrated in adults based on similar pathophysiology of chemotherapy-induced nausea and vomiting (CINV) as well as similar response to NK1 receptor antagonists in adults and children.

Further, since the conversion of fosaprepitant to aprepitant is rapid, efficacy following fosaprepitant administration can be expected to be derived from exposure to aprepitant. Based on this rationale, the MAH bridged the efficacy of 3-day fosaprepitant treatment in children from that demonstrated with the paediatric 3-day oral aprepitant regimen.

Unfavourable effects do not differ significantly from those found in a paediatric population treated with aprepitant. Thus, the extrapolation of efficacy and safety data on the basis of pharmacokinetics is considered acceptable.

3.7.2. Balance of benefits and risks

The primary endpoints have been met in the studies reviewed and the extrapolation and modelling considerations are acceptable. The safety is considered adequately documented in a paediatric population and does not raise any concerns.

Alignment with the indications of aprepitant (by deleting "cisplatin – based chemotherapy) is acceptable based on the fact that fosaprepitant is rapidly converted in the body to its active form aprepitant following intravenous (IV) administration (see EPAR Ivemend).

Thus, the B/R balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Ivemend in the indication: "Prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults and paediatric patients older than 6 months" is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication "prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults" to include: "paediatric patients aged 6 months and older". As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance.

The RMP version 5.0 has also been submitted.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk management plan (RMP)

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

In addition, 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.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0010/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include adolescents, infants, toddlers and children aged 6 months and older for prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy.
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance.

The RMP version 5.0 has also been submitted.

Summary

Please refer to the Scientific Discussion Ivemend EMEA/H/C/000743/II/0037.

Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 22 March 2018.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 06 April 2018. The principles to be applied for the deletion of CCI are published on the EMA website at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf.

2. The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

3. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, or prior to the next regulatory activity, whichever is first. For additional guidance see chapter 4.1 of the *Harmonised Technical Guidance for eCTD Submissions in the EU*.