Office of Clinical Pharmacology Review

NDA or BLA Number	22023/S-17
Link to EDR	\\CDSESUB1\evsprod\NDA022023\022023.enx
Submission Date	10/3/2017
Submission Type	Efficacy Supplement
Brand Name	Emend™ for Injection
Generic Name	Fosaprepitant dimeglumine
Dosage Form and Strength	Lyophilized powder (150 mg fosaprepitant) to be reconstituted for IV infusion
Route of Administration	Intravenous Infusion
Proposed Indication	In pediatric patients six months of age and older, combination with other antiemetic agents for the prevention of • acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin. • delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).
Applicant	Merck Sharp & Dohme Corp
Associated IND	048924
OCP Primary Reviewer	Elizabeth Shang, Ph.D., R.Ph. (Clinical Pharmacology and Pharmacometrics)
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1. EXECUTIVE SUMMARY

Fosaprepitant (Emend) for injection has been approved since 2008 for adults in combination with other antiemetic agents for the prevention of: 1) acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin; and 2) delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC). The approved regimen in adults is a single intravenous infusion of 150 mg fosaprepitant over 20 to 30 minutes approximately 30 minutes prior to chemotherapy. It has not been studied for the treatment of established nausea and vomiting. Fosaprepitant is a prodrug of aprepitant. Aprepitant (Emend) oral capsule and suspension have been approved for chemotherapy-induced nausea and vomiting (CINV) in adults (2003) and pediatric patients (2015) as a three-day oral regimen.

To support the proposed expansion of the indications to pediatric patients, the sponsor completed one phase 2b dose-ranging PK/PD study for a single-day regimen and one PK study including cohorts where 1) fosaprepitant IV was administered on Day 1 followed by oral aprepitant on Days 2 and 3 in adolescent patients; and 2) single-dose dose-ranging PK study of fosaprepitant IV was conducted in patients less than 12 years old. The sponsor proposed two dosing regimens for the use of fosaprepitant in pediatric patients 6 months and older: a single-day regimen and a three-day regimen.

The doses for both regimens were derived by using exposure-matching strategy since the efficacy of aprepitant has been established in 1) pediatric patients 6 months and older administered oral aprepitant in a three-day regimen, and 2) adult cancer patients receiving single-day regimen of fosaprepitant. For the single-day regimen, the dose for fosaprepitant was derived from matching systemic exposures (Cmax and AUC) in pediatric cancer patients to those in adult healthy subjects. For the three-day regimen, the systemic exposure (AUC) of aprepitant following IV fosaprepitant on Day 1 and oral aprepitant on Days 2 and 3 (IV/PO/PO) was matched to those in pediatric patients receiving three-day oral aprepitant (PO/PO/PO), an approved regimen in pediatric patients. Because the minimum body weight of subjects enrolled in the studies was 6.80 kg, the sponsor's proposal to not dose fosaprepitant for pediatric patients with body weight less than 6 kg is reasonable.

The sponsor initially also proposed a three-day regimen with fosaprepitant given on Days 1, 2, and 3 (IV/IV/IV). However, the option of using fosaprepitant IV for three consecutive days has been foundunacceptable based upon the review of PK data. The Cmax from the proposed IV administration on Days 2 and 3 with the same infusion duration as Day 1 was about 2-fold those from oral aprepitant administration. An infusion duration of 8 to16 hours is needed to match the Cmax of aprepitant following IV infusion to that following oral administration, and is thus considered impractical. In addition, there was no safety data for pediatric patients on Days 2 and 3 with higher Cmax of aprepitant. Thus, the review team recommends that only the three-day regimen with IV/PO/PO route be approved.

The data in this sNDA were also used to support the fulfillment of Postmarketing Requirement (PMR) under the Pediatric Research Equality Act (PREA) and the Pediatric Written Request (PWR).

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed this application and found this supplemental NDA acceptable from a clinical pharmacology perspective with the following recommendations on the dosage regimens. PREA PMR 1663-3 is fulfilled from a Clinical Pharmacology perspective.

The key review issue with specific recommendations/comments are summarized below:

Review Issues	Recommendations and Comments
Proposed one-day regimen	Acceptable
Proposed three-day regimen using IV/PO/PO	Acceptable
Proposed three-day regimen using IV/IV/IV or IV/IV/PO	Given that a) the Cmax from proposed IV on Days 2 and 3 with the same infusion duration as Day 1 was about 2-fold that from oral aprepitant administration, and b) there was no safety data for pediatric patients on Days 2 and 3 with higher Cmax of aprepitant, the review team recommends that only the three-day regimen with IV/PO/PO route be labeled.

1.2 Post-Marketing Requirements and Commitments

No Clinical Pharmacology related PMR or PMC.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK-1) receptors. Animal and human Positron Emission Tomography (PET) studies have shown that aprepitant crosses the blood brain barrier and occupies brain NK-1 receptors. Animal and human studies have shown that aprepitant augments the antiemetic activity of the 5-HT3 receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis. Fosaprepitant is a prodrug of aprepitant and accordingly, its antiemetic effects are attributable to aprepitant.

The pharmacokinetics (PK) for fosaprepitant and aprepitant were studied following a single dose of fosaprepitant in pediatric patients 6 months and older. In pediatric patients 2 to <12 years of age and in adolescents (12 - 17 years) following single dose 3 mg/kg IV fosaprepitant and 150 mg IV, respectively, aprepitant exhibited a biphasic decline with a mean (%CV) terminal half-life ($t_{½}$) ranging from 6.55 (55.3%) to 10.5 (9.6%) hours (Study P029). Similarly, the mean (%CV) terminal t1/2 of aprepitant was 7.94 (36%) hours in patients 6 months to < 2 years following single dose of 5 mg/kg IV fosaprepitant.

A summary for systemic exposures to aprepitant following fosaprepitant administration with proposed therapeutic doses in pediatric patients and healthy adults (comparator) is provided below. For details, see Section 3.2. Refer to the product label for detailed PK and PD information, intrinsic and extrinsic effects on fosaprepitant and aprepitant PK, as well as related dose adjustment in adults. Also refer to the oral Emend product label for the PK information in pediatrics. Excerpts of this information are provided in Section 3.2.

2.1.1 Single-day regimen

Adolescents

The systemic exposures to aprepitant in adolescents following 150 mg IV dose is shown in Table 1.

Table 1. Geometric Mean of Observed Aprepitant Following Single Dose of 150 mg IV Infusion in Adolescent Patients and Healthy Adults.

Study (Subjects)	Descriptive Statistics	AUC0-∞ (ng×hr/mL)	AUC0-24hr (ng×hr/mL)	Cmax (ng/mL)	C24hr (ng/mL)
P029 (12-17 years)	N	3	12	12	12
	Geometric Mean	33300	29400	3360	675
P134 (12-17 years)	N	8	11	11	11
	Geometric Mean	42000	30000	5380	769
P165^ (Healthy Adults)	N	41	41	41	41
	Geometric Mean	35031	24500	4010	577
^ Historical data					
Source data: Table 11-1 of CSR P029, Table 11-2 of CSR P134, Tables 11-1 and 11-2 of CSR P165					

6 months to < 12 years

Table 2. Geometric Mean of Simulated Aprepitant Following Single Dose of 4 mg/kg IV Infusion in Pediatric Patients 2 to < 12 Years Old and 5 mg/kg IV Infusion in Patients 6 months to < 2 Years Old and Observed Aprepitant Following Single Dose of 150 mg IV Infusion in Healthy Adults.

Dose	Age Group (years)	AUC0-∞ (ng×hr/mL)	AUC0-24hr (ng×hr/mL)	Cmax (ng/mL)	C24hr (ng/mL)
4 mg/kg	6 to < 12	53031	35235	3591.4	682.25
4 mg/kg	2 to < 6	37909	28205	3080.2	443.78
5 mg/kg	6 months to < 2	40021	30125	3115.7	480.64
150 mg^	Healthy Adults	35031	24500	4010	577
^ Historical data from Study P165					
Source data: Section 2.7.2 Summary of Clinical Pharmacology, Table 2.7.2:11					

2.1.2 Three-day regimen

The simulated systemic exposures to aprepitant after the administration of the following dosing regimens are shown in Table 3:

Adolescents:

- Day 1: Either 115 mg IV fosaprepitant or 125 mg oral aprepitant
- Days 2 and 3: Either 80 mg IV fosaprepitant or 80 mg oral aprepitant

6 months to < 12 years:

- Day 1: Either 3 mg/kg IV fosaprepitant or 3 mg/kg oral aprepitant
- Days 2 and 3: 2 mg/kg IV fosaprepitant or 2 mg/kg oral aprepitant

Table 3. The Geometric Mean of Simulated Systemic Exposures (AUC0-24h, Cmax, Cmin) to Aprepitant Following a Three-Day Regimen

Day 1				Day 2				Day 3			
	AUC	**Cmax**	**Cmin**		**AUC**	**Cmax**	**Cmin**		**AUC**	**Cmax**	**Cmin**
Adolescents											
PO	17958	1152.8	364.35	PO	17491	1097.1	376.96	PO	16833	1055.9	365.86
IV	20938	2424.5	424.79	PO	16820	1061.1	361.25	PO	16508	1036.1	359.34
IV	21083	2451	428.6	IV	20142	2154.7	391.75	IV	20127	2143.8	389.54
6 - < 12 years											
PO	21354	1489.2	384.31	PO	18832	1343.7	310.17	PO	18140	1291.9	298.9
IV	25659	2699.3	474.82	PO	19604	1403.9	321.35	PO	18260	1299.7	301.23
IV	25639	2686.5	474.92	IV	22704	2284	389.11	IV	22169	2235.5	377.58
2 - < 6 years											
PO	16398	1230.9	234.82	PO	13297	1034.9	167.56	PO	12710	987.39	160.23
IV	20196	2287.3	296.53	PO	13707	1070.8	172.06	PO	12724	988.1	160.66
IV	20336	2307.3	300.77	IV	16544	1860.1	219.27	IV	15941	1803.3	209.54
6 months to < 2 years											
PO	13431	1023.2	180.87	PO	10611	842.31	123.58	PO	10120	801.92	117.96
IV	16616	1864.4	227.82	PO	10915	870.12	126.6	PO	10125	802.06	118.2
IV	16715	1872.1	229.07	IV	13217	1495.5	159.94	IV	12674	1443.6	152.02

Units for AUC0-24h, Cmax, and Cmin are ng×hr/mL, ng/mL, ng/mL, respectively.

2.1.3 Fosaprepitant

Limited PK samples for fosaprepitant in pediatric patients were collected. The summary of the Cmax values is shown in Table 4. Since fosaprepitant is administered through IV infusion, the Tmax of fosaprepitant occurs at the end of infusion. Similar to adults, the concentrations of fosaprepitant were negligible within 15 to 30 minutes after the end of infusion in pediatric patients. For more details of fosaprepitant PK parameters, see Sections 3.2.2, 4.2.2.3, and 4.2.2.5.

Table 4. Summary of Plasma Fosaprepitant Cmax Values in Pediatric Patients Following a Single Dose of IV Fosaprepitant

Dose	Age Group (years)	Mean Cmax ± SD (ng/mL)
115 mg Infuse over 15 minutes	Healthy Adults^	5635 ± 1544[#]
3 mg/kg Infuse over 60 minutes	6 Months to < 2 (n = 7)	2756 ± 3364
	2 to < 6 (n = 8)	3034 ± 1718
	6 to < 12 (n = 8)	1654 ± 1995
150 mg Infuse over 30 minutes	12 to 17 (n = 11)	1310 ± 964

^ Historical data submitted to original NDA 22023.
[#] C_{15min}. Reported Cmax is 5900 ng/mL occurred at 10 minutes post the start of infusion, which was likely due to sampling error. Refer to Clinical Pharmacology Review of the original NDA published in 2008.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The doses for both regimens were derived by using exposure-matching strategy since the efficacy of aprepitant has been established in 1) pediatric patients 6 months and older receiving oral aprepitant in a three-day regimen for single or multi-day chemotherapy regimen, and 2) adult cancer patients receiving single day fosaprepitant for single-day chemotherapy regimen. For the single-day regimen, the dose for fosaprepitant was derived from matching systemic exposures (Cmax and AUC) in pediatric cancer patients to those in adult healthy subjects. For the three-day regimen, the systemic exposure (AUC) of aprepitant following IV fosaprepitant was matched to those in pediatric patients receiving oral aprepitant.

Single-day regimen for patients receiving single-day chemotherapy

The proposed doses for the single-day chemotherapy in patients 6 months and older (≥ 6 kg) and associated infusion durations are shown in Table 5 and are acceptable. The dosing instruction for the concomitant anti-emetics, corticosteroid, and 5-HT_3 antagonist is appropriate. Of note, unlike in adult patients for whom fosaprepitant is given as a combination therapy with dexamethasone and 5-HT_3 antagonist, the use of dexamethasone was optional for pediatric patients due to the difference in clinical practice. Nevertheless, when needed, dexamethasone dose should be reduced by half. The proposed infusion duration of 30 minutes in adolescents is similar to that in adult patients, i.e., 20 to 30 minutes, which is acceptable. In patients 6 months to < 12 years old, the infusion duration of one hour was proposed to reduce the Cmax. This is acceptable. The completion of infusion of fosaprepitant approximately 30 minutes prior to chemotherapy is proposed regardless of the infusion duration and age group. Since Emend is indicated for the prevention of delayed phase of CINV, this approach is acceptable.

Table 5. Single-Day Regimen for Single-Day Chemotherapy

Drug	Age	Regimen
EMEND for injection	12 Years to 17 Years	150 mg intravenously over 30 minutes,
	2 Years to less than 12 Years	4 mg/kg intravenously over 60 minutes (maximum dose 150 mg)
	6 Months to less than 2 Years	5 mg/kg intravenously over 60 minutes, (maximum dose 150 mg)
Dexamethasone	6 Months to 17 Years	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	6 Months to 17 Years	See selected 5-HT_3 antagonist prescribing information for the recommended dosage

Three-day regimen for patients receiving multiple-day chemotherapy

For the three-day regimen given as IV/PO/PO, the systemic exposure (AUC) of aprepitant on Day 1 was matched to those in pediatric patients receiving oral aprepitant on Day 1. The simulated Cmax on Day 1 following IV infusion was about 2-fold the Cmax following oral administration. However, the safety profiles from adolescents receiving 150 mg IV (a dose 30% higher than 115 mg) and patients < 12 years old receiving 5 mg/kg IV (a dose 67% higher than 3 mg/kg) support the use of the IV dose on Day 1. The doses of 115 mg IV for adolecents and 3 mg/kg for patients < 12 years old on Day 1 for a three-day regimen are acceptable. The Cmax and AUC of aprepitant on Days 2 and 3 with oral aprepitant following IV fosaprepitant on Day 1 were similar to the pediatric patients who received the same oral doses on Days 2 and 3 following oral aprepitant dose on Day 1.

Table 6. Three-Day Regimen for Single-Day or Multi-Day Chemotherapy

Age Group	Drug	Day 1	Day 2	Day 3
12 Years to less than 17 Years	EMEND for injection	115 mg intravenously over 30 minutes	--	--
	EMEND capsules	--	80 mg orally	80 mg orally
6 Months to Less than 12 Years	EMEND for injection	3 mg/kg (maximum dose is 115 mg) intravenously over 60 minutes (maximum dose is 115 mg)	--	--
	EMEND for oral suspension	--	2 mg/kg orally (maximum 80 mg)	2 mg/kg orally (maximum 80 mg)
6 Months to 17 Years	Dexamethasone	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 through 4		
6 Months to 17 Years	5-HT_3 antagonist	See selected 5-HT_3 antagonist prescribing information for the recommended dosage		

The sponsor initially also proposed a three-day regimen with fosaprepitant given on Days 1, 2, and 3 (IV/IV/IV). However, the option of using fosaprepitant IV for three consecutive days was deemed unacceptable based upon the review of PK data. The Cmax from the proposed IV administration on Days 2 and 3 with the same infusion duration as Day 1 was about 2-fold those from oral aprepitant administration (Table 3, Table 25, Table 26, Units for AUC0-24h, Cmax, and Cmin are ng×hr/mL, ng/mL, ng/mL, respectively.

Table 27, Table 28). An infusion duration of 8 to16 hours is needed to match the Cmax of aprepitant following IV infusion to that following oral administration, and is thus considered impractical. In addition, there was no safety data for pediatric patients on Days 2 and 3 with higher Cmax of aprepitant. Thus, the review team recommends that only the three-day regimen with IV/PO/PO route be approved.

Details on how the review team reached the recommendation on these dosing regimens are in Section 3.3.1.1 and Section 3.3.1.2.

2.2.2 Therapeutic individualization

Not applicable.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The labeling recommendations included the revision of the dosing regimens based upon the review team's recommendations. Labeling revisions are ongoing. Please refer to the final approved labeling when available.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Proposed product

The proposed product is the currently approved fosaprepitant for injection. It is a sterile, lyophilized formulation containing fosaprepitant dimeglumine, a prodrug of aprepitant, a substance P/neurokinin-1 (NK-1) receptor antagonist, an antiemetic agent. Fosaprepitant dimeglumine is a white to off-white amorphous powder with a molecular weight of 1004.83 Da. It is freely soluble in water. Each vial of EMEND for injection for administration as an intravenous infusion contains 150 mg of fosaprepitant (equivalent to 245.3 mg of fosaprepitant dimeglumine) and the following inactive ingredients: edetate disodium (5.4 mg), polysorbate 80 (75 mg), lactose anhydrous (375 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment).

Approved therapy

Fosaprepitant 150 mg IV has been approved in adults as a single-day regimen since 2010 in the US. It was first approved in 2008 for the prevention of CINV in adults as a three-day regimen: 115 mg IV on Day 1 followed by oral aprepitant 80 mg on Days 2 and 3. This three-day regimen in adults was discontinued in 2010 not for safety or efficacy reasons.[1]

[1] https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022023, last assessed on March 5, 2018.

Oral aprepitant has been approved in adults and pediatric patients as a three-day regimen since 2003 and 2015, respectively.

Table 7. Currently Approved Dosing Regimens of Fosaprepitant IV and Oral Aprepitant in Adults and Pediatric Patients.

Patient Population	Product	Route of Administration	Day 1	Day 2	Day 3
1-Day Regimen					
Adults	Fosaprepitant	IV infusion over 20 to 30 minutes	150 mg	n/a	n/a
3-Day Regimen					
Adults and Pediatric Patients 12 Years and Older	Aprepitant	PO	125 mg	80 mg	80 mg
Pediatric Patients 6 Months to Less than12 Years or Pediatric and Adult Patients Unable to Swallow Capsules	Aprepitant	PO	3 mg/kg Maximum 125 mg	2 mg/kg Maximum 80 mg	2 mg/kg Maximum 80 mg

Source data: Reviewer's summary

Other approved NK-1 receptor antagonists for CINV in adults include netupitant (one of the active ingredients in Akynzeo oral capsule) and rolapitant (Varubi). Neither of them has been approved in pediatric patients.

Clinical development program and relevant regulatory background

Studies completed to support the clinical development program

The fosaprepitant pediatric clinical development program consists of one Phase 1 trial (Study P134, Part I and Part V), one Phase 2b trial (Study P029) and one Phase 3 trial (Study P044). See Table 8 below. The program was initially designed to demonstrate efficacy, safety, and tolerability of fosaprepitant as a 1-day IV regimen and as part of a 3-day regimen (IV fosaprepitant given on Day 1 and oral aprepitant on Days 2 and 3) in children from birth to 17 years of age receiving HEC or MEC. While the pediatric fosaprepitant program was ongoing, the 3-day oral aprepitant regimen was approved for the prevention of CINV in children, confirming that NK-1 receptor blockade with aprepitant has similar antiemetic effects in children as in adults. Refer to PWR Amendment 4 issued in February 2017. Accordingly, the sponsor adjusted the scope of the fosaprepitant pediatric program based on the ability to extrapolate efficacy for pediatric patients, and the pivotal efficacy/safety phase 3 Study P044 for a single-day regimen was discontinued. Study P029 was conducted in response to Study 2 in the PWR, submitted in this sNDA related to the fulfillment of the PMR and PWR.

Also refer to the Division Director's reviews of NDA 21549/S-25 Emend oral capsule in adolescents approved on 8/28/2015 and NDA 207865 for Emend oral suspension in patients less than 12 years old approved on 12/17/2015 for the basis of the approval of oral aprepitant for CINV in pediatric patients. Results from Part II to Part IV of Study P134 were submitted to NDA 207865

for EMEND suspension and used to support the use of oral aprepitant suspension in pediatric patients less than 12 years old.

Table 8. Clinical Trials Used to Support the Proposed Indication in Pediatric Population

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
2012-002340-24 [Ref. 5.3.3.2: P029MK0517] Study P029	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

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

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
2014-001783-34 [Ref. 5.3.5.1: P044MK0517] Study P044	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

Source data: Section 5.2 Tabular Listing of All Clinical Studies

The summary of doses studied in the clinical development program is provided in Table 9.

Table 9. Summary of Intravenous (IV) Fosaprepitant Regimens Studied in Study P029 and Study P134

Intravenous (IV) Regimens	Age Cohorts [yrs]			
	12 - 17*	6 - <12**	2 - <6**	0.5 - <2**
115 mg fosaprepitant Day 1, 80 mg oral aprepitant on Days 2 and 3	P134, Part I A	N/A	N/A	N/A
150 mg or 3.0 mg/kg (up to 150 mg)	P134, Part I B; P029; P044	P134, Part V; P029	P134, Part V; P029	P134, Part V; P029
5.0 mg/kg (up to 150 mg)	N/A	P029; P044	P029; P044	P029
60 mg or 1.2 mg/kg (up to 60 mg)	P029	P029	P029	N/A
20 mg or 0.4 mg/kg (up to 20 mg)	P029	P029	P029	N/A

*Fosaprepitant infused over 30 minutes
**Fosaprepitant infused over 60 minutes

Source data: Section 2.7.2 Summary of Clinical Pharmacology, Table 2.7.2:1

PREA PMR and PWR

Currently, the Postmarketing Requirement (PMR 1663-3) Study under the Pediatric Research Equity Act (PREA) is as follows: [2]

> "A PK/PD study to characterize aprepitant PK parameters following administration of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist and dexamethasone, in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation. Use modeling and simulation including the results of the above study to identify 1-Day and 3-Day intravenous fosaprepitant doses in pediatric patients 0 to 17 years of age that provide similar aprepitant PK exposures to pediatric aprepitant doses and exposures which have demonstrated acceptable safety and efficacy profiles in patients receiving single and multi-day chemotherapy regimens, respectively."

Results from Study P029 and population PK analysis and simulation fulfilled the PMR of 1-day and 3-day regimens using fosaprepitant from a clinical pharmacology perspective. The Agency also considered that the sponsor provided a fair complete response to the PWR. For details, refer to Clinical Review and DPMH Review of this sNDA.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Refer to Section 2.1 for the mechanism of action of aprepitant.

Refer to the product label for detailed PK and PD information, intrinsic and extrinsic effects on fosaprepitant and aprepitant PK as well as related dose adjustment. An excerpt of clinical PK information in adults is summarized here based upon the approved fosaprepitant product label (Table 10). Note that the units for AUC and concentrations of apreppitant in the label are mcg·hr/mL and mcg/mL, respectively.

Table 10. Excerpt of PK from the Approved Fosaprepitant Product Label

12.3 Pharmacokinetics Aprepitant after Fosaprepitant Administration Following administration of a single intravenous 150-mg dose of fosaprepitant, a prodrug of aprepitant administered as a 20-minute infusion to healthy subjects, the mean AUC of aprepitant was 37.4 (± 14.8) mcg·hr/mL and the mean maximal aprepitant concentration was 4.2 (± 1.2)

[2] https://www.accessdata fda.gov/scripts/cder/pmc/index.cfm?StartRow=2&StepSize=1&Paging=Yes, last accessed March 5th, 2018

mcg/mL. Plasma concentrations of fosaprepitant are below the limits of quantification (10 ng/mL) within 30 minutes of the completion of infusion.

Distribution

Aprepitant is greater than 95% bound to plasma proteins. The mean apparent volume of distribution at steady state (Vd) was approximately 70 L in humans. Aprepitant crosses the blood brain barrier in humans *[see Clinical Pharmacology (12.1)]*.

Elimination

Metabolism

Fosaprepitant is converted to aprepitant in *in vitro* incubations with human liver preparations and in S9 preparations from multiple other human tissues including kidney, lung and ileum. Thus, it appears that the conversion of fosaprepitant to aprepitant can occur in multiple extrahepatic tissues in addition to the liver.

Aprepitant undergoes extensive metabolism. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism is largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6, CYP2C9, or CYP2E1 was detected.

In healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300-mg dose of [^{14}C]-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma.

Excretion

Following administration of a single intravenous 100-mg dose of [^{14}C]-fosaprepitant to healthy subjects, 57% of the radioactivity was recovered in urine and 45% in feces.

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. The apparent terminal half-life ranged from approximately 9 to 13 hours.

Hepatic impairment: The PK of aprepitant in patients with mild and moderate hepatic impairment were similar to those of healthy subjects with normal hepatic function. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 9). There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score greater than 9). Therefore, additional monitoring for adverse reactions in these patients may be warranted when EMEND is administered.

Renal impairment: No dose adjustment is needed as aprepitant is not renally excreted.

Drug interaction: Because of the quick conversion of fosaprepitant to aprepitant, drug interaction is likely to occur with drugs that interact with aprepitant. Aprepitant is a substrate, a weak inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. Refer to Sections 7.1 and 7.2 of fosaprepitant label for detailed drug-drug interaction and dosage adjustment.

3.2.1 PK of aprepitant in pediatric patients

The PK of aprepitant following oral aprepitant administration in pediatric patients was evaluated in NDA 207865 (EMEND suspension) and NDA 21549/S-25 (EMEND oral capsule). An excerpt of clinical PK information in pediatric patients following oral Emend administration is provided below. Note that the units for AUC and concentrations of apreppitant in the label are mcg×hr/mL and mcg/mL, respectively.

Age: Pediatric Population

As part of a 3-day regimen, dosing of aprepitant capsules (125-mg/80-mg/80-mg) in 18 pediatric patients (aged 12 through 17 years) achieved a mean AUC0-24hr of 17 mcg×hr/mL on Day 1 with mean peak plasma concentration (Cmax) at 1.3 mcg/mL occurring at approximately 4 hours. The mean concentrations at the end of Day 2 (N=8) and Day 3 (N=16) were both at 0.6 mcg/mL.

As part of a 3-day regimen, weight-based dosing of aprepitant powder for oral suspension (3-mg/kg; 2- mg/kg; 2-mg/kg) in 18 pediatric patients aged 6 months to less than 12 years achieved a mean AUC0-24hr of 20.9 mcg×hr/mL on Day 1 with mean peak plasma concentration (Cmax) at 1.8 mcg/mL (N=19), occurring at approximately 6 hours. The mean concentrations at the end of Day 2 (N=18) and Day 3 (N=19) were 0.4 mcg/mL and 0.5 mcg/mL, respectively.

A population pharmacokinetic analysis of aprepitant in pediatric patients (aged 6 months through 17 years) suggests that sex and race have no clinically meaningful effect on the pharmacokinetics of aprepitant.

3.2.1.1 PK of aprepitant following fosaprepitant IV infusion

Adolescents

Following a single dose of fosaprepitant 150 mg IV infused over 30 minutes in adolescents, the mean AUC0-24hr of aprepitant ranged from 30400 ng×hr/mL to 30800 ng×hr/mL with mean Cmax ranged from 3500 ng/mL to 5870 ng/mL. The median Tmax was 0.5 hour.

Table 11. Descriptive Statistics of Observed Aprepitant Plasma Pharmacokinetic Parameters Following Administration of *150 mg* IV Fosaprepitant in Patients 12 to 17 Years Old

Study P029

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

Study P134

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

Source data: Summary of Clinical Pharmacology, Table 2.7.2:3 and Table 2.7.2:5

Following a single dose of fosaprepitant 115 mg IV infused over 30 minutes on Day 1 and 80 mg oral aprepitant on Days 2 and 3 in adolescents, mean AUC0-24hr was 19500 ng×hr/mL with mean Cmax on Day 1 reaching 3240 ng/mL. The median Tmax on Day 1 was 0.25 hour. The mean concentrations at the end of Days 2 and 3 were 310 ng/mL and 199 ng/mL, respectively.

Table 12. Descriptive Statistics of Observed 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 Patients 12 to 17 Years Old

12 to 17 Years	C_{max} (ng/mL)	T_{max} (hr)	C_{24hr} (ng/mL)	$AUC_{0\text{-}24\ hr}$ (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

Source data: Summary of Clinical Pharmacology, Table 2.7.2:2

2 to < 12 years

The PK parameters of aprepitant following 3 mg/kg fosaprepitant IV infused over 60 minutes in patients 2 to < 12 years are shown in Table 13.

Table 13. Descriptive Statistics of Observed Aprepitant Plasma Pharmacokinetic Parameters Following Administration of *3 mg/kg* IV Fosaprepitant in Patients 2 to < 12 Years Old

Study P134

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

Study P029

6 to <12 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	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

Source data: Summary of Clinical Pharmacology, Table 2.7.2:4 and Table 2.7.2:5

The PK parameters of aprepitant following 5 mg/kg IV infused over 60 minutes in patients 2 to < 12 years old are shown in Table 14.

Table 14. Descriptive Statistics of Observed Aprepitant Plasma Pharmacokinetic Parameters Following Administration of *5 mg/kg* IV Fosaprepitant in Patients 2 to < 12 Years Old

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	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	55000	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
2 to <6 Year-Olds								
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

Source data: Summary of Clinical Pharmacology, Table 2.7.2:6

6 months to < 2 years

Following a single dose of fosaprepitant 5 mg/kg IV infused over 60 minutes in patients 6 months to 2 years old, the mean AUC0-24 hr of aprepitant was 36800 ng×hr/mL with mean Cmax of 3550 ng/mL. The median Tmax was 1.08 hours.

Table 15. Descriptive Statistics of Observed Aprepitant Plasma Pharmacokinetic Parameters Following Administration of *3 mg/kg* IV and *5 mg/kg* Fosaprepitant in Patients 6 Months < 2 Years Old

Study P134 – 3 mg/kg

0.5 - < 2 years	C_{max} (ng/mL)	T_{max} (hr)	C_{24hr} (ng/mL)	$AUC_{0\text{-}24\ hr}$ (hr*ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)
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

Study P029 – 5 mg/kg

0 to <2 Year-Olds	$AUC_{0\text{-}\infty}$ (hr*ng/mL)	$AUC_{0\text{-}24hr}$ † (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	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

Source data: Summary of Clinical Pharmacology, Table 2.7.2:4 and Table 2.7.2:6

Effects of sex and race on the PK of aprepitant

A population PK analysis of IV and oral aprepitant in pediatric patients (aged 6 months through 17 years) suggests that sex and race have no clinically meaningful effect on the PK of aprepitant.

3.2.2 *PK of fosaprepitant following IV infusion*

The PK of fosprepitant 150 mg IV in adults was not evaluated. However, PK of fosaprepitant 115 mg IV in adults was evaluated in the original NDA. Following IV infusion of fosaprepitant 115 mg over 15 minutes, fosaprepitant plasma concentrations fell near or below the lower limit of quantitation (10 ng/mL) within 30 minutes after the end of infusion and conversion of fosaprepitant to aprepitant was nearly complete. The exact identity of the enzyme(s) involved in the conversion of fosaprepitant to aprepitant has not been identified but is thought not to involve the CYP family of enzymes. Mean fosaprepitant Cmax was approximately 5900 ng/mL and mean AUC was 1483 ng×hr/mL after 115 mg IV infusion over 15 minutes. The elimination half-life for fosaprepitant

was estimated to be 2 to 3 minutes. Refer to the Clinical Pharmacology Review of the original NDA approved in 2008.

The PK of fosaprepitant in patients ≤ 17 years old is summarized in Table 16. The Tmax occurred at the end of infusion. The variability of Cmax of fosaprepitant in patients < 2 years are particularly large with Cmax ranging from 20.2 ng/mL (minimum) to 7260 ng/mL (maximum). The cause is unknown. However, altered conversion of IV administered prodrugs in infants has been observed.[3,4] The values of Cmax across all age groups appear to be much lower than the historical value of 5900 ng/mL in adults receiving single dose of 115 mg IV infused over 15 minutes which was reported in the original NDA. The concentrations of fosaprepitant were negligible with 15 to 30 minutes after the end of infusion. Due to limited sampling time for fosaprepitant, AUC values were not estimated. The effect of age and weight on Cmax of fosaprepitant was not explored, either.

[3] G. Burckart, F.F. Barrett, A.R. Straughn, and S.R. Ternullo, Chloramphenicol Clearance in Infants. J Clin Pharmacol. 1982; 22:49-52.
[4] G. Burckart, F.F. Barrett, R. Della Valle, and M.C. Meyer, Chloramphenicol Dosage and Pharmacokinetics in Infants and Children. J Clin Pharmacol. 1983; 23:106-112.

Table 16. Summary of Plasma Fosaprepitant Cmax and Tmax Values Following Fosaprepitant IV Single Dose (Study P134)

Dose	Age Range		Tmax (hr)	Cmax (ng/mL)
3 mg/kg Infuse over 1 hour§	6 Months to <2 Years Old	N	7	7
		Mean	1.13	2756
		SD	0.175	3364
		Median [min – max]	1.00 [1.00 – 1.42]	159 [20.2 – 7260]
	2 to <6 Years Old	N	7	8
		Mean	1.05	3034
		SD	0.089	1718
		Median [min – max]	1.02 [1.00 – 1.25]	3292 [BLQ – 5240]
	6 to <12 Years Old	N	8	8
		Mean	1.04	1654
		SD	0.088	1995
		Median [min – max]	1.00 [1.00 – 1.25]	910 [357 – 6200]
150 mg Infuse over 30 minutes‡	12 to 17 Years Old	N	11	11
		Mean	0.614	1310
		SD	0.251	964
		Median [min – max]	0.5 [0.5 – 1.33]	1020 [26.6 – 3300]
	§ In patients < 12 years old: the PK samples were collected at pre-dose, 1 hour (at the end of fosaprepitant infusion), 1.25 hour (30 minutes prior to chemotherapy), 1.75 hour ((at the start of chemotherapy), and 2.25 hour (30 minutes after the chemotherapy). ‡ In patients 12 to 17 years old: the PK samples were collected at pre-dose, 0.5 hour (at the end of fosaprepitant infusion), 0.75 hour (30 minutes prior to chemotherapy), 1.3 hour (at the start of chemotherapy), 1.8 (30 minutes after the chemotherapy). BLQ: below limit of quantification Source data: Clinical Study Report P134, Table 2-6 and Table 2-19, Tables 11-3 and 11-16			

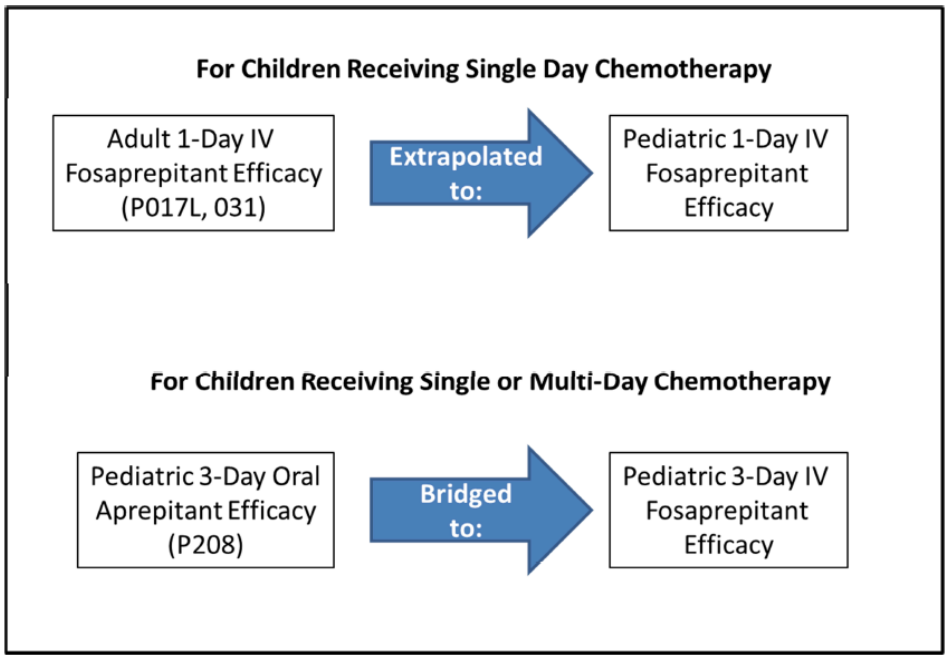
3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

As mentioned in Section 3.1, the 3-day oral aprepitant regimen was approved for the prevention of CINV in children based upon efficacy and safety data obtained in pediatric patients while the pediatric fosaprepitant program was ongoing. This also confirmed that NK-1 receptor blockade with aprepitant has similar antiemetic effects in children as in adults and allows using exposure-matching strategy to identify doses of fosaprepitant in pediatric patients.

The bridging scheme is showed in Figure 1.

Figure 1. Efficacy Extrapolation/Bridging for One-Day and Three-Day Pediatric Fosaprepitant Regimens



Source data: Section 2.5 Clinical Overview, Figure 2.5:1

3.3.1.1 Single-day regimen

The dose selection for single-day regimen is based solely upon matching the systemic exposures (Cmax and AUC) of aprepitant in patients ≤ 17 years to healthy adults. Studies P029 and P134 also provided safety data for single dose fosaprepitant in pediatric cancer patients.

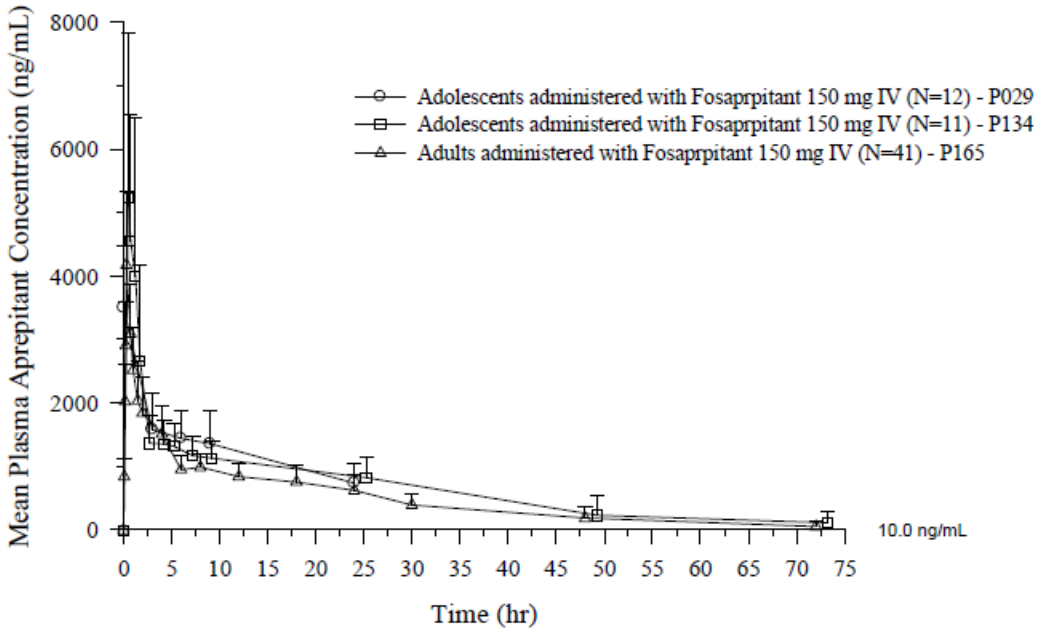
The sponsor's proposed single-day regimen is as follows:

Drug	Age	Regimen
EMEND for injection	12 Years to 17 Years	150 mg intravenously over 30 minutes, completing the infusion approximately 30 minutes prior to chemotherapy
	2 Years to less than 12 Years	4 mg/kg (maximum dose 150 mg) intravenously over 60 minutes, completing the infusion approximately 30 minutes prior to chemotherapy
	6 Months to less than 2 Years	5 mg/kg (maximum dose 150 mg) intravenously over 60 minutes, completing the infusion approximately 30 minutes prior to chemotherapy
Dexamethasone**	6 Months to 17 Years	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	6 Months to 17 Years	See selected 5-HT_3 antagonist prescribing information for the recommended dosage

3.3.1.1.1 Adolescents (12 to 17 years)

PK similarity was demonstrated by comparing the PK parameters from Studies P029 and P134 to those obtained in healthy adult subjects receiving single150 mg fosaprepitant IV (Study P165) (Table 17). The concentration – time profiles of aprepitant were superimposable (Figure 2).

Figure 2. Mean Concentration-Time Profiles (± Standard Deviation) of Aprepitant from Adolescents in Study P134 and Study P029 Receiving 150 mg Fosaprepitant and Healthy Adult Subjects Receiving the Same Dose in Study P165



Source data: Summary of Clinical Pharmacology, Figure 2.7.2:3

Overall, the Cmax achieved in adolescents ranged from 84% to 134% of the Cmax achieved in the healthy adults. Concentrations at 24 hours post dose (C24hr) in adolescents were 17 to 33% more than that in the healthy adults. The AUC0-inf ranged from 95% to 120 % of that achieved in the adults. The AUC0-24hr was 20 to 23% more than that in the healthy adults. Given that these are cross-study comparisons, the systemic exposures (AUC and C24) to aprepitant are considered comparable.

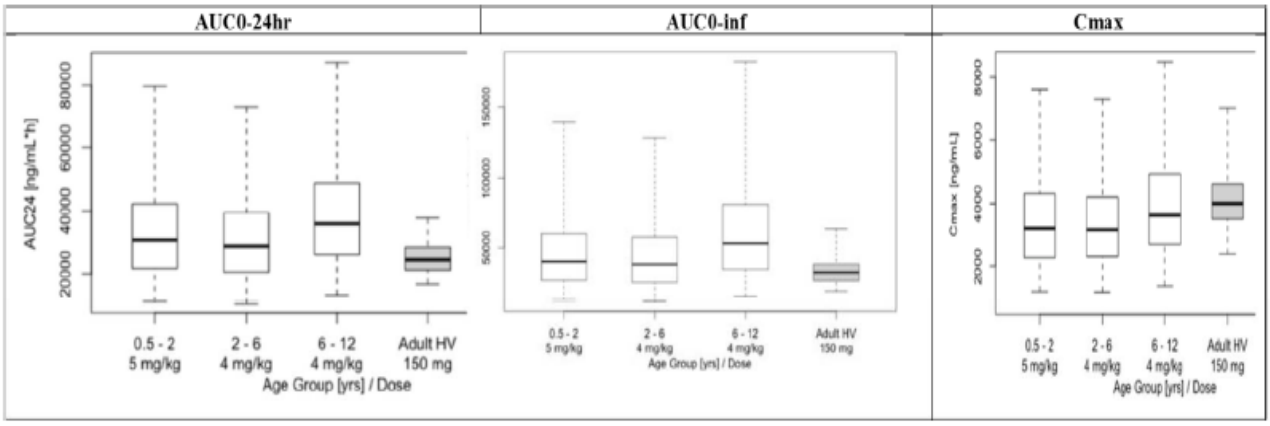
Table 17. Descriptive Statistics in key PK Parameters of Observed Aprepitant Following Single Dose of 150 mg IV Infusion in Adolescent Patients and Healthy Adults.

Study (Subjects)	Descriptive Statistics	AUC0-∞ (ng×hr/mL)	AUC0-24hr (ng×hr/mL)	Cmax (ng/mL)	C24hr (ng/mL)
P029 (12-17 years)	N	3	12	12	12
	Arithmetic Mean	33800	30400	3500	735
	CV%	21.3	27.3	27.7	42.2
	Geometric Mean	33300	29400	3360	675
P134 (12-17 years)	N	8	11	11	11
	Arithmetic Mean	43600	30800	5870	825
	CV%	26.8	22.8	47.1	38.9
	Geometric Mean	42000	30000	5380	769
P165 (Healthy Adults)	N	41	41	41	41
	Arithmetic Mean	37375	25105	4154	--
	CV%	39.5	23.0	27.7	--
	Geometric Mean	35031	24444	4005	577
--: not reported					
Source data: Table 11-1 of CSR P029, Table 11-2 of CSR P134, Tables 11-1 and 11-2 of CSR P165					

3.3.1.1.2 6 months to < 12 years

The comparison of systemic exposures (AUC and Cmax) to aprepitant in pediatric patients < 12 years and adults is provided in Figure 3.

Figure 3. Comparison of Observed 1-day 150 mg IV Fosaprepitant Regimen in Adult Healthy Subjects and Model- Simulated Aprepitant PK Parameters (AUCinf, AUC24, Cmax) After Administration of 4 mg/kg in Pediatric Subjects 2 to 12 Years Old and 5 mg/kg in <2 Years Old Subjects



Source data: Figure 23 in Section 4.3.1.5

3.3.1.1.2.1 6 to < 12 years

The AUC0-inf, AUC0-24hr, Cmax, and C24hr in patients aged 2 to 6 years following 3 mg/kg IV dose were all lower than that in the healthy adult subjects receiving 150 mg IV dose (Table 18). Similar pattern was observed in the patients aged 6 to < 12 years except AUC0-24hr from Study P029 (Table 19).

Table 18. Cross-Study Comparison of Observed Systemic Exposures to Aprepitant Following Single 3 mg/kg IV Infusion over 60 Minutes in Pediatric Patients (2 to < 6 years) to Healthy Adult Subjects Given 150 mg IV Infusion over 30 Minutes (Study P165)

PK Parameter	Study	Age Group	N	Geometric Mean
AUC0-∞ (ng•hr/mL)	P029	2 to <6 years	5	13100
	P134 (Part V)		6	19800
	P165	Adult	41	35100
AUC0-24hr (ng•hr/mL)	P029	2 to <6 years	6	15900
	P134 (Part V)		7	15200
	P165	Adult	41	24500
Cmax (ng/mL)	P029	2 to <6 years	6	1960
	P134 (Part V)		7	2200
	P165	Adult	41	4010
C24hr (ng/mL)	P029	2 to <6 years	6	115
	P134 (Part V)		--	--
	P165	Adult	41	577
Source data: Clinical Study Reports P029 and P134				

Table 19. Cross-Study Comparison of Observed Systemic Exposures to Aprepitant Following Single 3 mg/kg IV Infusion over 60 Minutes in Pediatric Patients (6 to < 12 years) to Healthy Adult Subjects Given 150 mg IV Infusion over 30 Minutes (Study P165)

PK Parameter	Study	Age Group	N	Geometric Mean
AUC0-∞ (ng•hr/mL)	P029	6 to <12 years	8	29200
	P134 (Part V)		8	22500
	P165	Adult	41	35100
AUC0-24hr (ng•hr/mL)	P029	6 to <12 years	14	26000
	P134 (Part V)		8	18700
	P165	Adult	41	24500
Cmax (ng/mL)	P029	6 to <12 years	14	2930
	P134 (Part V)		8	2780
	P165	Adult	41	4010
C24hr (ng/mL)	P029	6 to <12 years	14	419
	P134 (Part V)		8	239
	P165	Adult	41	577
Source data: Clinical Study Reports P029 and P134				

3.3.1.1.2.2 2 to < 6 years

PK simulation analysis showed that systemic exposures would be comparable to the adults if a 4 mg/kg IV infusion over 60 minutes in patients aged 2 to < 6 years is given (Table 20).

Table 20. Simulated Aprepitant Exposure in Pediatric Patients Age 2 to < 6 Years vs Observed in Healthy Adults

	Geometric Mean				Ratio of Geometric Mean (ped/adults)		
	2 to < 6 years (Simulated)			Adults (Observed)			
Dose (mg/kg)	4	3.5	3	150 mg	4	3.5	3
AUC0-24hr	28205	24190	20249	24500	1.15	0.99	0.83
Cmax	3080.20	2690.5	2301.3	4010	0.77	0.67	0.57
C24	443.78	366.93	293.93	577	0.77	0.64	0.51
C48	83.933	65.661	49.231				
C72	15.877	11.752	8.2471				
AUCinf	37909	32069	26436	35100	1.08	0.91	0.75
Source Data: Population PK Modeling and Simulation Report, Table II- 2					Reviewer's analysis		

Simulation analysis showed that systemic exposures would be comparable to the adults if a 3.5 mg/kg IV infusion over 60 minutes in patients age 6 to < 12 years is given (Table 21). On the other hand, the predicted AUC0-24hr following a 4 mg/kg dose is 44% higher than that in adults. However, 4 mg/kg dose is also reasonable given that 5 mg/kg dose was studied in this age group and found to have an acceptable safety profile. The Agency also believe that a simplified dosing regimen, i.e. 4 mg/kg for the ages ranging from 2 to < 12 years, instead of 3.5 mg/kg for 6 to < 12 years and 4 mg/kg for 2 to < 6 years, may help avoid potential medication error.

Table 21. Simulated Aprepitant Exposure in Pediatric Patients Age 6 to < 12 Years vs Observed in Healthy Adults

	Geometric Mean				Ratio of Geometric Mean (ped/adults)		
	6 to < 12 years (Simulated)			Adults (Observed)			
Dose (mg/kg)	4	3.5	3	150 mg	4	3.5	3
AUC0-24hr	35235	30301	25446	24500	1.44	1.24	1.04
Cmax	3591.4	3137.9	2684.8	4010	0.90	0.78	0.67
C24	682.3	570.4	463.1	577	1.18	0.99	0.80
C48	181.2	144.9	111.6				
C72	48.1	36.8	26.9				
AUCinf	53031	44860	36981	35100	1.51	1.28	1.05
Source Data: Population PK Modeling and Simulation Report, Table II- 3					Reviewer's analysis		

3.3.1.1.2.3 6 months to < 2 years

The AUC0-inf, AUC0-24hr, Cmax, and C24hr in patients aged 6 months to < 2 years following 3 mg/kg IV dose were all lower than that in the healthy adult subjects receiving 150 mg IV dose

(Table 22). The AUC0-inf, AUC0-24hr, Cmax, and C24hr following 5 mg/kg IV were comparable to that in the healthy adults. Simulation also showed that 5 mg/kg would provide similar exposures to those in adults.

Table 22. Cross-Study Comparison of Observed Systemic Exposures to Aprepitant Following Single 3 mg/kg and 5 mg/kg IV Infusion over 60 Minutes in Pediatric Patients (6 Months to < 2 years) to Healthy Adult Subjects Given 150 mg IV Infusion over 30 Minutes (Study P165)

PK Parameter	Study	Age Group	Does (mg/kg)	N	Geometric Mean
AUC0-∞ (ng•hr/mL)	P029	< 2 years	5	16	34200
	P134 (Part V)		3	6	10600
	P165	Adult	150§	41	35100
AUC0-24hr (ng•hr/mL)	P029	< 2 years	5	21	32700
	P134 (Part V)		3	6	9170
	P165	Adult	150§	41	24500
Cmax (ng/mL)	P029	< 2 years	5	22	3280
	P134 (Part V)		3	7	1580
	P165	Adult	150§	41	4010
C24hr (ng/mL)	P029	< 2 years	5	21	436
	P134 (Part V)		3	--	--
	P165	Adult	150§	41	577
Source data: Clinical Study Reports P029 and P134; --: Not reported; §: unit in mg					

Simulation analysis showed that systemic exposures would be comparable to the adults when a 5 mg/kg IV infusion over 60 minutes in patients aged 6 months to < 2 years is given (Table 23).

Table 23. Simulated Aprepitant Exposure in Pediatric Patients Age 6 months to < 2 Years vs Observed in Healthy Adults

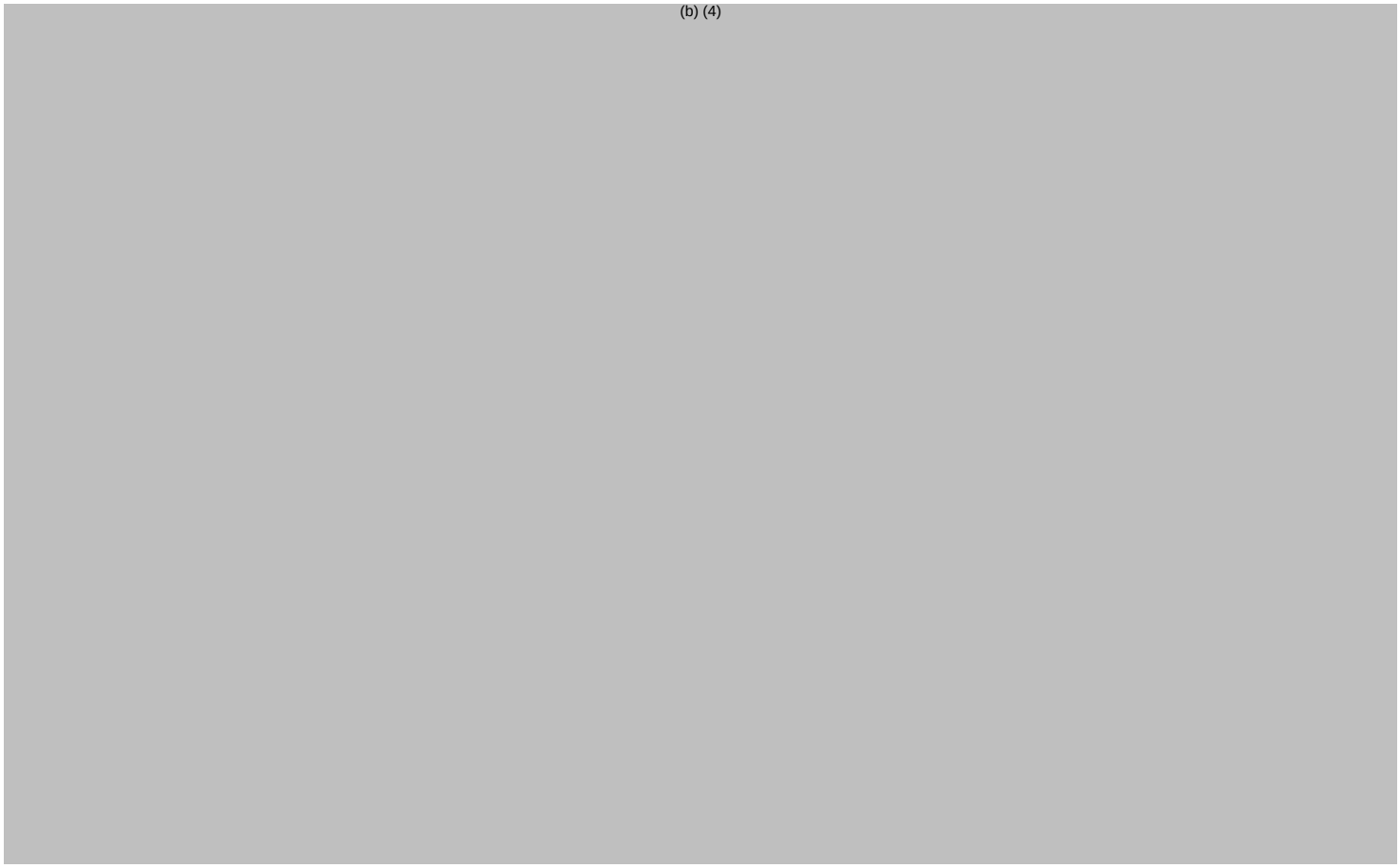
	Geometric Mean				Ratio of Geometric Mean (ped/adults)		
	6 months < 2 years (Simulated)			Adults (Observed)			
Dose (mg/kg)	5	4.5	4	150 mg	5	4.5	4
AUC0-24hr	30125	26688	23300	24500	1.23	1.09	0.95
Cmax	3115.7	2800.5	2485.7	4010	0.78	0.70	0.62
C24	480.6	413.8	349.5	577	0.83	0.72	0.61
C48	90.8	74.8	60.1				
C72	17.2	13.5	10.3				
AUCinf	40021	35072	30260	35100	1.14	1.00	0.86
Source data: Population PK Modeling and Simulation Report, Table II- 1					Reviewer's analysis		

3.3.1.2 Three-day regimen

Three-day regimen using oral Emend has been approved in pediatric patients age 6 months and older since 2015. The Agency agreed that the efficacy of a 3-day IV fosaprepitant regimen for the pediatric patients could be extrapolated from oral aprepitant by identifying an IV dose regimen to match aprepitant exposures in pediatric subjects for each day of the 3-day oral aprepitant regimen through PK modeling. The 3-day IV regimen may include 3-day IVs (IV/IV/IV) or IV/PO/PO regimens. Refer to Preliminary Comments of July 13, 2016 issued under IND 048924. The sponsor proposed a three-day IV regimen with an option to substitute the second and third day dose with oral aprepitant.

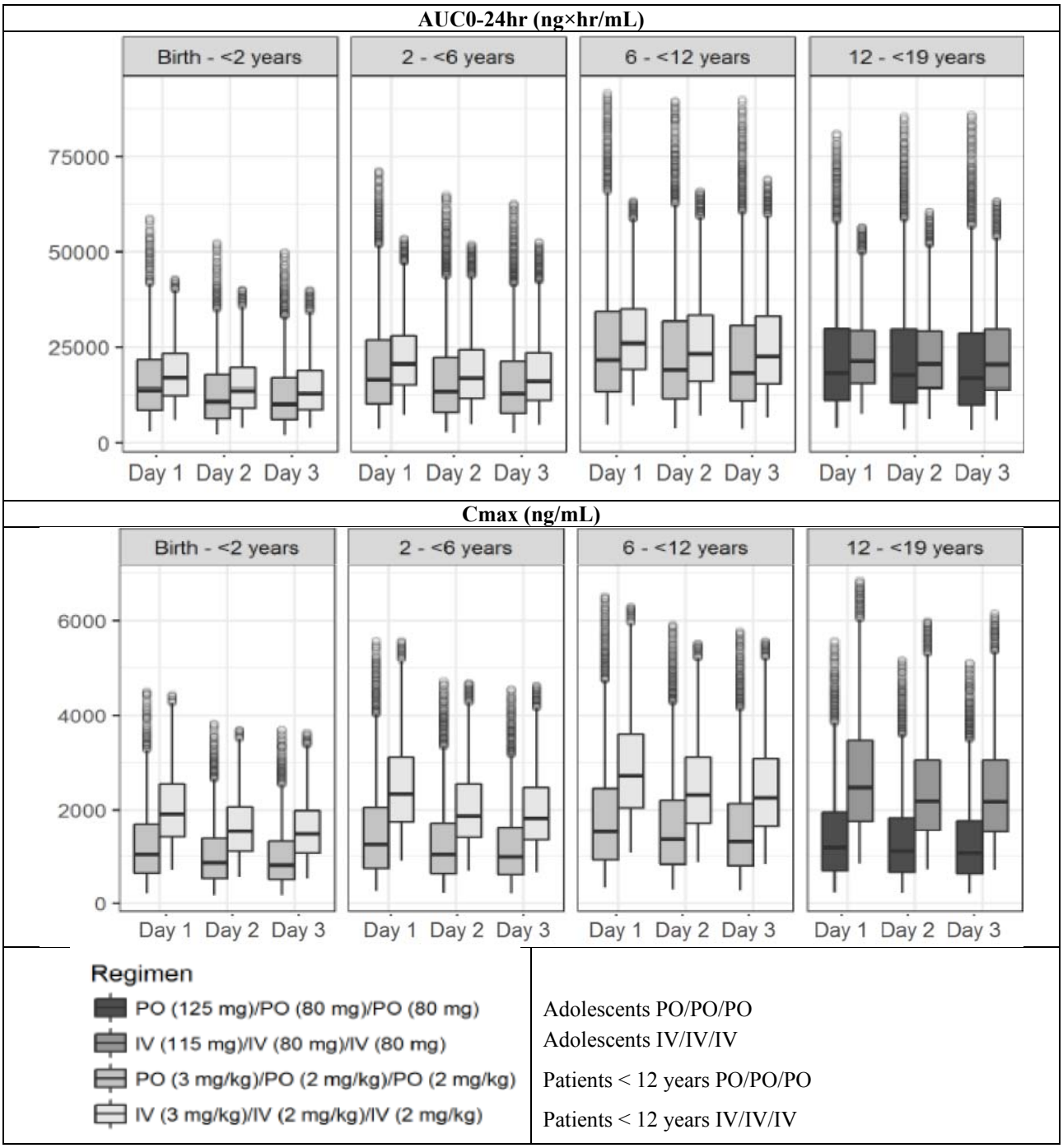
The sponsor's initial proposed three-day regimen is as follows:

(b) (4)



Comparison of systemic exposures (AUC and Cmax) to aprepitant following IV/IV/IV or PO/PO/PO regimen is provided in the Figure 4.

Figure 4. Comparison of 3-day Oral Aprepitant Regimens in Adolescent (125 mg on Day 1 and 80 mg on Days 2 and 3) and Pediatric Subjects <12 Years Old (3 mg/kg on Day 1 ad 2 mg/kg on Days 2 and 3) with Simulated 3-day IV Fosaprepitant Regimens, 115 mg on Day 1 and 80 mg on Days 2 and 3 in Adolescents and 3 mg/kg and 2 mg/kg on Days 2 and 3 in Pediatric Subjects < 12 Years Old



Source data: Figure 24, Section 4.3.1.5

3.3.1.2.1 Adolescents (12 to 17 years)

Fosaprepitant 115 mg IV on Day 1 and aprepitant 80 mg PO using Emend oral suspension on Days 2 and 3 were studied in adolescent cancer patients. The observed AUC0-24hr on Day 1 was 26% higher than that in the three-day oral regimen in adolescents given aprepitant 125 mg on Day 1 and aprepitant 80 mg on Days 2 and 3 (Study P097, oral capsules used). The observed Cmax of aprepitant on Day 1 was 183% higher than that in the three-day oral regimen. Although the Cmax is much higher following IV dosing (Table 24), the safety of the higher Cmax is supported by the acceptable safety profile in adolescents given single dose of 150 mg IV infusion.

Table 24. The Observed AUC, Cmax, and Cmin (C24hr, C48hr, and C72hr) in 12 to 17 Years from Studies P134 and P097

Dose (mg) (Days 1/2/3)		AUC0-24hr (hr*ng/ml)	Cmax (ng/ml)	C24hr (ng/mL)	C48hr (ng/mL)	C72hr (ng/mL)
IV/PO/PO (115/80/80) (Study P134[♯])	N	8	12	8	10	11
	AM	19500	3240	433	310	199
	CV%	41.1	39.4	73.6	93.1	141
	GM	18000	3030	348	210	--
PO/PO/PO (125/80/80) (Study P097[§])	N	18	18	9	9	16
	AM	16648.5	1268.6	512.4	624.7	595.8
	CV%	42.9	60.2	48.9	75.6	92.2
	GM	14318	1070	449.7	460.6	367.0

[♯] Oral suspension was used on Days 2 and 3.
[§] Oral capsules were used. Results submitted to NDA 21549/S-25 for EMEND oral capsule
AM: arithmetic mean; GM: Geometric mean; --: not reported
Source data: Reviewer's summary table based upon the sponsor's clinical study reports to NDA 21549/S-25 and NDA 22023/S-17

For both studies (P134 and P097), the Cmax on Days 2 and 3 were not measured. PK samplings for Days 2 and 3 were only for trough concentrations (Cmin), i.e. C24hr, C48hr, and C72hr. Cross-study comparison showed that Cmin at Hour 24 and Hour 48 from IV/PO/PO group were 22.5% and 54.4% lower than the PO/PO/PO regimen, respectively.

Reviewer's comment: Emend oral capsules have been approved for patients 12 years and older. Emend oral suspension has been approved for patients < 12 years old. The two formulations are not interchangeable due to lack of a dedicated bioequivalence study. Population PK analysis showed that CL is similar between the two oral formulations. Therefore, even though the suspension was used in adolescents on Days 2 and 3 (Part I, Study P134), Emend oral capsule is recommended on Days 2 and 3 for the IV/PO/PO regimen.

The simulated geometric means of systemic exposures to aprepitant from three different types of three-day regimens (IV/IV/IV 115/80/80 mg, IV/IV/PO 115/80/80 mg, IV/PO/PO 115/80/80 mg) and corresponding differences in exposures compared to PO/PO/PO (125/80/80 mg) regimen are shown in Table 25.

Table 25. The Simulated Geometric Means of Aprepitant Following IV/PO/PO, IV/IV/PO, and IV/IV/IV and Corresponding Ratios Compared to Simulated Values from PO/PO/PO Regimen.

	Day 1				Day 2				Day 3			
		AUC0-24h	Cmax	Cmin		AUC 0-24h	Cmax	Cmin		AUC0-24h	Cmax	Cmin
PO/PO/PO	PO	17958	1152.8	364.35	PO	17491	1097.1	376.96	PO	16833	1055.9	365.86
IV/PO/PO	IV	20938	2424.5	424.79	PO	16820	1061.1	361.25	PO	16508	1036.1	359.34
IV/IV/PO	IV	20938	2424.5	424.79	IV	19996	2132.7	387.79	PO	16783	1057.6	360.32
IV/IV/IV	IV	21083	2451	428.6	IV	20142	2154.7	391.75	IV	20127	2143.8	389.54
Geometric mean ratio, PO/PO/PO as reference												
	Day 1				Day 2				Day 3			
IV/PO/PO	IV	1.17	2.10	1.17	PO	0.96	0.97	0.96	PO	0.98	0.98	0.98
IV/IV/PO	IV	1.17	2.10	1.17	IV	1.14	1.94	1.03	PO	1.00	1.00	0.98
IV/IV/IV	IV	1.17	2.13	1.18	IV	1.15	1.96	1.04	IV	1.20	2.03	1.06

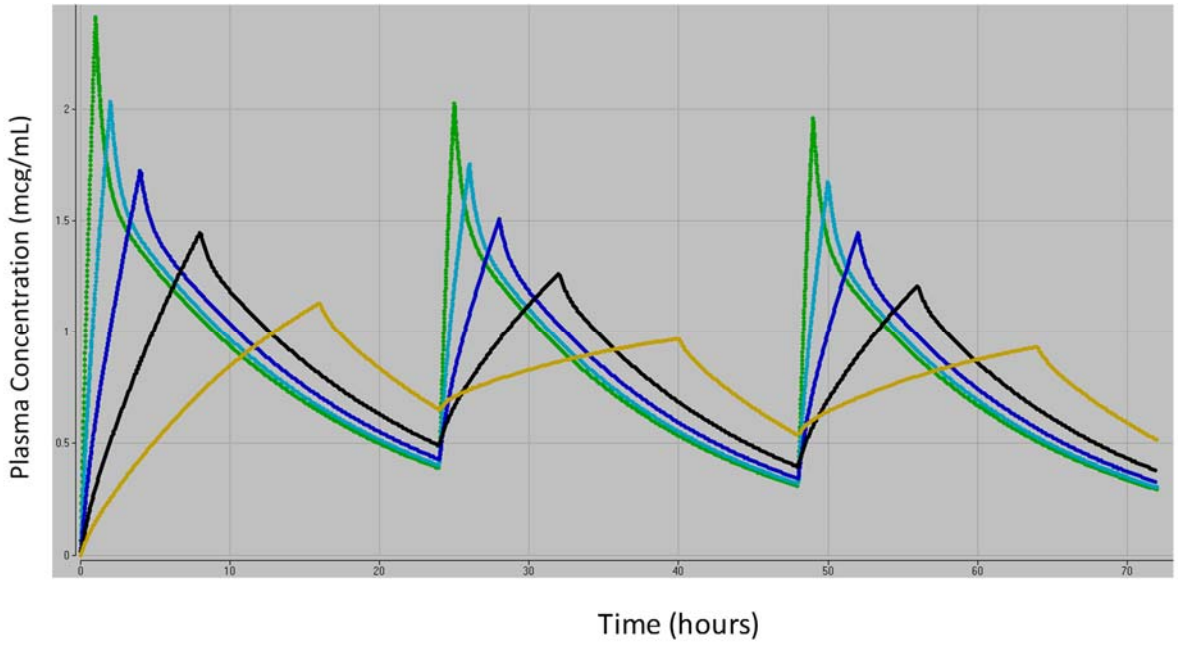
Units for AUC0-24h, Cmax, and Cmin are ng×hr/mL, ng/mL, ng/mL, respectively.

The simulated AUC0-24 and Cmin on Day 1 following IV infusion were 17% higher than those achieved following oral administration on Day 1. The AUC, Cmax, and Cmin of aprepitant on Days 2 and 3 with 80 mg oral aprepitant following IV fosaprepitant on Day 1 were similar to the adolescents who received the same oral doses on Days 2 and 3 following 125 mg oral aprepitant dose on Day 1.

The simulated Cmax on Day 1 following IV infusion was about 2-fold the Cmax following oral administration. However, as discussed earlier, the safety profile from adolescents receiving 150 mg, a dose 30% higher than 115 mg, was acceptable. The dose of 115 mg IV on Day 1 for a three-day regimen is acceptable.

The simulated values of Cmax on Days 2 and 3 following IV infusion were still about 2-fold the Cmax following oral administration. As fosaprepitant IV given beyond Day 1 has never been studied in pediatric patients, there is no safety data to support the 2-fold increase in Cmax when fosaprepitant IV is given repetitively for additional two days even though the simulated Cmax values on Days 2 and 3 were not higher than on Day 1. In order to reduce the Cmax values by 50% the infusion duration needs to be increased significantly beyond 60 minutes on Days 2 and 3 (**Error! Reference source not found.**).

Figure 5. Population PK Predicted Time Course of Plasma Aprepitant Concentrations (mcg/mL) after IV/IV/IV 115/80/80 mg Dosing in Adolescents for Various Infusion Durations



Infusion duration: Green represents 1 hour, light blue 2 hours, blue 4 hours, black 8 hours, yellow/tan 16 hours
Source data: Reviewer's analysis using Berkeley Madona software

Given that adjustment, because infusion duration on Days 2 and 3 duration will be different from Day 1, potential medication errors could occur. Consequently, the Agency and the sponsor agreed that IV infusion on Days 2 and 3 would be impractical in clinical settings. Thus, only the three-day regimen of IV/PO/PO is acceptable.

3.3.1.2.2 6 months to < 12 years

The three-day regimen with IV dosing on Day 1 has not been studied in pediatric patients < 12 years.

The simulated geometric means of systemic exposures to aprepitant from three different types of three-day regimens (IV/IV/IV 3/2/2 mg/kg, IV/IV/PO 3/2/2 mg/kg, IV/PO/PO 3/2/2 mg/kg) and corresponding differences in exposures compared to PO/PO/PO (3/2/2 mg/kg) regimen are shown in Table 26, Units for AUC0-24h, Cmax, and Cmin are ng×hr/mL, ng/mL, ng/mL, respectively.

Table 27 and Table 28, respectively.

Table 26. The Simulated Geometric Means of Aprepitant Following IV/PO/PO, IV/IV/PO, and IV/IV/IV and Corresponding Ratios Compared to Simulated Values from PO/PO/PO Regimen: 6 to < 12 years

	Day 1				Day 2				Day 3			
		AUC0-24h	Cmax	Cmin		AUC0-24h	Cmax	Cmin		AUC0-24h	Cmax	Cmin
PO/PO/PO	PO	21354	1489.2	384.31	PO	18832	1343.7	310.17	PO	18140	1291.9	298.9
IV/PO/PO	IV	25659	2699.3	474.82	PO	19604	1403.9	321.35	PO	18260	1299.7	301.23
IV/IV/PO	IV	25659	2699.3	474.82	IV	22733	2293.2	389.45	PO	19099	1363.3	313.21
IV/IV/IV	IV	25639	2686.5	474.92	IV	22704	2284	389.11	IV	22169	2235.5	377.58
Geometric mean ratio, PO/PO/PO as reference												
	Day 1				Day 2				Day 3			
IV/PO/PO	IV	1.20	1.81	1.24	PO	1.04	1.04	1.04	PO	1.01	1.01	1.01
IV/IV/PO	IV	1.20	1.81	1.24	IV	1.21	1.71	1.26	PO	1.05	1.06	1.05
IV/IV/IV	IV	1.20	1.80	1.24	IV	1.21	1.70	1.25	IV	1.22	1.73	1.26

Units for AUC0-24h, Cmax, and Cmin are ng×hr/mL, ng/mL, ng/mL, respectively.

Table 27. The Simulated Geometric Means of Aprepitant Following IV/PO/PO, IV/IV/PO, and IV/IV/IV and Corresponding Ratios Compared to Simulated Values from PO/PO/PO Regimen: 2 to < 6 years

	Day 1				Day 2				Day 3			
		AUC 0-24h	Cmax	Cmin		AUC0-24h	Cmax	Cmin		AUC0-24h	Cmax	Cmin
PO/PO/PO	PO	16398	1230.9	234.82	PO	13297	1034.9	167.56	PO	12710	987.39	160.23
IV/PO/PO	IV	20196	2287.3	296.53	PO	13707	1070.8	172.06	PO	12724	988.1	160.66
IV/IV/PO	IV	20196	2287.3	296.53	IV	16364	1841.7	215	PO	13146	1023.6	165.15
IV/IV/IV	IV	20336	2307.3	300.77	IV	16544	1860.1	219.27	IV	15941	1803.3	209.54
Geometric mean ratio, PO/PO/PO as reference												
	Day 1				Day 2				Day 3			
IV/PO/PO	IV	1.23	1.86	1.26	PO	1.03	1.03	1.03	PO	1.00	1.00	1.00
IV/IV/PO	IV	1.23	1.86	1.26	IV	1.23	1.78	1.28	PO	1.03	1.04	1.03
IV/IV/IV	IV	1.24	1.87	1.28	IV	1.24	1.80	1.31	IV	1.25	1.83	1.31

Units for AUC0-24h, Cmax, and Cmin are ng×hr/mL, ng/mL, ng/mL, respectively.

Table 28. The Simulated Geometric Means of Aprepitant Following IV/PO/PO, IV/IV/PO, and IV/IV/IV and Corresponding Ratios Compared to Simulated Values from PO/PO/PO Regimen: 6 months to < 2 years

	Day 1				Day 2				Day 3			
		AUC 0-24h	Cmax	Cmin		AUC0-24h	Cmax	Cmin		AUC0-24h	Cmax	Cmin
PO/PO/PO	PO	13431	1023.2	180.87	PO	10611	842.31	123.58	PO	10120	801.92	117.96
IV/PO/PO	IV	16616	1864.4	227.82	PO	10915	870.12	126.6	PO	10125	802.06	118.2
IV/IV/PO	IV	16616	1864.4	227.82	IV	13140	1487.9	159.19	PO	10428	828.5	121.17
IV/IV/IV	IV	16715	1872.1	229.07	IV	13217	1495.5	159.94	IV	12674	1443.6	152.02
	Geometric mean ratio, PO/PO/PO as reference											
	Day 1				Day 2				Day 3			
IV/PO/PO	IV	1.24	1.82	1.26	PO	1.03	1.03	1.02	PO	1.00	1.00	1.00
IV/IV/PO	IV	1.24	1.82	1.26	IV	1.24	1.77	1.29	PO	1.03	1.03	1.03
IV/IV/IV	IV	1.24	1.83	1.27	IV	1.25	1.78	1.29	IV	1.25	1.80	1.29

Units for AUC0-24h, Cmax, and Cmin are ng×hr/mL, ng/mL, ng/mL, respectively.

The simulated AUC0-24 and Cmin on Day 1 following IV infusion were 20% to 26% higher than those achieved following oral administration on Day 1. The simulated Cmax on Day 1 following IV infusion was about 2-fold the Cmax following oral administration. However, as discussed earlier, the safety profile from patients < 12 years old receiving 5 mg/kg IV, a dose 67% higher than 2 mg/kg, was acceptable. The dose of 3 mg/kg IV on Day 1 for a three-day regimen is acceptable.

The AUC, Cmax, and Cmin of aprepitant on Days 2 and 3 with 2 mg/kg oral aprepitant following IV fosaprepitant on Day 1 were similar to the those who received the same oral doses on Days 2 and 3 following 3 mg/kg oral aprepitant dose on Day 1.

Similar to what was found in the adolescent group, the simulated values of Cmax on Days 2 and 3 following IV infusion were still close to 2-fold the Cmax following oral administration. As fosaprepitant IV given beyond Day 1 has never been studied in pediatric patients, there is no safety data to support the near 2-fold increase in Cmax when it is given repetitively for additional two days. It is noteworthy that Cmax values on Days 2 and 3 were not higher than on Day 1. In order to lower the Cmax values, the infusion duration would also have to be increased significantly beyond 60 minutes on Days 2 and 3. As such, infusion duration on Days 2 and 3 would be different from Day 1 which may potentially lead to mediation errors. The Agency and the sponsor agreed that IV infusion on Days 2 and 3 were impractical in clinical settings. Thus, only the three-day regimen of IV/PO/PO would be approved.

3.3.1.3 Fosaprepitant

The safety of fosaprepitant IV in pediatric patients was deemed to be acceptable. Refer to Clinical Review of the supplement NDA 22023/S-17 for details.

According to the sponsor, the fosaprepitant level on Day 1 following 115 mg IV in adolescents in the three-day regimen (IV/PO/PO) was not reported in Study P134 because the samples were mishandled. However, single dose fosaprepitant 150 mg IV in adolescents was evaluated (Table 16). No safety issue was found to be associated with single dose fosaprepitant in this age group. No safety issue was found to be associated with 115 mg fosaprepitant IV on Day 1 of the three-day regimen in this age group even though the systemic exposures to fosaprepitant following 115 mg IV were not available.

The three-day regimen (IV/PO/PO) was not studied in patients < 12 years. However, 3 mg/kg and 5 mg/kg were studied in the single-day regimen and were found to be safe. Fosaprepitant levels following 3 mg/kg single dose were evaluated (Table 16). The proposed dose of 3 mg/kg IV on Day 1 was also lower than 5 mg/kg studied in the single-day regimen in patients < 12 years.

3.3.1.4 Cardiac Electrophysiology

A single 200 mg dose of fosaprepitant had no effect on the QTc interval. Maximum aprepitant concentrations after a single 200 mg dose of fosaprepitant were 4- and 9-fold higher than that achieved with oral EMEND 125 mg and 40 mg (for PONV), respectively.[5] QT prolongation with the oral EMEND dosing regimens for CINV and PONV is not expected. The maximum proposed dose for pediatric patients is 150 mg IV which is 30% lower than 200 mg dose.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

No. See discussion in Section 3.3.1.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. Population PK analysis showed that sex and race do not affect systemic exposures of aprepitant. The dosing regimens for fosaprepitant IV have factored in the effect of age and body weight on the PK.

[5] Fosaprepitant product label (rev 8/2017) and aprepitant product label (rev 5/2017)

The CL of aprepitant increases with the increase of body weight. Across the range of pediatric body weights, CL change nearly 2-fold. For 150 mg IV aprepitant administered to a 9-year old with the body weight of 29.7 kg (median age and weight in the 6 to 12 years old group, Table 40), the predicted CL of aprepitant is 2.50 L/hr. For the same dose in a 9-year old with body weight of 68.4 kg (maximum weight in the 6 to 12 years old group, Table 40), the predicted CL is 4.67 L/hr.

The V2 (central compartment) of aprepitant decreases with the increase of age. The V2 for a 9-year old with a body weight of 29.7 kg is predicted to be 19.8 L. The V2 for a 6-year old with the same body weight is predicted to be 21.5 L.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-drug Interactions

Since fosaprepitant is administered by intravenous infusion, a food-effect study is not conducted as food-drug interactions are not anticipated nor applicable.

Drug-drug interactions

Yes. This has been addressed in the current approved label for oral aprepitant. Also see Section 3.2.

Dosage adjustment for a corticosteroid e.g. dexamethasone

Similar to what is recommended for oral aprepitant in pediatric cancer patients[6], a 50% dose reduction is recommended if a corticosteroid, such as dexamethasone, is co-administered. In the clinical trials evaluating PK and PK/PD of aprepitant following fosaprepitant IV, the dexamethasone dose was set to be reduced by 50%. This is because both aprepitant and dexamethasone are the substrates of CYP3A4 enzymes while aprepitant is also a moderate CYP3A4 inhibitor. In adults, co-administration of aprepitant resulted in a significant 2-fold increase in dexamethasone AUC and Cmax. Co-administration of single oral dose of aprepitant with midazolam given IV (a sensitive CYP3A4 substrate) resulted in a 1.5-fold increase in midazolam AUC. A 2.3-fold increase in midazolam AUC was observed when midazolam was given orally with a single dose of oral aprepitant. Fosaprepitant is quickly converted to aprepitant, thus, has minimal drug-drug interaction potential. Taken together, the proposed dose reduction of dexamethasone in pediatric patients is reasonable.

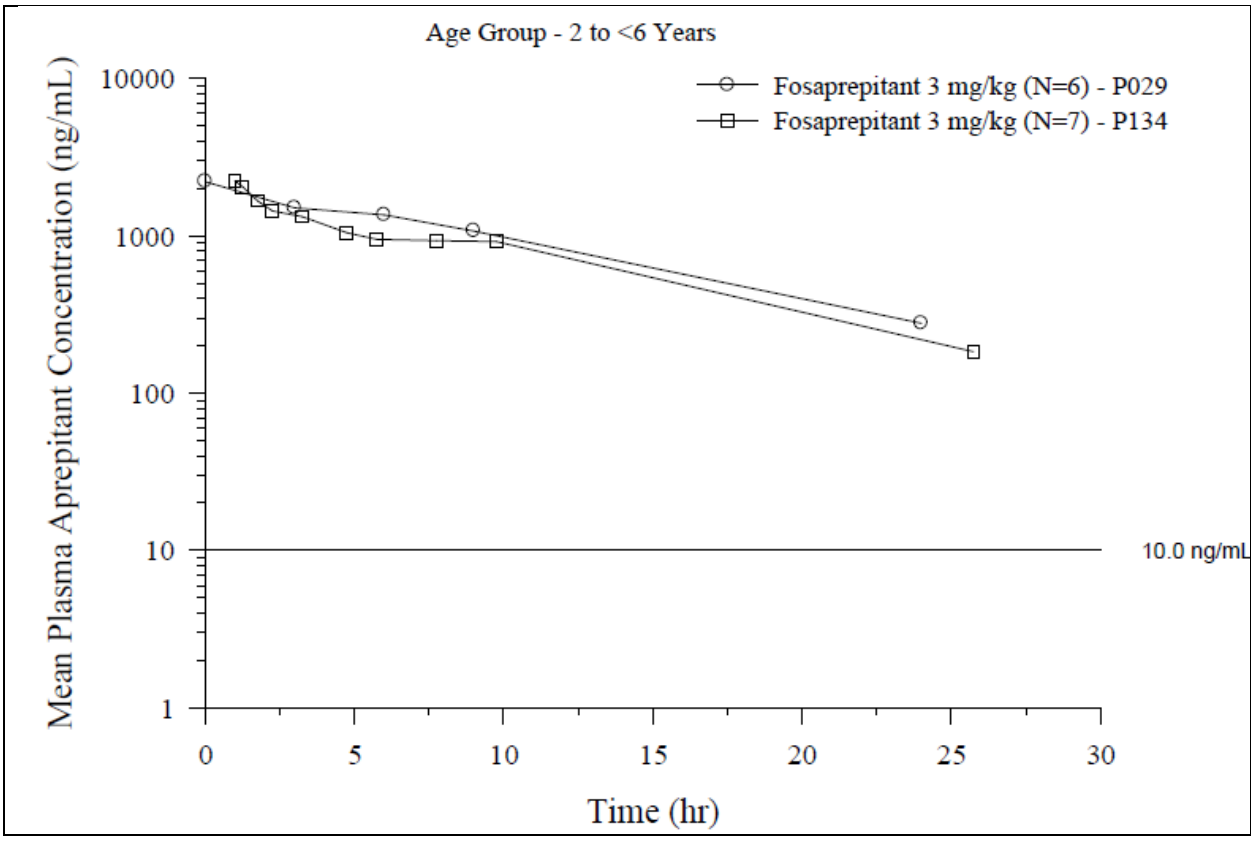
[6] Approved product label of oral aprepitant, Section 14.3

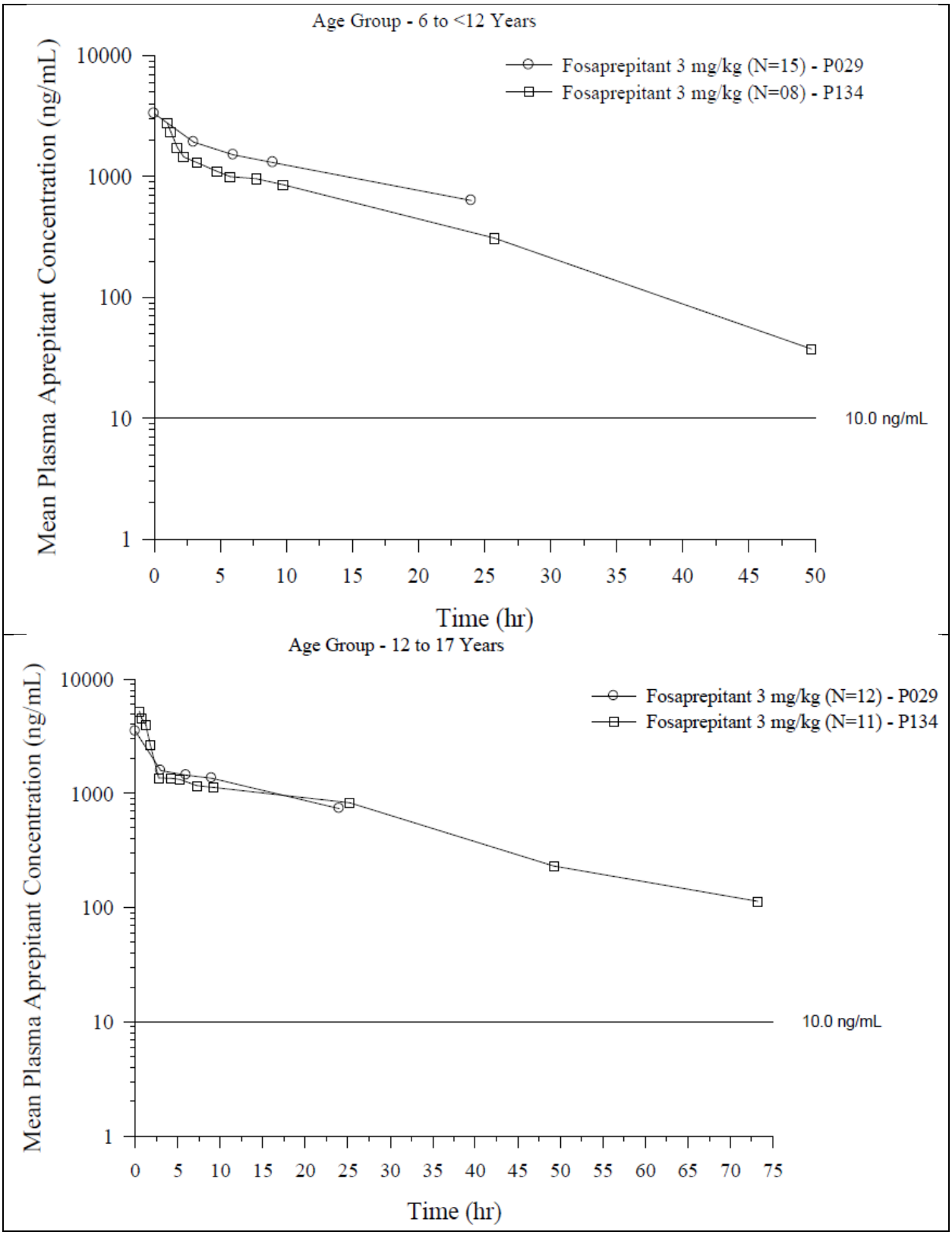
Effect of excipient -EDTA

The to-be-marketed formulation of fosaprepitant for pediatric patients is the currently approved formulation for use in adults. It contains 5.4 mg edetate disodium (EDTA) in a 150 mg dose vial ("reduced EDTA" formulation) which has been approved since 12/2/2016 (NDA 22023/S-14). This formulation was used in Study P029. However, fosaprepitant used in Study P134 was the "original" marketed IV fosaprepitant formulation approved in 2009 in adults. The formulation included 18.8 mg EDTA in a 150 mg dose vial ("high EDTA" formulation, "original EDTA" formulation).

The effect of EDTA in terms of "reduced" formulation vs "high" formulation on systemic exposures of aprepitant in pediatric population is negligible. As EDTA is not expected to affect the PK of aprepitant and the bioavailability of intravenous injection is 100%, the "reduced EDTA" formulation (NDA 22023/S-14) was approved without a relative bioavailability study. The cross-study comparison of the concentration-time profiles following 3 mg/kg of aprepitant in patients 2 to 12 years old and 150 mg in adolescents showed that the concentration-time profiles were superimposable except for age group of 6 to < 12 years (Figure 6). However, this difference could be due to an imbalance of the subject numbers between the two studies. Population PK analysis (Section 4.3) also found that the systemic exposures of aprepitant from "reduced" formulation is similar to that from "high" formulation.

Figure 6. Concentration-Time Profiles of Aprepitant in Adolescents Receiving 150 mg Fosaprepitant and 2 to < 12 Years Old Receiving 3 mg/kg (up to 150 mg) in Study P134 ("Original" EDTA, aka "High" EDTA) and Study P029 ("Reduced" EDTA) Across All Age Groups.

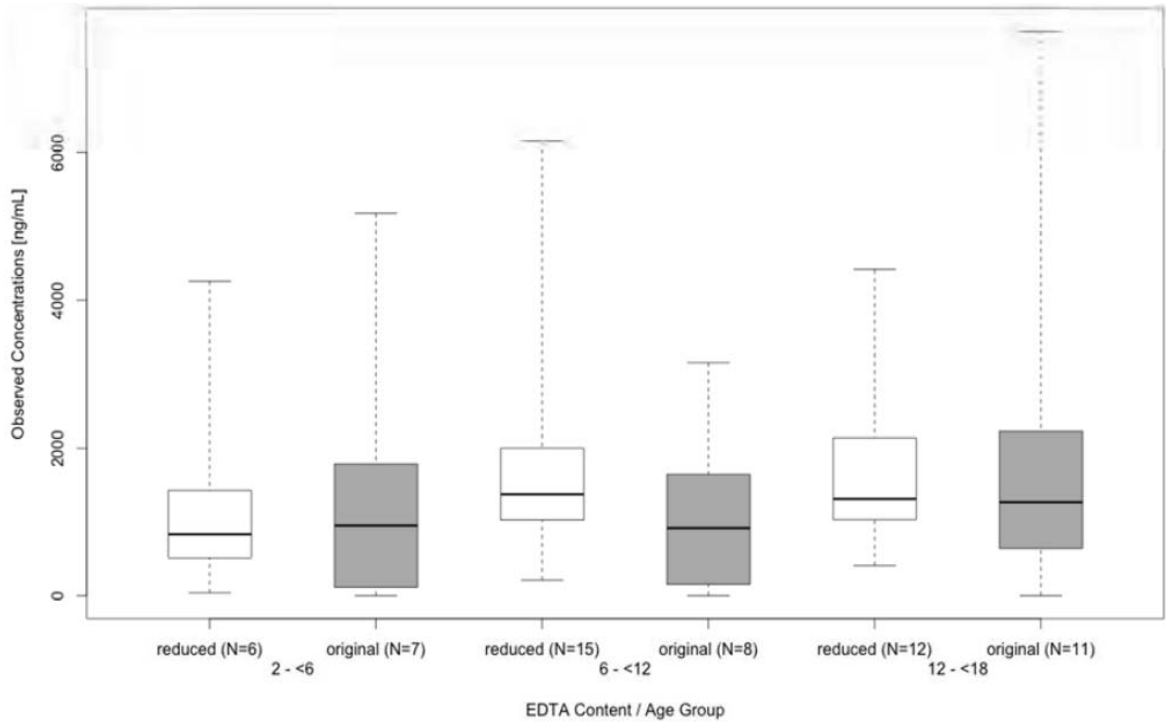




Source data: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Figure 2.7.1:2
10.0 ng/mL: LLOQ

In addition, the distributions of the observed concentrations from both studies were comparable (**Error! Reference source not found.**).

Figure 7. Distribution of Observed Aprepitant Concentration Data Following IV Administration of 3 mg/kg Fosaprepitant in Study P029 (Reduced EDTA) and Study P134 (Original EDTA, aka. High EDTA) in Pediatric Patients 2 – 17 Years Old



Source data: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Figure 2.7.1:3

4. APPENDICES

4.1. Summary of Bioanalytical Method Validation and Performance

Plasma aprepitant (MK-0869) was measured by an adequately validated high performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS) with acceptable accuracy and precision. Both methods showed in Table 29 were reviewed and deemed to be acceptable. Refer to Clinical Pharmacology Review of NDA21549/S-025 (Efficacy Supplement of Emend oral capsules) and original NDA 207865 (Emend oral suspension) for details.

Table 29. Laboratories That Developed and Validated the Bioanalytical Methods and Performed the Analyses

Laboratory	Laboratory Method	Matrix	Study Supported	Analyte	Laboratory Address
Merck Research Laboratories	DM-359O	Plasma	P097	MK-0869	770 Sumneytown Pk, West Point, PA 19486
(b) (4)	09BASM032V2	Plasma	P029, P044, P134, P148	MK-0869	(b) (4)

Source data: 2.7.1 Summary Of Biopharmaceutic Studies/Associated Analytical Methods (Pediatric), Table 2.7.1: 4

Plasma fosaprepitant (MK-0517) was measured by a validated high performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS) in the positive ion mode using a Heated Nebulizer interface. The analytical method numbered 12BAS0234 was performed by (b) (4) in 2014. The concentration range of detection was 10.000 – 5000.000 ng/mL with an r^2 of 0.9978. The intra-day, inter-day precision and accuracy, recovery were within acceptable range. Free-Thaw stability and twelve-months stability at ≤ 20°C and ≤70°C were also within acceptable range.

4.2. Individual Study Review

4.2.1 Study P029

Title: 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

Subtitle: Open-Label Cohort to Further Evaluate thePharmacokinetics/Pharmacodynamics, Safety, and Tolerability of Fosaprepitant in Pediatric Patients Birth to <12 Years Old

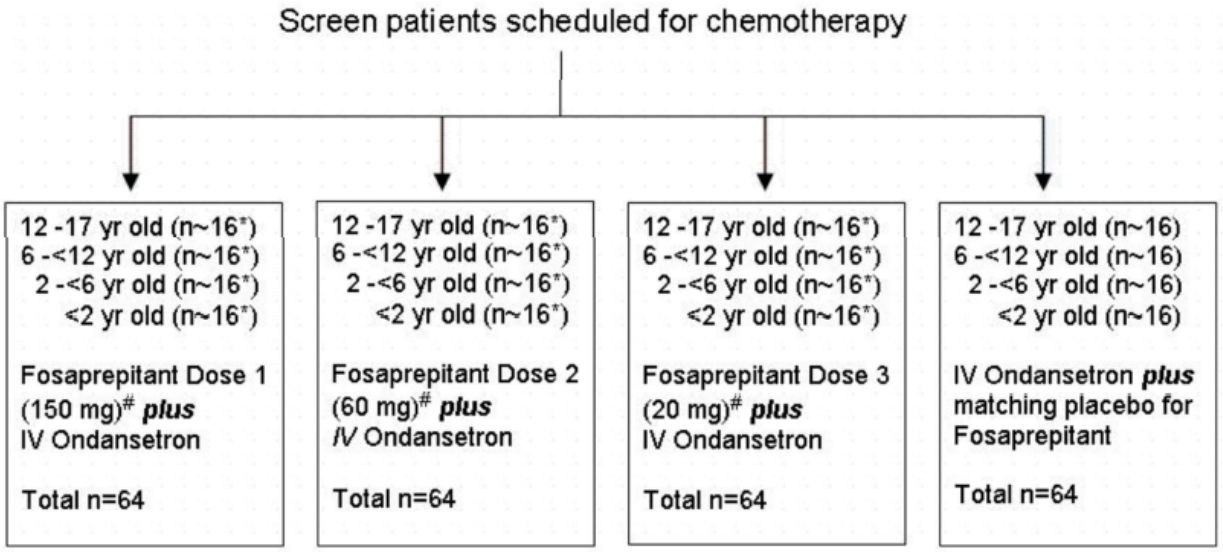
Study Design: This study was a Phase 2b, worldwide, multicenter, partially-blinded, randomized, parallel-group, pharmacokinetic (PK)/pharmacodynamics (PD), dose-ranging study, to evaluate the PK, PD, safety and tolerability of aprepitant, after administration of a single dose of fosaprepitant concomitantly with intravenous (IV) ondansetron, with or without

dexamethasone. Eligible subjects were male or female, birth to 17 years of age, with a documented malignancy and scheduled to receive chemotherapeutic agent(s) associated with moderate, high, or very high risk of emetogenicity.

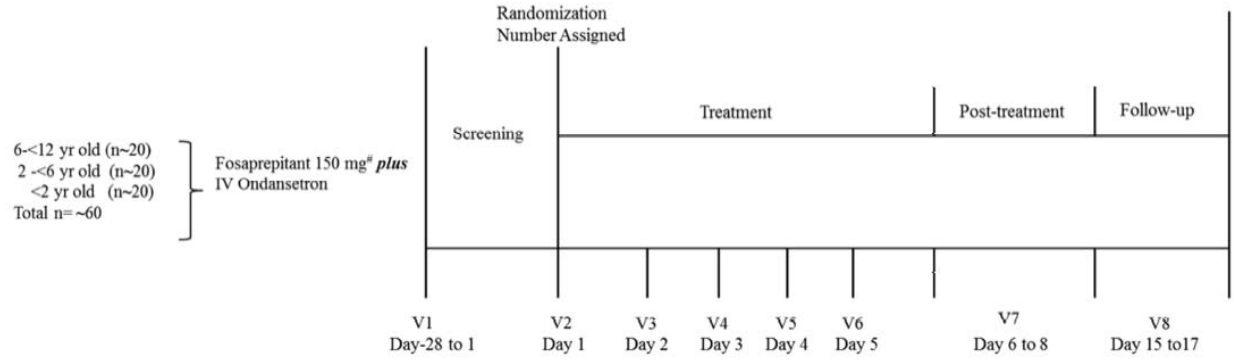
A cohort to evaluate the impact of aprepitant on the PK of dexamethasone in the pediatric age group birth to 1 year old was also implemented.

Reviewer's comment: Only one patient was studied. Thus, the results are not included in this review.

Figure 8. Study Design and Treatment Group. Top panel: Dose Ranging Study Part; Bottom Panel: Study of 5 mg/kg (Up to 150 mg) in < 12 years



* 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]



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

Pharmacokinetic analysis: Plasma for aprepitant PK assessment was obtained at the end of the fosaprepitant infusion, and 2 to 4 hours, 5 to 7 hours, 8 to 10 hours, and 23 to 25 hours after completion of fosaprepitant infusion. An additional optional plasma sample was collected 46 to 50 hours after completion of fosaprepitant infusion in the 5 mg/kg dose cohort. PK assessment was done in Cycle 1.

Pharmacokinetic Results

Demographics

	Fosaprepitant 3mg/kg Regimen		Fosaprepitant 1.2mg/kg Regimen		Fosaprepitant 0.4mg/kg Regimen		Control Regimen		Fosaprepitant 5mg/kg Regimen		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	42		43		40		35		74		234	
Gender												
Male	24	(57.1)	20	(46.5)	21	(52.5)	18	(51.4)	42	(56.8)	125	(53.4)
Female	18	(42.9)	23	(53.5)	19	(47.5)	17	(48.6)	32	(43.2)	109	(46.6)
Age (Months)												
birth to <2 years	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	23	(31.1)	23	(9.8)
2 to <6 years	8	(19.0)	10	(23.3)	10	(25.0)	9	(25.7)	26	(35.1)	63	(26.9)
6 to <12 years	17	(40.5)	16	(37.2)	13	(32.5)	9	(25.7)	25	(33.8)	80	(34.2)
12 to 17 years	17	(40.5)	17	(39.5)	17	(42.5)	17	(48.6)	0	(0.0)	68	(29.1)
Mean	124.5		121.6		120.7		124.3		60.2		103.0	
SD	51.8		51.3		54.0		55.7		42.3		57.4	
Median	123.5		127.0		129.0		140.0		54.0		102.0	
Range	29 to 210		38 to 202		27 to 209		28 to 206		4 to 142		4 to 210	
Race												
Asian	3	(7.1)	2	(4.7)	2	(5.0)	3	(8.6)	13	(17.6)	23	(9.8)
Black Or African American	1	(2.4)	1	(2.3)	4	(10.0)	2	(5.7)	1	(1.4)	9	(3.8)
Multiple	0	(0.0)	1	(2.3)	1	(2.5)	2	(5.7)	9	(12.2)	13	(5.6)
White	38	(90.5)	39	(90.7)	33	(82.5)	28	(80.0)	51	(68.9)	189	(80.8)
Ethnicity												
Hispanic Or Latino	6	(14.3)	8	(18.6)	10	(25.0)	3	(8.6)	17	(23.0)	44	(18.8)
Not Hispanic Or Latino	27	(64.3)	29	(67.4)	26	(65.0)	24	(68.6)	53	(71.6)	159	(67.9)

Subjects by Age Category and Gender

	Fosaprepitant 3mg/kg Regimen			Fosaprepitant 1.2mg/kg Regimen			Fosaprepitant 0.4mg/kg Regimen		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Subjects in population	24	18	42	20	23	43	21	19	40
Age (Months)									
birth to <2 years	0	0	0	0	0	0	0	0	0
2 to <6 years	4	4	8	5	5	10	5	5	10
6 to <12 years	10	7	17	5	11	16	5	8	13
12 to 17 years	10	7	17	10	7	17	11	6	17
Mean	128.3	119.3	124.5	131.6	113.0	121.6	126.5	114.3	120.7
SD	54.3	49.2	51.8	54.1	48.2	51.3	55.4	53.2	54.0
Median	119.5	125.0	123.5	147.0	118.0	127.0	148.0	113.0	129.0
Range	29 to 210	39 to 196	29 to 210	48 to 202	38 to 200	38 to 202	27 to 205	34 to 209	27 to 209

	Control Regimen			Fosaprepitant 5mg/kg Regimen			Total		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Subjects in population	18	17	35	42	32	74	125	109	234
Age (Months)									
birth to <2 years	0	0	0	12	11	23	12	11	23
2 to <6 years	3	6	9	14	12	26	31	32	63
6 to <12 years	6	3	9	16	9	25	42	38	80
12 to 17 years	9	8	17	0	0	0	40	28	68
Mean	128.6	119.8	124.3	65.5	53.3	60.2	107.5	97.8	103.0
SD	53.4	59.3	55.7	44.7	38.4	42.3	58.7	55.8	57.4
Median	142.0	136.0	140.0	60.5	48.5	54.0	109.0	101.0	102.0
Range	28 to 206	35 to 204	28 to 206	4 to 142	7 to 142	4 to 142	4 to 210	7 to 209	4 to 210

For Fosaprepitant 3mg/kg Regimen, subjects 12-17 years of age received a fixed 150 mg fosaprepitant dose.
For Fosaprepitant 1.2mg/kg Regimen, subjects 12-17 years of age received a fixed 60 mg fosaprepitant dose.
For Fosaprepitant 0.4mg/kg Regimen, subjects 12-17 years of age received a fixed 20 mg fosaprepitant dose.

Source: [P029MK0517: analysis-adsl]

4.2.1.1 Summary of PK parameters

Descriptive Summary of the PK parameters estimated by non-compartmental analysis is shown below:

Table 30. Descriptive Statistics of PK parameters After Single dose of 150 mg or 3 mg/kg by Age Cohorts

Table 11-1

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							
	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	3	12	12	12	0	12	3	3
AM	33800	30400	3500	735	NC	0.546	10.5	76.2
SD	7180	8290	972	310	NC	0.144	1.00	16.2
ACV (%)	21.3	27.3	27.7	42.2	NC	26.3	9.6	21.2
Med	33200	29400	3730	714	NC	0.500	10.7	75.2
Min	26900	21300	1800	343	NC	0.500	9.39	60.6
Max	41200	48100	4600	1240	NC	1.00	11.4	92.9
GM	33300	29400	3360	675	NC	0.534	10.5	75.1
GCV (%)	21.6	26.1	32.7	46.0	NC	20.1	9.8	21.6

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;

†Three out of 12 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 3 subjects.

Table 11-2

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 3 mg/kg (up to 150 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged 6 to <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	8	14	14	14	0	14	8	8
AM	34300	29200	3550	589	NC	1.99	7.69	69.2
SD	20300	14300	2460	433	NC	1.62	2.09	66.4
ACV (%)	59.1	48.8	69.2	73.5	NC	81.6	27.2	95.9
Med	28400	29500	2700	550	NC	1.14	7.64	46.6
Min	10900	9650	1210	81.0	NC	0.533	4.39	34.0
Max	69000	60700	9190	1260	NC	6.00	11.9	231
GM	29200	26000	2930	419	NC	1.55	7.45	55.0
GCV (%)	69.0	54.9	69.5	119.9	NC	79.6	28.1	68.8

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;

[†]AN # 201770 was excluded from PK parameter summary statistics due to dosing deviation.

[‡]Eight out of 14 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 8 subjects.

Table 11-3

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 3 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	5	6	6	6	0	6	5	5
AM	15300	21800	2320	278	NC	2.29	6.55	66.2
SD	11100	22200	1540	398	NC	2.14	3.62	25.5
ACV (%)	72.9	101.8	66.1	142.9	NC	93.5	55.3	38.5
Med	9830	10600	1590	63.2	NC	1.00	4.96	63.6
Min	9530	9140	1020	33.5	NC	1.00	4.29	31.9
Max	35100	65100	4550	1020	NC	6.08	12.9	101
GM	13100	15900	1960	115	NC	1.68	5.95	61.8
GCV (%)	60.6	94.7	69.8	255.1	NC	97.5	48.2	45.0

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;

[†]Five out of 6 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 5 subjects.

Table 31. Descriptive Statistics of PK parameters After Single dose of 60 mg or 1.2 mg/kg by Age Cohorts

Table 11-4

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 60 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							
	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	8	12	12	12	0	12	8	8
AM	12300	9700	1180	142	NC	0.722	7.92	91.7
SD	4660	4200	408	86.4	NC	0.608	1.38	32.5
ACV (%)	37.8	43.3	34.6	61.0	NC	84.2	17.4	35.5
Med	10400	8590	1200	121	NC	0.500	7.97	96.8
Min	7090	3980	487	63.0	NC	0.500	5.74	52.9
Max	18900	17300	1910	372	NC	2.60	9.88	141
GM	11600	8860	1110	124	NC	0.614	7.81	86.4
GCV (%)	38.9	47.5	39.9	55.5	NC	52.7	18.0	38.9

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;

†Eight out of 12 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 8 subjects.

Table 11-5

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 1.2 mg/kg (up to 60 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged 6 to <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	9	13	13	13	0	13	9	9
AM	10700	12000	1360	219	NC	2.14	8.23	78.8
SD	5440	11000	903	379	NC	1.96	1.83	39.1
ACV (%)	51.0	91.9	66.3	172.6	NC	91.5	22.3	49.6
Med	8920	8190	1030	98.6	NC	1.03	8.02	81.9
Min	2860	2670	471	18.7	NC	0.500	6.03	32.5
Max	21300	45600	3070	1440	NC	6.17	12.3	156
GM	9370	9310	1140	110	NC	1.56	8.06	70.3
GCV (%)	62.4	78.1	67.3	153.1	NC	92.8	21.3	55.8

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;
†Nine out of 13 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 9 subjects.

Table 11-6

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 1.2 mg/kg (up to 60 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	5	8	8	8	0	8	5	5
AM	16000	19700	2030	332	NC	1.36	7.27	29.6
SD	9680	18500	1780	430	NC	0.868	3.47	22.1
ACV (%)	60.4	93.6	87.5	129.7	NC	63.6	47.7	74.4
Med	12400	14200	1480	222	NC	1.00	5.51	22.0
Min	4820	4600	716	26.6	NC	1.00	3.73	12.1
Max	27700	62300	6180	1350	NC	3.50	11.6	65.7
GM	13400	14700	1600	170	NC	1.23	6.63	24.2
GCV (%)	80.3	93.8	77.0	216.5	NC	45.4	51.3	79.1

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;
†Five out of 8 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 5 subjects.

Table 32. Descriptive Statistics of PK parameters After Single dose of 20 mg or 0.4 mg/kg by Age Cohorts

Table 11-7

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 20 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							
	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	9	13	13	13	0	13	9	9
AM	3500	4820	582	101	NC	0.736	8.27	105
SD	1430	7240	437	247	NC	0.561	1.20	29.0
ACV (%)	40.9	150.3	75.1	244.8	NC	76.2	14.6	27.6
Med	2940	2400	437	34.3	NC	0.500	8.29	113
Min	2360	1010	173	0.00	NC	0.500	6.27	47.4
Max	7030	28500	1710	920	NC	2.50	10.4	141
GM	3310	3110	467	NC	NC	0.636	8.19	101
GCV (%)	34.3	94.0	76.2	NC	NC	51.3	14.9	34.3

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;
†Nine out of 13 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 9 subjects.

Table 11-8

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 0.4 mg/kg (up to 20 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged 6 to <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	8	12	12	12	0	12	8	8
AM	2860	4260	507	70.4	NC	1.68	6.58	89.6
SD	1120	5040	443	136	NC	2.46	2.36	40.9
ACV (%)	39.0	118.4	87.3	193.2	NC	146.3	35.9	45.6
Med	2950	2710	375	25.4	NC	1.00	6.76	84.0
Min	1270	1480	173	0.00	NC	0.667	3.85	30.8
Max	4180	19800	1820	485	NC	9.50	10.5	164
GM	2650	3090	407	NC	NC	1.17	6.21	80.9
GCV (%)	45.7	81.5	70.5	NC	NC	75.3	38.4	54.1

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;
†Eight out of 12 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 8 subjects.

Table 11-9

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 0.4 mg/kg (up to 20 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	4	5	6	6	0	6	4	4
AM	2070	1840	323	9.23	NC	1.34	6.18	48.5
SD	992	742	103	14.8	NC	0.771	3.51	28.4
ACV (%)	47.9	40.4	32.0	160.1	NC	57.4	56.8	58.5
Med	1930	1570	330	0.00	NC	1.03	4.88	42.3
Min	1230	1170	201	0.00	NC	1.00	3.67	23.6
Max	3190	3020	479	33.6	NC	2.92	11.3	85.6
GM	1890	1730	309	NC	NC	1.22	5.57	42.6
GCV (%)	53.0	39.0	33.6	NC	NC	44.7	53.7	64.5

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;

[†]AN # 201127 was excluded from PK parameter summary statistics due to dosing deviation.

[‡]For AN # 104463, the 0hr (End of Infusion) and 48hr samples were missing and other post dose samples are BLOQ. So PK parameters were not estimated for this subject.

[§]For AN # 104099 the AUC0-24 was not estimated due to insufficient data.

[%]Four out of 6 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 4 subjects.

Table 33. Descriptive Statistics of PK parameters After Single dose of 5 mg/kg by Age Cohorts (< 12 years)

Table 11-10

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 # 104816 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 11-11

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 11-12

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 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 # 103687, 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.

Reviewer's comment: All patients enrolled in 5 mg/kg dose cohort were age > 6 months.

Concentration-time profiles of aprepitant are shown below.

Figure 11-1

Arithmetic Mean Plasma Concentration (SD) vs. Time Profiles for Aprepitant Following Administration a Single IV Fosaprepitant Dose of 150 mg, 60 mg and 20 mg in Subjects Aged 12 to 17 Years (Top = Linear Scales; Bottom = Semi-Log Scale)

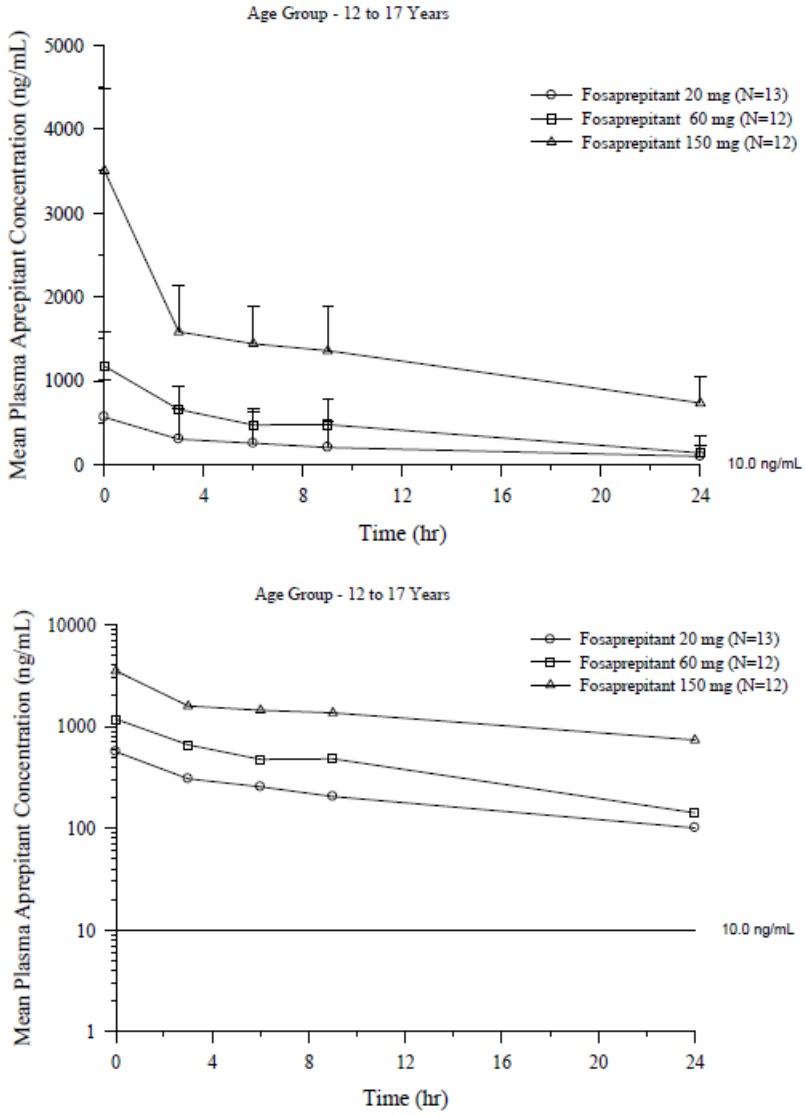


Figure 11-2

Arithmetic Mean Plasma Concentration (SD) vs. Time Profiles for Aprepitant Following Administration of a Single IV Fosaprepitant Dose of 5 mg/kg (up to 150 mg), 3 mg/kg (up to 150 mg), 1.2 mg/kg (up to 60 mg) and 0.4 mg/kg (up to10 mg) in Subjects Aged 6 to <12 Years (Top = Linear Scales; Bottom = Semi-Log Scale)

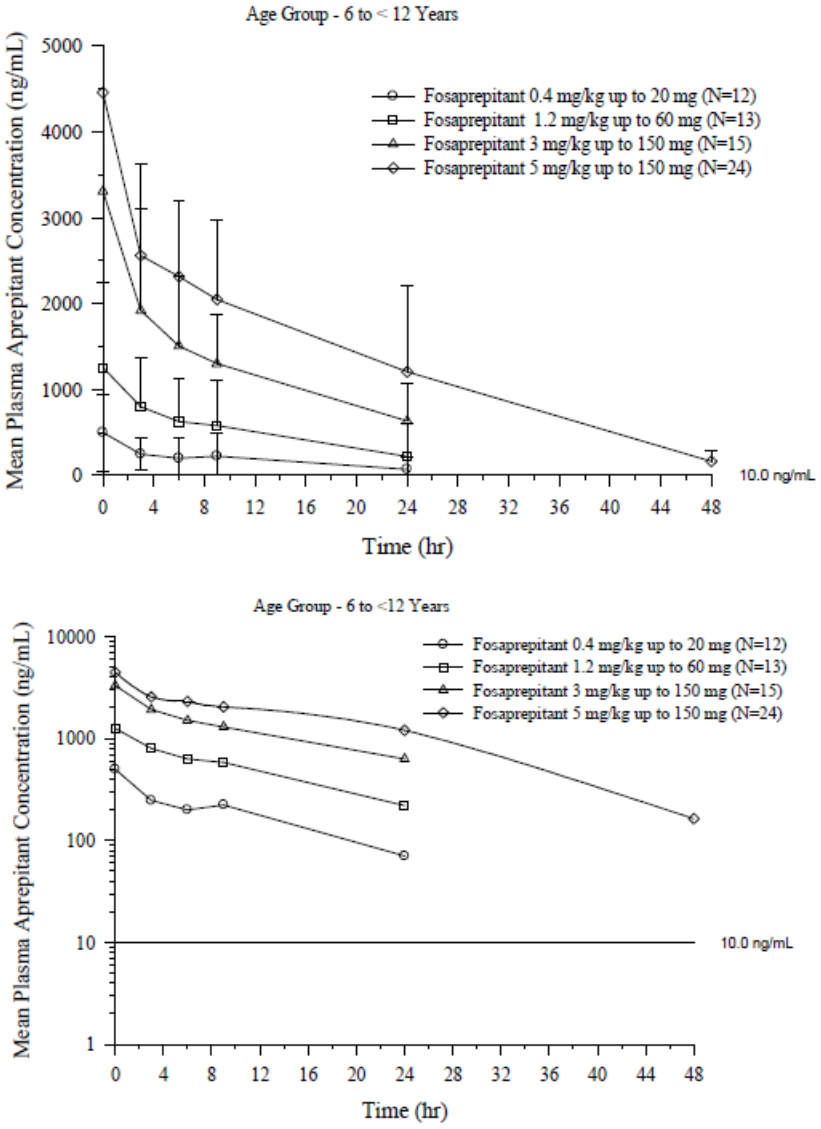


Figure 11-3

Arithmetic Mean Plasma Concentration (SD) vs. Time Profiles for Aprepitant Following Administration of a Single IV Fosaprepitant Dose of 5 mg/kg (up to 150 mg), 3 mg/kg (up to 150 mg), 1.2 mg/kg (up to 60 mg) and 0.4 mg/kg (up to10 mg) in Subjects Aged 2 to <6 Years (Top = Linear Scales; Bottom = Semi-Log Scale)

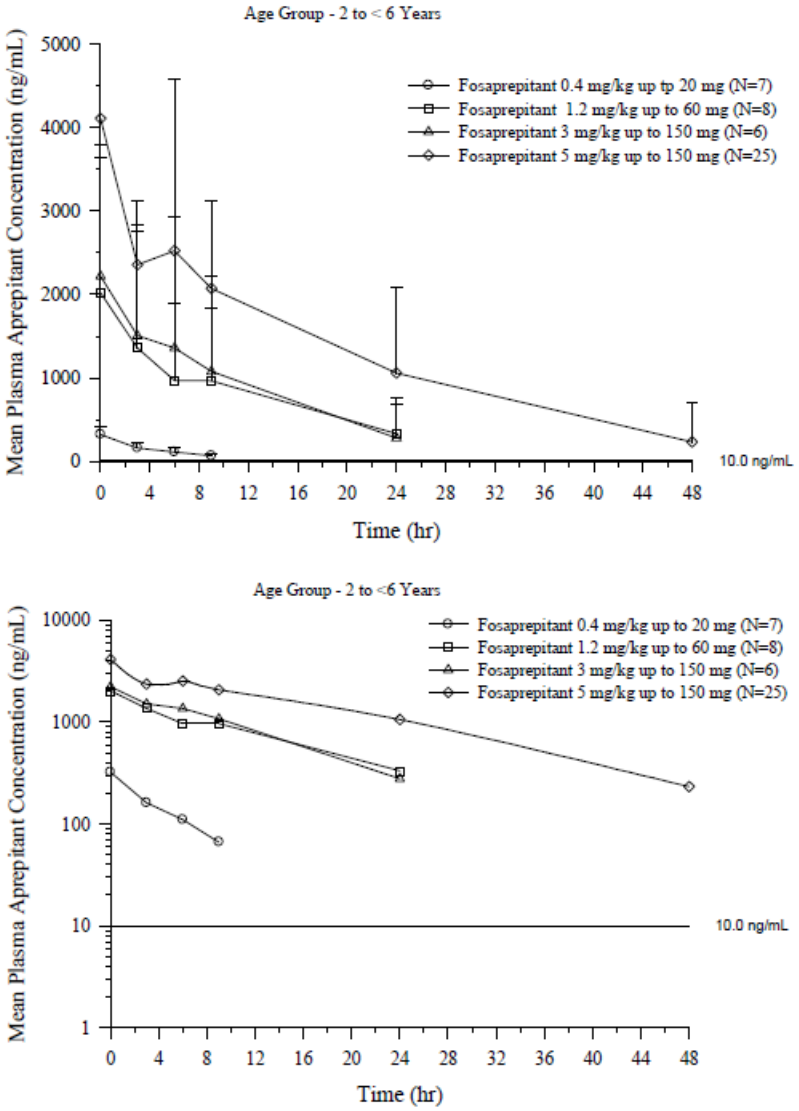
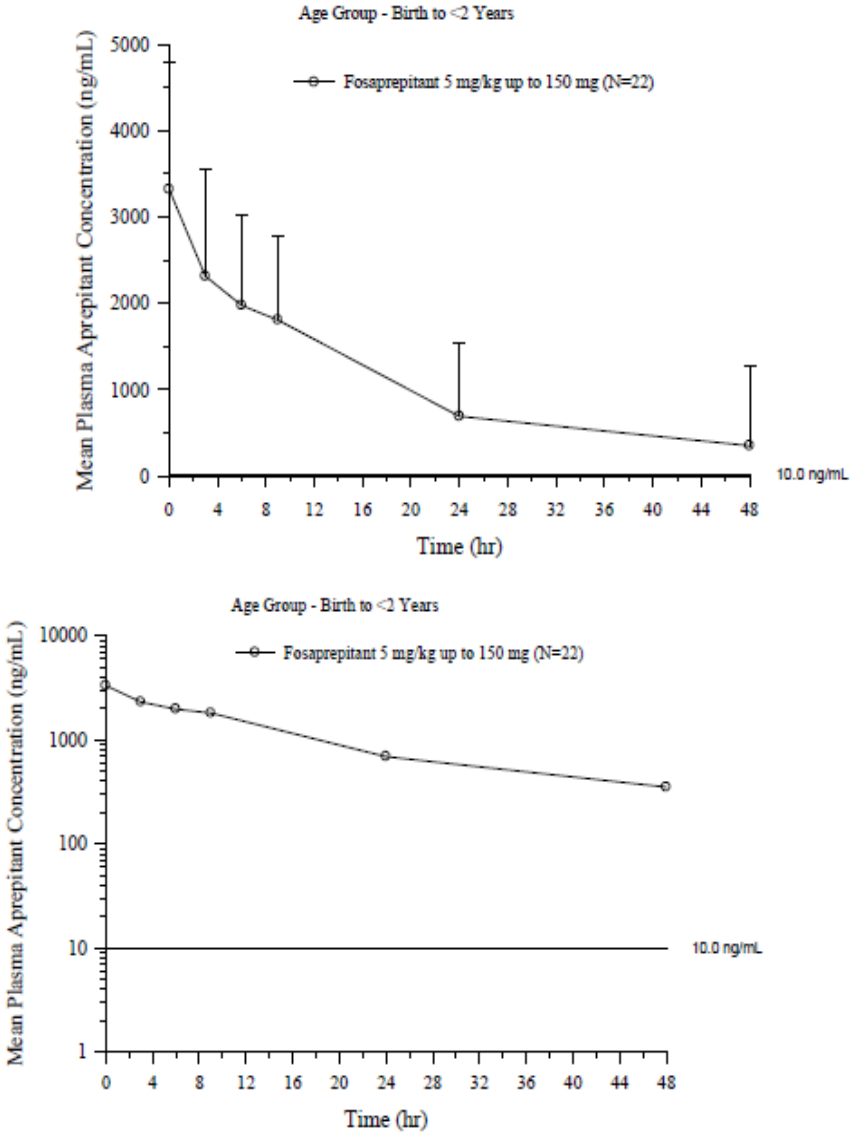


Figure 11-4

Arithmetic Mean Plasma Concentration (SD) vs. Time Profiles for Aprepitant Following Administration of a Single IV Fosaprepitant Dose of 5 mg/kg (up to 150 mg), 3 mg/kg (up to 150 mg), 1.2 mg/kg (up to 60 mg) and 0.4 mg/kg (up to10 mg) in Subjects Aged Birth to <2 Years (Top = Linear Scales; Bottom = Semi-Log Scale)

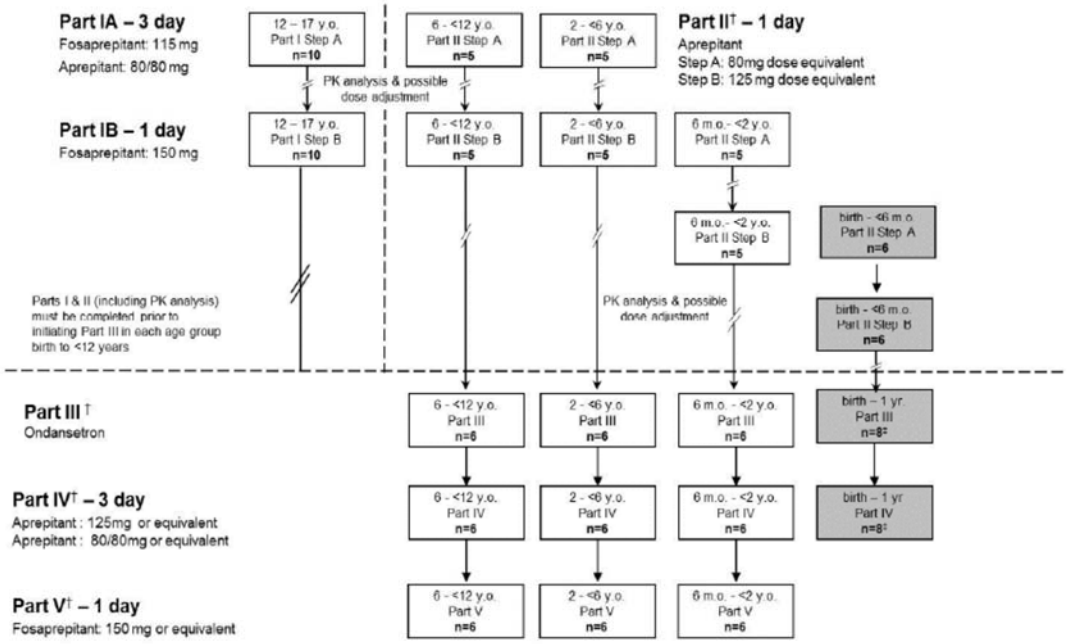


4.2.2 Study P134

Title: 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

Study Design: This is a multi-center, open-label, 5-part study to evaluate pharmacokinetics, safety, and tolerability of oral aprepitant and intravenous fosaprepitant dimeglumine. Eligible patients were male and female, birth to 17 years of age and scheduled to receive moderately or highly emetogenic chemotherapy or a chemotherapy regimen not previously tolerated due to nausea and/or vomiting for a documented malignancy.

Study Schematic



† Patients in Part II Steps A and B >6 months old were expected to be unique patients. Patients in Parts III, IV, and V were expected to be the same patients undergoing subsequent rounds of chemotherapy.

‡ Enrollment in the birth to 1-year cohort into Parts III and IV for dexamethasone evaluation were expected to include approximately 2 patients each from the following age groups: birth to 2 months, 2 to 4 months, 4 to 8 months, and 8 to 12 months.

Note: Patients <1 year in the 6-month to 2-year cohort may have had dexamethasone PK samples obtained (as applicable) but they were not required to do so; none were collected. Shaded cohorts were not enrolled.

Reviewer's comment: No PK data were collected from patients < 6 months old.

Treatment groups using fosaprepitant are summarized below by the reviewer:

						Age range (yr)			
Part	**Step**	**Route**	**Dose on Day 1**	**Regimen**	**Oral dose‡ on Days 2 and 3**	**12 to 17**	**6 to 12**	**2 to 6**	**0.5 to 2**
I	A	IV	115 mg	3-day	80	√			
I	B	IV	150 mg	1-day	--	√			
V	--	IV	3mg/kg	1-day	--		√	√	√
‡: Emend oral suspension was used; √: age group dosed									

Reviewer's comment: PK data from PO aprepitant regimens (Part II and IV) and the analytical methods for aprepitant were reviewed when they were submitted to NDA 207865 for the approval of oral suspension for pediatric patients. Refer to Clinical Pharmacology Review of NDA 207865.

Pharmacokinetic analysis

Aprepitant: The blood sampling schemes for aprepitant PK are as follows:

Part I, Step A: Predose, -45, -30, -15, 0 minutes (start of chemotherapy), 1.5, 3, 4, 6, 8, 24, 48, 72 hours post start of chemotherapy on Day 1 for aprepitant and/or fosaprepitant PK.

Part I, Step B: Predose, -45 minutes, -30 minutes, 0 minutes (start of chemotherapy), 30 minutes, and 1.5, 3, 4, 6, 8, 24, 48, 72 hours post start of chemotherapy on Day 1 for aprepitant and/or fosaprepitant PK.

Part V: Predose, -45, -30, 0 minutes (start of chemotherapy) and 30 minutes, 1.5, 3, 4, 6, 8, 24, 48, 72 hours post start of chemotherapy on Day 1.

Fosaprepitant: The blood sampling for fosaprepitant PK were collected in Part I Step A and Part V:

Part I, Step B: pre-dose, -45 min (immediately after the 30 min infusion of fosaprepitant), 30 min prior to the start of chemotherapy, 0 min (at start of chemotherapy) and at 30 minutes from the start of chemotherapy.

Part V: pre-dose, -45 min (immediately after the 60 min fosaprepitant infusion), -30 min (prior to chemotherapy), 0 min (start of chemotherapy).

Pharmacokinetic Results

Demographics:

Table 34. The Demographic Data of Patients Enrolled in the Fosaprepitant Cohorts

<Part I>

	Fosaprepitant (115 mg) Regimen (Step A)		Fosaprepitant (150 mg) Regimen (Step B)	
	n	(%)	n	(%)
Subjects in population	12		11	
Gender				
Male	5	(41.7)	4	(36.4)
Female	7	(58.3)	7	(63.6)
Age (Months)				
12 to 17 years	12	(100.0)	11	(100.0)
Mean	164.9		185.7	
SD	14.9		19.9	
Median	160.0		183.0	
Range	150 to 190		148 to 215	
Race				
Asian	0	(0.0)	1	(9.1)
Black Or African American	1	(8.3)	1	(9.1)
Multi-Racial	2	(16.7)	2	(18.2)
White	9	(75.0)	7	(63.6)
Ethnicity				
Hispanic Or Latino	6	(50.0)	9	(81.8)
Not Hispanic Or Latino	6	(50.0)	2	(18.2)
History of Motion Sickness				
No	6	(50.0)	11	(100.0)
Yes	5	(41.7)	0	(0.0)
Unknown	1	(8.3)	0	(0.0)

<Part V>

	Fosaprepitant Regimen (Part V)	
	n	(%)
Subjects in population	23	
Gender		
Male	7	(30.4)
Female	16	(69.6)
Age (Months)		
6 months to <2 years	7	(30.4)
2 to <6 years	8	(34.8)
6 to <12 years	8	(34.8)
Mean	57.8	
SD	39.6	
Median	49.0	
Range	11 to 123	
Race		
Asian	1	(4.3)
Black Or African American	1	(4.3)
Multi-Racial	10	(43.5)
White	11	(47.8)
Ethnicity		
Hispanic Or Latino	9	(39.1)
Not Hispanic Or Latino	14	(60.9)
History of Motion Sickness		
No	23	(100.0)
Yes	0	(0.0)
Unknown	0	(0.0)
History of Vomiting Post Chemotherapy		
No	6	(26.1)
Yes	17	(73.9)

4.2.2.1 Summary of PK parameters of aprepitant – Part I, Step A (Adolescents)

Patients received single IV dose of 115 mg fosaprepitant on Day 1 followed by 80 mg oral aprepitant on Days 2 and 3.

The descriptive statistics of the PK parameters estimated by non-compartmental analysis are provided in the table below.

Table 35. Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant (MK-0869) Following Administration of a 3-Day Regimen that includes 115 mg IV Fosaprepitant on Day 1 Followed by 80 mg Oral Aprepitant on Days 2 and 3 to 12- to 17-Year-Old Patients Undergoing Chemotherapy

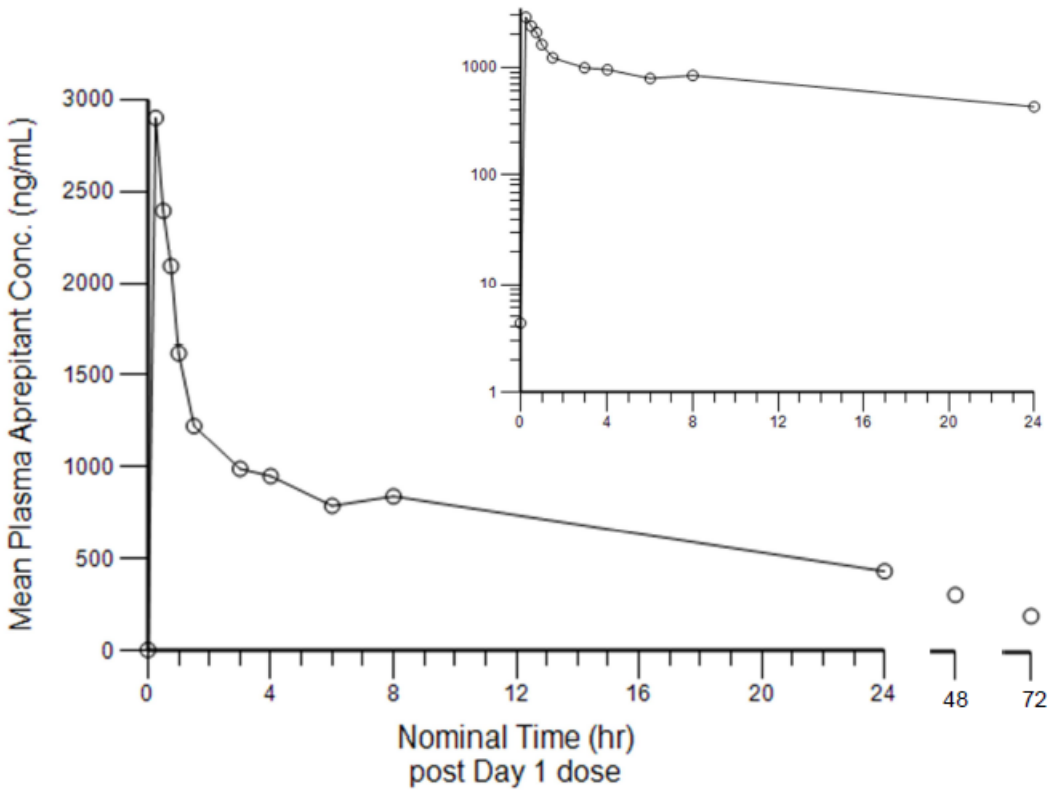
12- to 17-Year-Olds	Cmax (ng/ml)	Tmax (hr)	C_{24hr} (ng/mL)	$t_{½}^{\#}$ (hr)	CL (ml/hr)	AUC_{0-24hr} (hr*ng/ml)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)
N	12	12	8	6	5	8	10	11
AM	3240	0.41	433	11.0	6310	19500	310	199
SD	1280	0.27	318	4.42	2750	8010	288	281
Min	1650	0.25	133	6.87	3140	9940	66.2	BLQ
Median	3080	0.25	407	10.2	7210	19300	171	84.9
Max	6210	1.00	1120	19.2	8880	33100	904	796
"CV%	39.4	65.9	73.6	40.2	43.6	41.1	93.1	141
HM	2840	0.31	284	9.84	5210	16700	151	--
Pseudo SD	1060	0.12	200	3.25	2830	7200	118	--
GM	3030	0.35	348	10.4	5760	18000	210	--
*CV%	39.4	57.81	80.0	37.7	52.9	44.4	117	--
Adults (Protocol 012L1)						$AUC_{0-\infty}$		
AM	3267					31724		
SD	1159					14287		
GM	3095					29611		

Pseudo SD = Jackknife estimate of the standard deviation of the harmonic mean.
N: Number of observations; AM: Arithmetic Mean; SD: Standard Deviation.
BLQ = Below limit of quantitation (<10.0 ng/mL); BLQ values have been considered as zero for calculation of descriptive statistics.
Min: Minimum; Max: Maximum; GM: Geometric Mean; HM: Harmonic Mean.
"CV%: Arithmetic Coefficient of Variation, where "CV% = SD/AM*100.
*CV%: Geometric Coefficient of Variation, where *CV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.
#: (Apparent) terminal half-life.
= Not evaluable since λz could not be estimated from the available data.
† excluded from descriptive statistics since samples were taken after next day dose.
§ excluded from descriptive statistics since AUC%extrap >25% of total AUC (AUC0-∞).
ß excluded from descriptive statistics since t1/2 > tlast.

Source data: Study P134 CSR, Table 11-1

The mean concentration-time profile in linear and semi-log scales is show in the figure below.

Figure 9. The Mean Concentration-Time Profile of Aprepitant. Inset Represents the Profile in Semi-Log Scale.



Source data: Study P134 CSR, Figure 11-1

4.2.2.2 Summary of PK parameters of aprepitant – Part I, Step B (Adolescents)

Patients received single IV dose of 150 mg fosaprepitant on Day 1 only.

The descriptive statistics of the PK parameters estimated by non-compartmental is shown in the table below.

Table 36. Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant (MK-0869) Following Administration of a Single Day IV Regimen at a Dose of 150 mg Fosaprepitant (MK-0517) to 12- to 17-Year-Old Patients Undergoing Chemotherapy

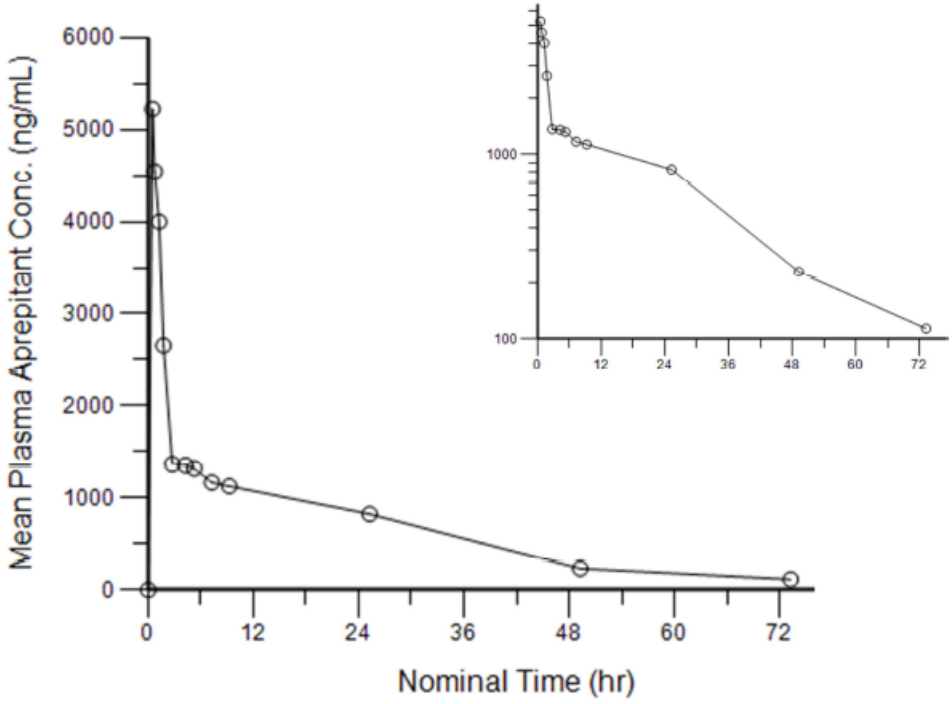
	Cmax (ng/mL)	Tmax (hr)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)	$t_{½}^{\#}$ (hr)	CL (mL/hr)	AUC_{0-24hr} (hr*ng/mL)	AUC_{0-48hr} (hr*ng/mL)	AUC_{0-72hr} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)
12- to 17-Year-Olds											
N	11	11	11	10	11	11	8	11	11	11	8
AM	5870	0.64	825	230	114	22.2	3750	30800	42300	46900	43600
SD	2770	0.30	321	324	186	19.8	1390	7020	11600	15900	11700
Min	2880	0.50	413	BLQ	BLQ	7.91	2630	17800	21300	21500	21700
Median	4960	0.50	742	112	14.5	12.1	3450	31000	42200	43700	43500
Max	12300	1.50	1360	1080	498	67.8	6920	42200	64200	83000	57000
"CV%	47.1	46.7	38.9	141	164	89.3	37.1	22.8	27.5	34.0	26.8
HM	4980	0.58	718	--	--	13.8	3440	29100	39100	42100	40000
Pseudo SD	1980	0.14	284	--	--	7.49	907	8250	13500	16700	16200
GM	5380	0.60	769	--	--	16.8	3570	30000	40800	44500	42000
*CV%	44.8	35.27	40.9	--	--	84.7	32.2	25.3	30.2	35.5	32.2
Adults (Protocol 165)											
AM	4145							25105			
SD	1152							5778			

Pseudo SD = Jackknife estimate of the standard deviation of the harmonic mean.
N: Number of observations; AM: Arithmetic Mean; SD: Standard Deviation.
BLQ = Below limit of quantitation (<10.0 ng/mL); BLQ values have been considered as zero for calculation of descriptive statistics;
Min: Minimum; Max: Maximum; GM: Geometric Mean; HM: Harmonic Mean.
"CV%: Arithmetic Coefficient of Variation, where "CV% = SD/AM*100.
*CV%: Geometric Coefficient of Variation, where *CV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.
#: (Apparent) terminal half-life.
* excluded from descriptive statistics since AUC% extrap >25% of total AUC (AUC0-∞).
† excluded from descriptive statistics since sample result > 2 times higher than the predicted concentration by the best fitted terminal slope without this value.

Source data: Study P134 CSR, Table 11-2

The mean concentration-time profile in linear and semi-log scales is show in the figure below.

Figure 10. The Mean Concentration-Time Profile of Aprepitant. Inset Represents the Profile in Semi-Log Scale.



Source data: Study P134 CSR, Figure 11-2

4.2.2.3 Summary of PK parameters of fosaprepitant – Part I, Step B (Adolecents)

Table 37. Summary Plasma Fosaprepitant Cmax and Tmax Values Following IV Administration of 150 mg Fosaprepitant in 12- to 17-Year-Old Patients Undergoing Chemotherapy

	Tmax (hr)	Cmax (ng/ml)
N	11	11
Mean	0.614	1310
SD	0.251	964
Min	0.500	26.6
Median	0.500	1020
Max	1.33	3300
CV%"	40.9	73.9
Geometric Mean	0.583	851
CV%* Geometric Mean	30.9	207

Although individual parameters and descriptive statistics are reported to three significant digits, descriptive statistics are calculated from the un-rounded parameters;

AN: Allocation Number; N: Number of observations; AM: Arithmetic Mean; SD: Standard Deviation;

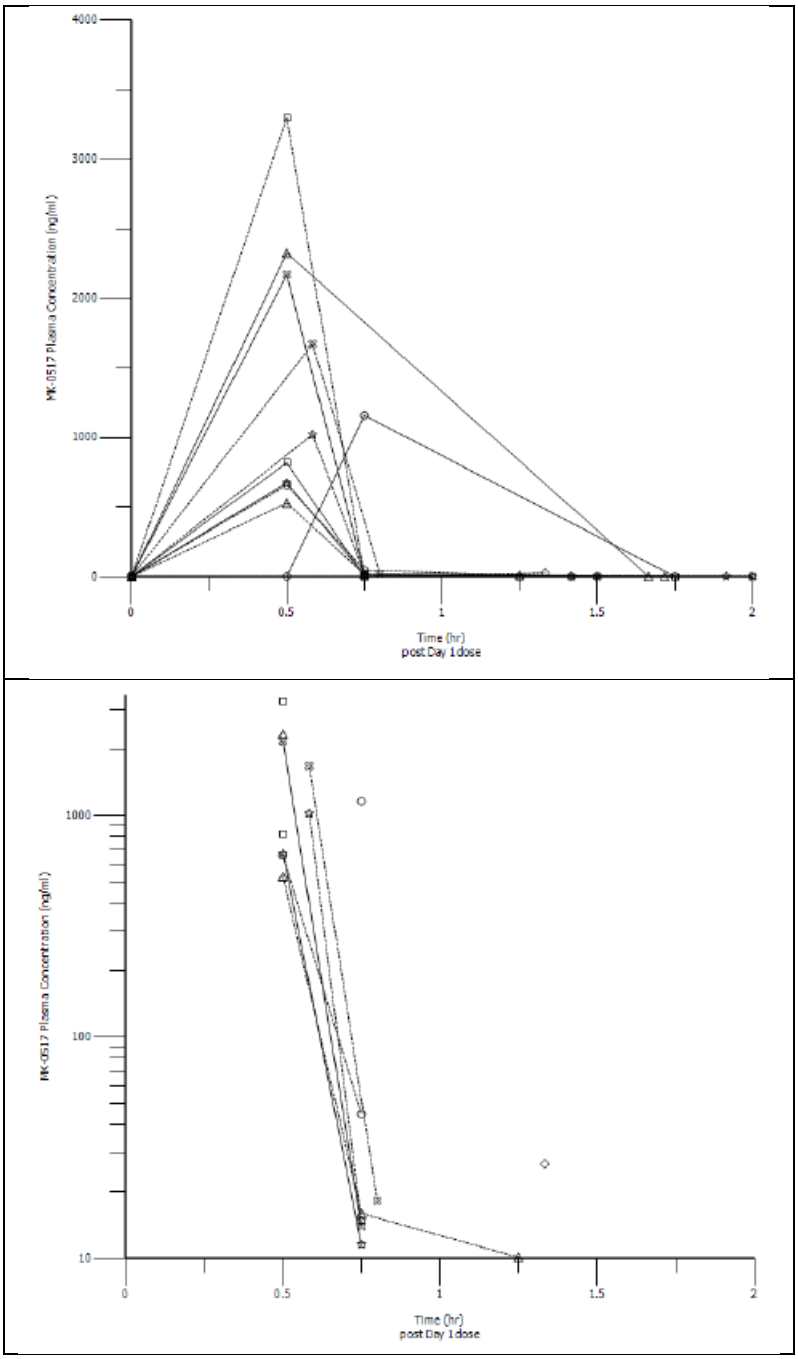
"CV%: Arithmetic Coefficient of Variation, where "CV% = SD/AM*100;

*CV%: Geometric Coefficient of Variation, where *CV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale;

Min: Minimum; Max: Maximum; GM: Geometric Mean

Source data: Study P134 CSR, Table 11-3

Figure 11. The Individual Concentration-Time Profile of Fosaprepitant. Top panel: Linear Scale; Bottom Panel: Semi-log Scale.



Source data: Study P134 CSR, Figures 14-3 and 14-4

4.2.2.4 Summary of PK parameters of aprepitant – Part V

Patients age 6 months to < 12 years received single IV dose of 3 mg/kg fosaprepitant.

The descriptive statistics of the PK parameters estimated by non-compartmental analysis in different age groups (6mon - 2yr, 2-6 years, 6 to < 12 years) were provided in the tables below.

Table 38. Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant (MK-0869) Following Administration of a Single Day IV Regimen at a Dose of 3 mg/kg Fosaprepitant (MK-0517) to 6-Month- to <12-Year-Old Patients Undergoing Chemotherapy

	Cmax (ng/ml)	Tmax (hr)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)	$t_{½}^{\#}$ (hr)	CL (ml/hr)	AUC_{0-24hr} (hr*ng/ml)	AUC_{0-48hr} (hr*ng/ml)	AUC_{0-72hr} (hr*ng/ml)	$AUC_{0-\infty}$ (hr*ng/ml)
6-Month- to <2-Year-Olds											
N	7	7	6	6	6	6	6	6	6	6	6
AM	1700	1.13	150	--$^{\downarrow}$	--$^{\downarrow}$	7.71	5010	11700	13300	13800	13800
SD	636	0.17	103	--$^{\downarrow}$	--$^{\downarrow}$	3.10	6270	6980	7770	7940	7980
Min	838	1.00	BLQ	BLQ	BLQ	2.76	1580	1810	1890	1890	1760
Median	1730	1.00	169	BLQ	BLQ	7.74	2280	11300	13900	14600	14800
Max	2470	1.42	282	50.8	19.8	12.4	17600	19800	21900	22100	22100
"CV%	37.4	15.4	69.0	--$^{\downarrow}$	--$^{\downarrow}$	40.3	125	59.7	58.3	57.7	57.8
HM	1460	1.11	--	--	--	6.24	2560	6120	6640	6750	6470
Pseudo SD	723	0.16	--	--	--	4.96	1370	12500	15100	15900	16600
GM	1580	1.12	--	--	--	7.05	3250	9170	10400	10700	10600
*CV%	44.8	15.01	--	--	--	53.6	113	110	116	118	123

	Cmax (ng/ml)	Tmax (hr)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)	$t_{½}^{\#}$ (hr)	CL (ml/hr)	AUC_{0-24hr} (hr*ng/ml)	AUC_{0-48hr} (hr*ng/ml)	AUC_{0-72hr} (hr*ng/ml)	$AUC_{0-\infty}$ (hr*ng/ml)
2- to <6-Year-Olds											
N	7	7	7	7	7	7	6	7	7	7	6
AM	2430	1.41	184	--$^{\downarrow}$	--$^{\downarrow}$	6.44	3460	18300	20600	21100	23400
SD	1100	0.83	189	--$^{\downarrow}$	--$^{\downarrow}$	2.35	2680	11100	12900	13200	12800
Min	1260	1.00	BLQ	BLQ	BLQ	3.69	1370	6190	6890	6890	7350
Median	2570	1.03	182	BLQ	BLQ	5.94	1990	20600	22400	23200	25400
Max	3880	3.27	462	114	22.1	10.9	7000	36000	40000	40200	40200
"CV%	45.3	58.8	102	--$^{\downarrow}$	--$^{\downarrow}$	36.4	77.3	60.6	62.5	62.5	54.7
HM	1990	1.20	--	--	--	5.81	2270	12400	13400	13600	16100
Pseudo SD	972	0.34	--	--	--	2.00	1250	8950	9900	10200	13700
GM	2200	1.28	--	--	--	6.11	2730	15200	16800	17100	19800
*CV%	51.6	44.84	--	--	--	35.7	84.3	78.2	83.4	84.7	77.2

	Cmax (ng/ml)	Tmax (hr)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)	$t_{½}^{\#}$ (hr)	CL (ml/hr)	AUC_{0-24hr} (hr*ng/ml)	AUC_{0-48hr} (hr*ng/ml)	AUC_{0-72hr} (hr*ng/ml)	AUC(0-∞) (hr*ng/ml)
6- to <12-Year-Olds											
N	8	8	8	8	8	8	8	8	8	8	8
AM	2850	1.07	308	37.5	--$^{\downarrow}$	8.76	3590	19500	23100	24000	24100
SD	641	0.11	240	56.5	--$^{\downarrow}$	3.34	1880	6720	9660	10500	11100
Min	1800	1.00	100	BLQ	BLQ	5.73	1460	14000	15200	15300	15400
Median	2830	1.00	210	16.2	BLQ	7.49	3360	16300	19700	20500	20800
Max	3630	1.25	751	159	92.5	14.4	7670	34000	44700	47800	49500
"CV%	22.5	10.5	77.8	151	--$^{\downarrow}$	38.1	52.3	34.4	41.8	43.9	46.0
HM	2710	1.06	192	--	--	7.89	2900	18000	20700	21300	21300
Pseudo SD	730	0.10	128	--	--	2.40	1570	4580	6100	6450	6560
GM	2780	1.07	239	--	--	8.28	3220	18700	21700	22400	22500
*CV%	24.5	10.11	87.5	--	--	35.8	52.6	30.7	36.5	38.0	39.3
Adults (Protocol 165)											
AM	4145							25105			
SD	1152							5778			

Pseudo SD = Jackknife estimate of the standard deviation of the harmonic mean.

N: Number of observations; AM: Arithmetic Mean; SD: Standard Deviation; HM: Harmonic Mean; Min: Minimum; Max: Maximum; GM: Geometric Mean..

BLQ = Below limit of quantitation (<10.0 ng/mL); BLQ values have been considered as zero for calculation of descriptive statistics.

"CV%: Arithmetic Coefficient of Variation, where "CV% = SD/AM*100.

*CV%: Geometric Coefficient of Variation, where *CV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.

#: (Apparent) terminal half-life.

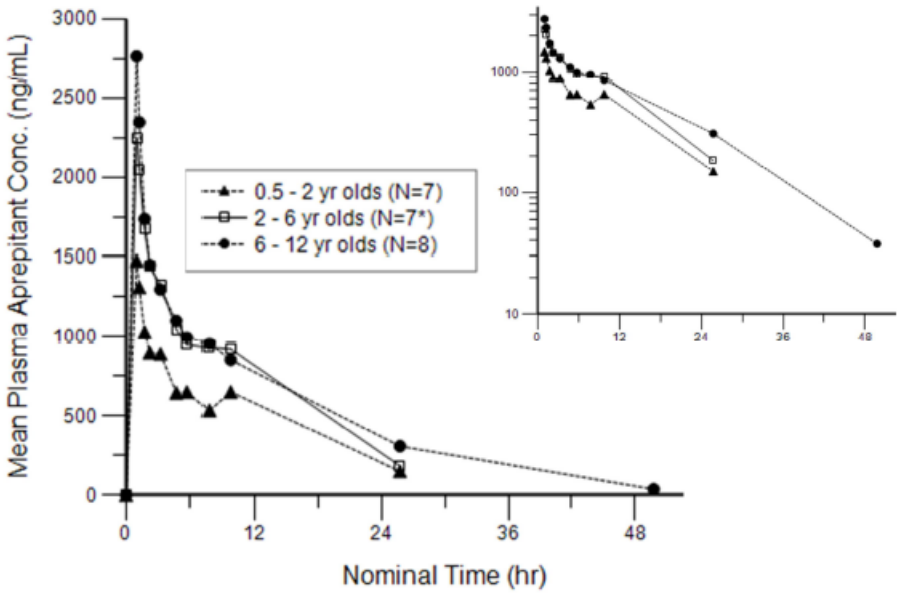
C24, C48 and C72 refer to concentrations 24hr, 48hr and 72hr after start chemotherapy, resp. (i.e. 25.75hr, 49.75hr and 73.75hr after start fosaprepitant infusion, resp.).

$^{\downarrow}$ Not reportable since <50% of the concentration results ≥ Lower Limit of Quantitation (LLOQ).

In some cases AUC0-∞ results are < AUC0-72 results. This can be explained by the fact that AUC0-∞ is calculated based on the last predicted concentration, i.e., concentration at the final observation time estimated using the linear regression performed to estimate λz. Whereas AUC0-72 is calculated based on interpolation only.

Source data: Study P134 CSR, Tables 11-13, 11-14, and 11-15

Figure 12. Mean Plasma Concentration vs. Time Profiles for Aprepitant (MK-0869) Following Administration of a Single Day IV Regimen at a Dose of 3 mg/kg Fosaprepitant (MK-0517) to 6-Month- to <12-Year-Old Patients Undergoing Chemotherapy. The profiles in semi-log scale are in the inlet.



Source data: Study P134 CSR, Figure 11-5

4.2.2.5 Summary of PK parameters of fosaprepitant – Part V

Table 39. Summary of Plasma Fosaprepitant Cmax and Tmax Values Following IV Administration of 3 mg/kg Fosaprepitant by Age Group

Age Range		Tmax (hr)	Cmax (ng/mL)
6 Months to <2 Years Old	N	7	7
	Mean	1.13	2756
	SD	0.175	3364
	Min	1.00	20.2
	Median	1.00	159
	Max	1.42	7260
	CV%	15.4	122
	Geometric Mean	1.12	494
	CV% Geometric Mean	15.0	2138
2 to <6 Years Old	N	7	8
	Mean	1.05	3034
	SD	0.089	1718
	Min	1.00	BLQ
	Median	1.02	3292
	Max	1.25	5237
	CV%	8.5	56.6
	Geometric Mean	1.05	NR
	CV% Geometric Mean	7.92	NR
6 to <12 Years Old	N	8	8
	Mean	1.04	1654
	SD	0.088	1995
	Min	1.00	357
	Median	1.00	910
	Max	1.25	6202
	CV%	8.50	121
	Geometric Mean	1.04	1009
	CV% Geometric Mean	7.91	133

Although individual parameters and descriptive statistics are reported to three significant digits, descriptive statistics are calculated from the un-rounded parameters.

N: Number of observations; AM: Arithmetic Mean; SD: Standard Deviation.

BLQ = Below limit of quantitation (<10.0 ng/mL); BLQ values have been considered as zero for calculation of descriptive statistics.

Min: Minimum; Max: Maximum; GM: Geometric Mean.

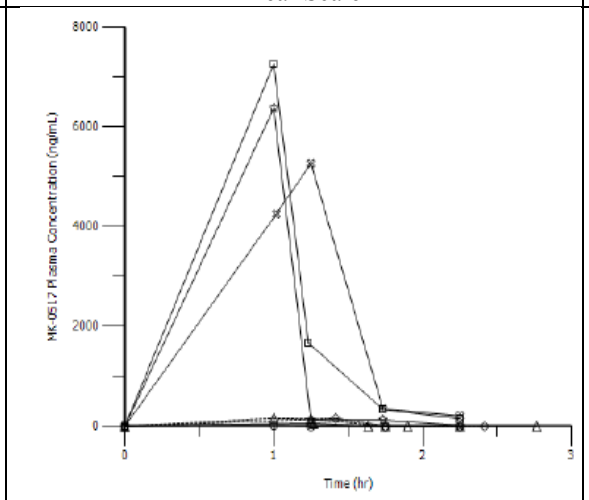
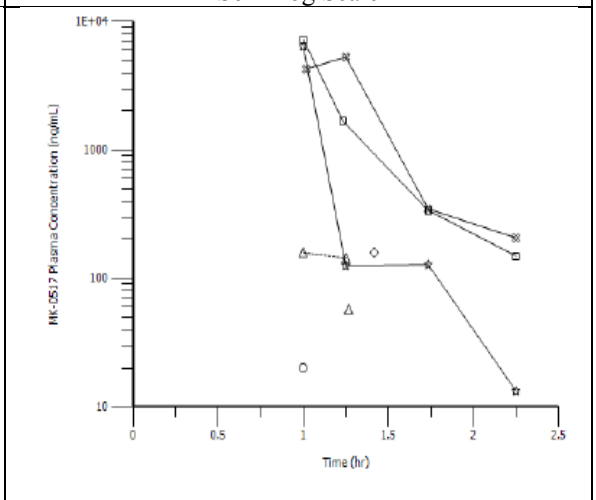
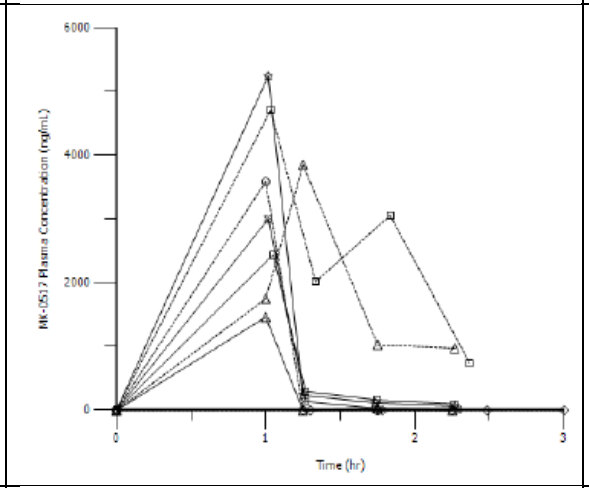
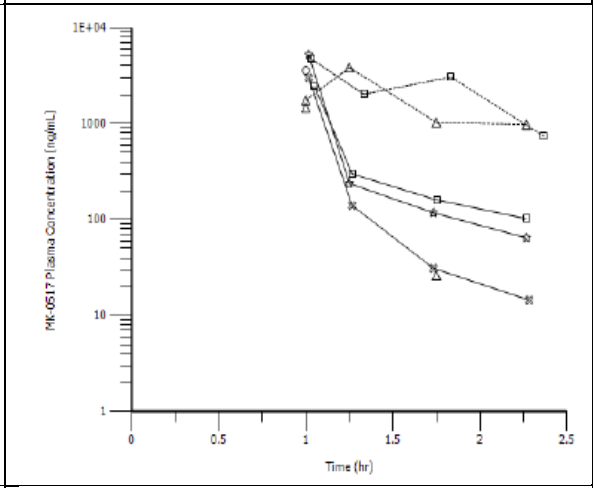
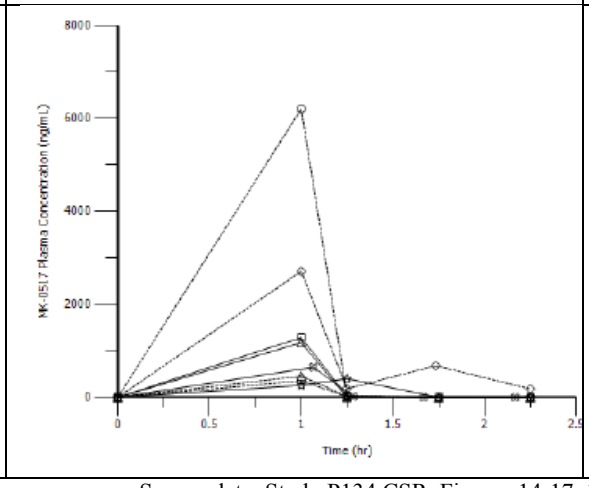
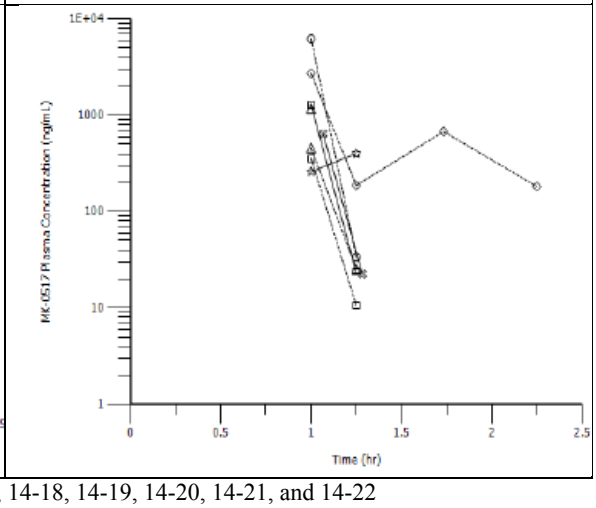
"CV%: Arithmetic Coefficient of Variation, where "CV% = SD/AM*100.

*CV%: Geometric Coefficient of Variation, where *CV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.

NR: Not reportable since <50% of the concentration results > Lower Limit of Quantitation (LLOQ).

Source data: Study P134 CSR, Table 11-16

Figure 13. The Individual Concentration-Time Profile of Fosaprepitant by Age Groups

	Linear Scale	Semi-log Scale
0.5 to < 2 years		
2 to < 6 years		
6 to < 12 years		

Source data: Study P134 CSR, Figures 14-17, 14-18, 14-19, 14-20, 14-21, and 14-22

4.3. Pharmacometrics Review

4.3.1 Sponsor's Analysis

In this section, the sponsor's verbatim text and figures are in normal font. The reviewer's comments are in Italic.

4.3.1.1 Objectives

- 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 model-based simulations to 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).

4.3.1.2 Datasets

Concentration-time data of aprepitant collected from 316 pediatric subjects with PONV and CINV from clinical studies P097, P148, P134 and P029 were used to construct the population PK model.

- Protocol P097 CINV, a PK/PD study in adolescents aged 12 – 17 years receiving the adult 3-day oral dosing regimen (final market capsules, 125 mg on Day 1, 80 mg on Days 2-3).
- Protocol P134 CINV, a study in adolescents aged 12 – 17 years receiving the adult 3-day IV EMEND regimen (115 mg IV EMEND on Day 1, 80 mg oral suspension EMEND on Days 2-3), and single doses of aprepitant as oral suspension to pediatric patients aged 6 months – 12 years (doses adjusted by body size);
- Protocol P148 Post-operative induced nausea and vomiting (PONV), a study in adolescents aged 12 – 17 years receiving the adult 40 mg capsule single dose, and pediatrics aged 2 – 12 years receiving single doses of aprepitant as oral suspension (doses adjusted by body size).

Table 40. 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) 1.17 [0.500-1.92]	4.05 (29.0) 4.08 [2.00-5.92]	9.17 (18.4) 9.33 [6.00-11.9]	14.7 (11.4) 14.5 [12.0-19.0]
Body mass index (kg/m^2)	16.9 (11.3) 16.8 [12.3-21.0]	15.4 (12.9) 15.2 [11.8-24.4]	17.0 (20.3) 16.2 [11.6-28.3]	20.2 (22.0) 19.6 [12.5-34.3]
Height (cm)	76.4 (8.7) 77.6 [63.5-88.0]	101 (9.5) 101 [83.0-125]	136 (8.9) 135 [112-165]	165 (5.3) 163 [146-185]
Weight (kg)	9.94 (18.1) 9.95 [6.80-14.3]	15.8 (23.0) 15.4 [9.20-33.8]	32.0 (31.8) 29.7 [15.9-68.4]	55.3 (26.4) 54.4 [32.0-104]

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=# (b) (6) (Study P029, 8.3 years old, female) 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.

Source data: Population PK and Simulation Report, Table 4

Table 41. 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	34(65.4%)	66(81.5%)	84(87.5%)	68(78.2%)
	Black	1(1.92%)	3(3.70%)	3(3.13%)	5(5.75%)
	Asian	7(13.5%)	4(4.94%)	5(5.21%)	2(2.30%)
	American Indian/native	1(1.92%)	0	0	1(1.15%)
	Multi/Other	9(17.3%)	8(9.88%)	4(4.17%)	11(12.6%)
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=# (b) (6) Study P029, 8.3 years old, female) 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.

Source data: Population PK and Simulation Report, Table 5

4.3.1.3 Model

All PK data were evaluated using nonlinear mixed-effects modeling implemented in NONMEN v7.3 with first order conditional estimation (FOCE) interaction and Perl speaks NONMEM (PsN) v4.4.8 software. Dataset preparation, exploration and visualization of the data were performed using R® V3.3.1 with comprehensive R archive network (CRAN) and Certara Strategic Consulting (CSC) packages.

The population pharmacokinetic model previously developed based on final locked data of studies P097 P134 and P148 with was used as a starting point.

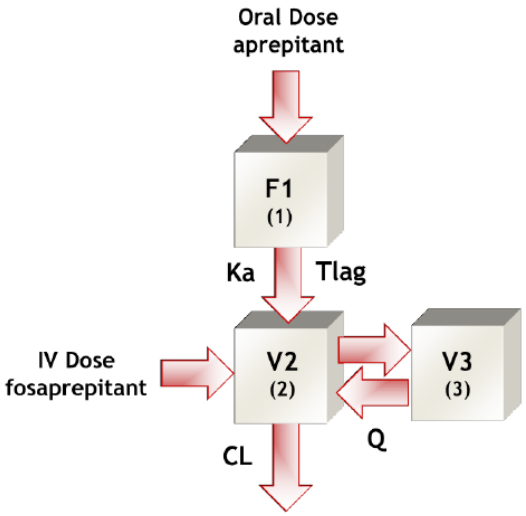
Reviewer's comment: This model was used to support the approval of oral Emend in pediatric patients. Refer to Clinical Pharmacology Review of NDA21549/S-025 (Efficacy Supplement of Emend oral capsules) and original NDA 207865 (Emend oral suspension) for details.

The structural model was a 2-compartment linear model with first-order rate of absorption and lag-time of absorption. The structural model included 1) effect of formulation on Tlag to adequately capture the delay caused by the degradation of the capsule administrated to adolescents (Study P097); 2) 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).

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

ADVAN4 and TRANS4 NONMEM subroutines were used to allow for a closed-form solution and simultaneous fit of oral (aprepitant) and IV (fosaprepitant) data, as well as relative bioavailability estimation. Log10-transformed concentration data and actual observation time were used as the model input. Log-additive model for the residual error allowed using FOCE estimation method without INTERACTION term.

Table 42. The Schematic Drawing of the Structure Model



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.

Source data: Population PK and Simulation Report, Figure 2

The final population PK model included the following covariate effects:

- Age on V2: × (Age/8)-0.205 with 95CI%= (-0.288, -0.122),
- Dose on CL: × (Dose/80)-0.253 with 95CI%= (-0.333, -0.172)
- Formulation on Ka with capsule (P097) for reference: × exp(0.369) for suspension (P134) with 95%CI=(-0.363, 1.10) and × exp(0.821) for suspension for excipients (P148) with 95CI%= (0.0228, 1.62)
- Reduced level of EDTA (P029) on CL: × exp(-0.295) for Study P029 with 95%CI=(-0.421, -0.168)

4.3.1.4 Results

4.3.1.4.1 Base model

Table 43. Typical Values for the Structure (Base) Population PK Model of Aprepitant/Fosaprepitant

Parameter	Units	Estimate	SE	RSE	Shrinkage	Equation
OFV		-4037.3347				
CL	L/h	5.25	0.228	4.4%		$CL = tvCL \times (Weight/70)^{0.75} \times \exp(\eta_{CL})$
V2	L	46.3	5.96	12.9%		$V2 = tvV2 \times (Weight/70) \times \exp(\eta_{V2})$
Q	L/h	45.3	12.1	26.6%		$Q = tvQ \times (Weight/70)^{0.75} \times \exp(\eta_{Q})$
V3	L	41.5	6.53	15.7%		$V3 = tvV3 \times (Weight/70) \times \exp(\eta_{V3})$
Ka	1/h	0.588	0.0887	15.1%		$Ka = tvKa \times \exp(\eta_{Ka})$
Tlag – suspension	h	0	fixed	.		$Tlag = 0$
Tlag - capsule	h	0.947	0.0216	2.3%		$Tlag = Caps\_Tlag$
F1		0.839	0.0606	7.2%		$F1 = tvF1 \times \exp(\eta_{F1})$
IIV CL		64.7%	0.0619	14.8%	10.2%	ω^2_{CL}
IIV V2		65.5%	0.0782	18.2%	22.7%	ω^2_{V2}
IIV Q		84.0%	0.273	38.6%	59.6%	ω^2_{Q}
IIV V3		54.4%	0.0849	28.7%	35.9%	ω^2_{V3}
IIV Ka		108.4%	0.253	21.5%	51.0%	ω^2_{Ka}
IIV F1		56.4%	0.101	31.9%	51.2%	ω^2_{F1}
Log10ResErr		0.161	.		17.6%	$\log_{10}(C_{obs}) = \log_{10}(C_{pred}) + Log10ResErr$

CL = Systemic clearance; F1 = Relative bioavailability for oral administration; IIV = Inter-individual variability; Ka = First-order rate constant of absorption; Log10ResErr= Log-Additive Residual Error; 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; tvKa = Typical value of first-order rate constant of absorption; 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 $100\% \times (\omega^2)^{0.5}$.

Source data: Population PK and Simulation Report (04lvbw), Table I-1

4.3.1.4.2 Final model

Table 44. Typical Values for the Final Population PK Model of Aprepitant/Fosaprepitant

Parameter	Units	Estimate	SE	RSE	Shrink	Equation
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, study 134)		0.369	0.374	101.3%		Ka=Ka×exp(Form_Ka)
Form_Ka (Excipients, study 148)		0.821	0.407	49.6%		Ka=Ka×exp(Form_Ka)
EDTA_CL (study 029)		-0.295	0.0645	21.9%		CL=CL× exp(EDTA_CL for low – P029)
IIV CL		0.369(60.7%)	.0564	15.3%	11.0%	ω^2_{CL}
IIV V2		0.346(58.8%)	0.0641	18.5%	21.4%	ω^2_{V2}
IIV Q		0.521(72.2%)	0.257	49.4%	64.5%	ω^2_{Q}
IIV V3		0.380(61.6%)	0.0934	24.6%	34.1%	ω^2_{V3}
IIV Ka		1.07(103.6%)	0.231	21.6%	50.2%	ω^2_{Ka}
IIV Tlag		0.00	fixed;			ω^2_{Tlag}
IIV F1		0.304(55.1%)	0.0969	31.9%	51.3%	ω^2_{F1}
Log10ResErr		0.159		.	17.2%	log10(Cobs) = log10(Cpred)+Log10ResErr

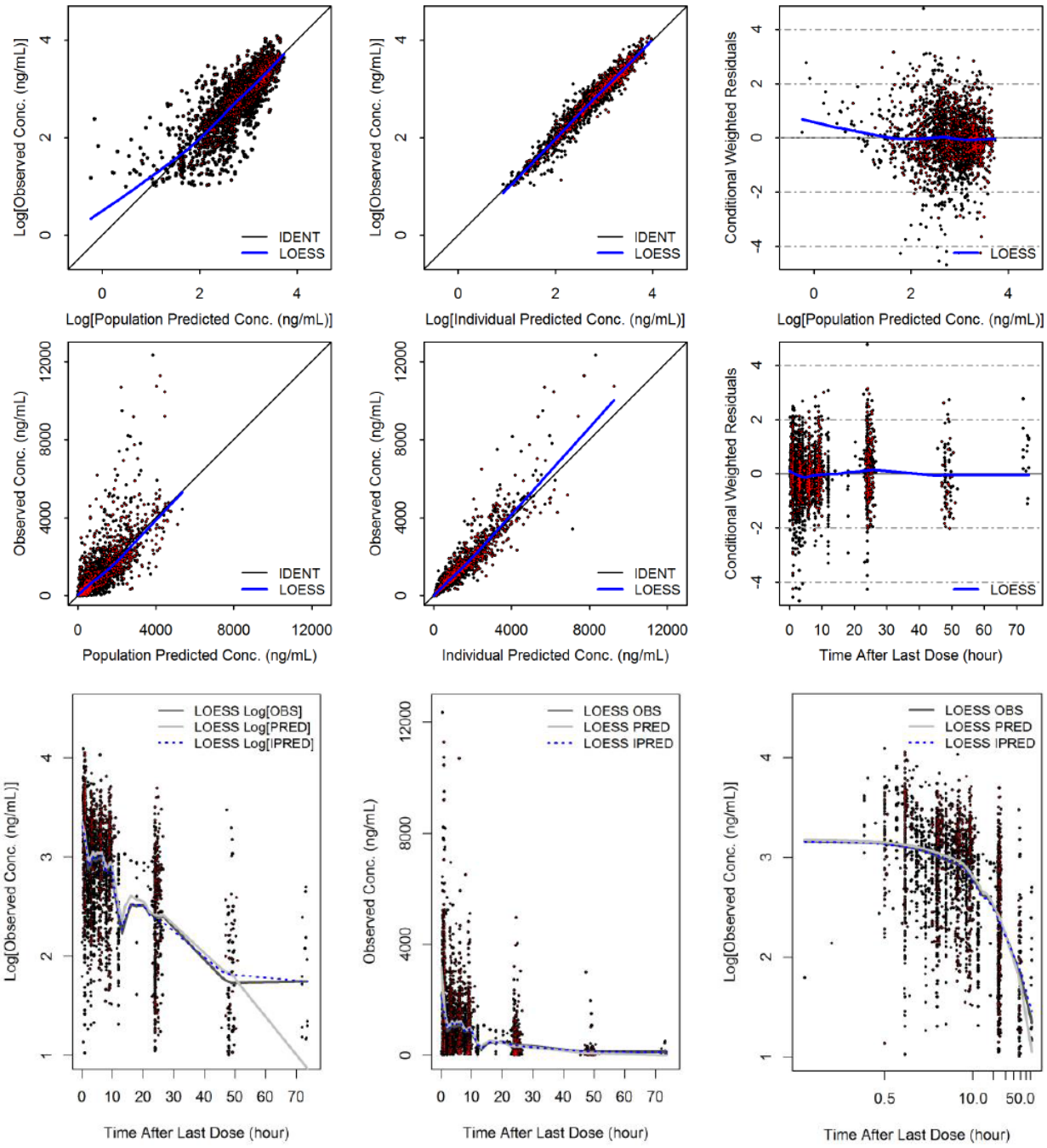
AGE_V2= Effect of age on central volume of distribution; CL = Systemic clearance; Dose_CL= Effect of dose on systemic clearance; EDTA_CL= Effect of ethylenediaminetetraacetic acid on systemic clearance; F1 = Relative bioavailability for oral administration; Form_Ka= Effect of formulation on the first-order rate constant of absorption; IIV = Inter-individual variability; Ka = First-order rate constant of absorption; Log10ResErr= Log-Additive Residual Error; 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; tvKa = Typical value of first-order rate constant of absorption; 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 $100\% \times (\omega^2)^{0.5}$.

Source data: Population PK and Simulation Report, Table I- 5

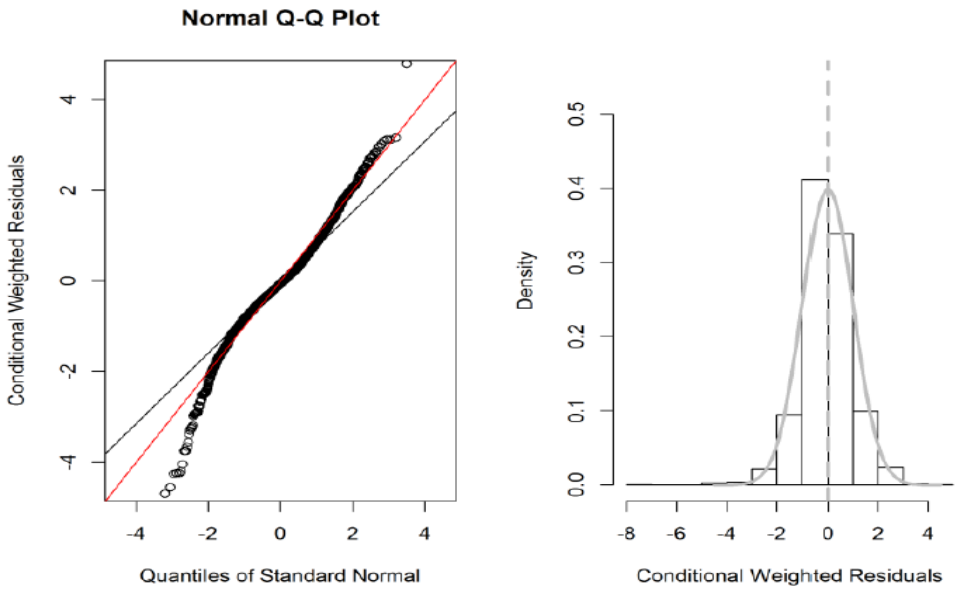
4.3.1.4.3 Model Evaluation

Figure 14. Diagnostic Plots for Final Population Pharmacokinetic Model of Aprepitant in Pediatric Population: Goodness-of-Fit



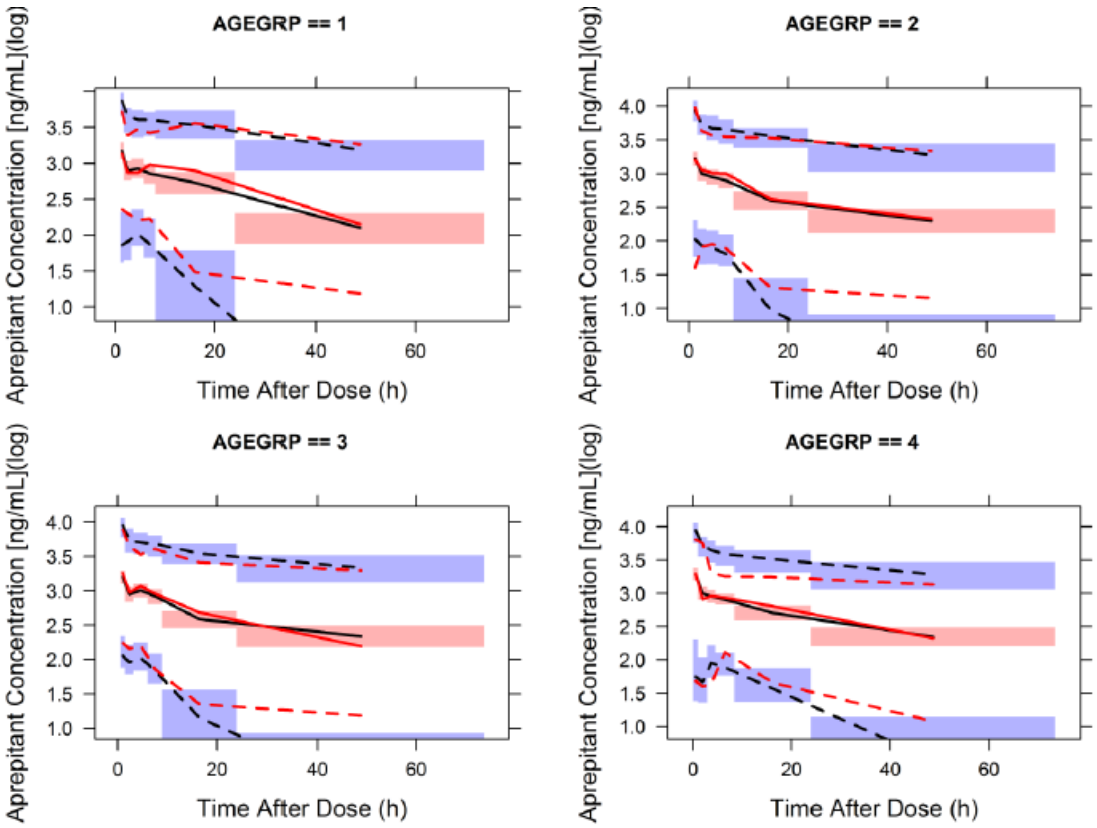
Source data: Table I-42, Table I-43

Figure 15. Diagnostic Plots for Final Population Pharmacokinetic Model of Aprepitant in Pediatric Population: Goodness-of-Fit



Source data: Table I-44

Figure 16. Visual Predictive Check – Final Population PK Model (Linear Scale, Locked Data P029)



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).

The visual predictive check (VPC) plot showed that the observed 2.5th, 50th and 97.5th percentiles of concentrations in each age bin were almost all within the 95%CI of the corresponding simulated percentiles. However, the 2.5th percentile of the observed concentration 24 hour after the dose was higher than the 95%CI of the simulated 2.5th percentiles and the simulated concentrations after 24 h under-estimated the observed concentrations. Due to the limited number of PK samples in this time range (*Reviewer's note: only Cmin at Hour 24, 48, and 72 were measured in all the pediatric studies*).

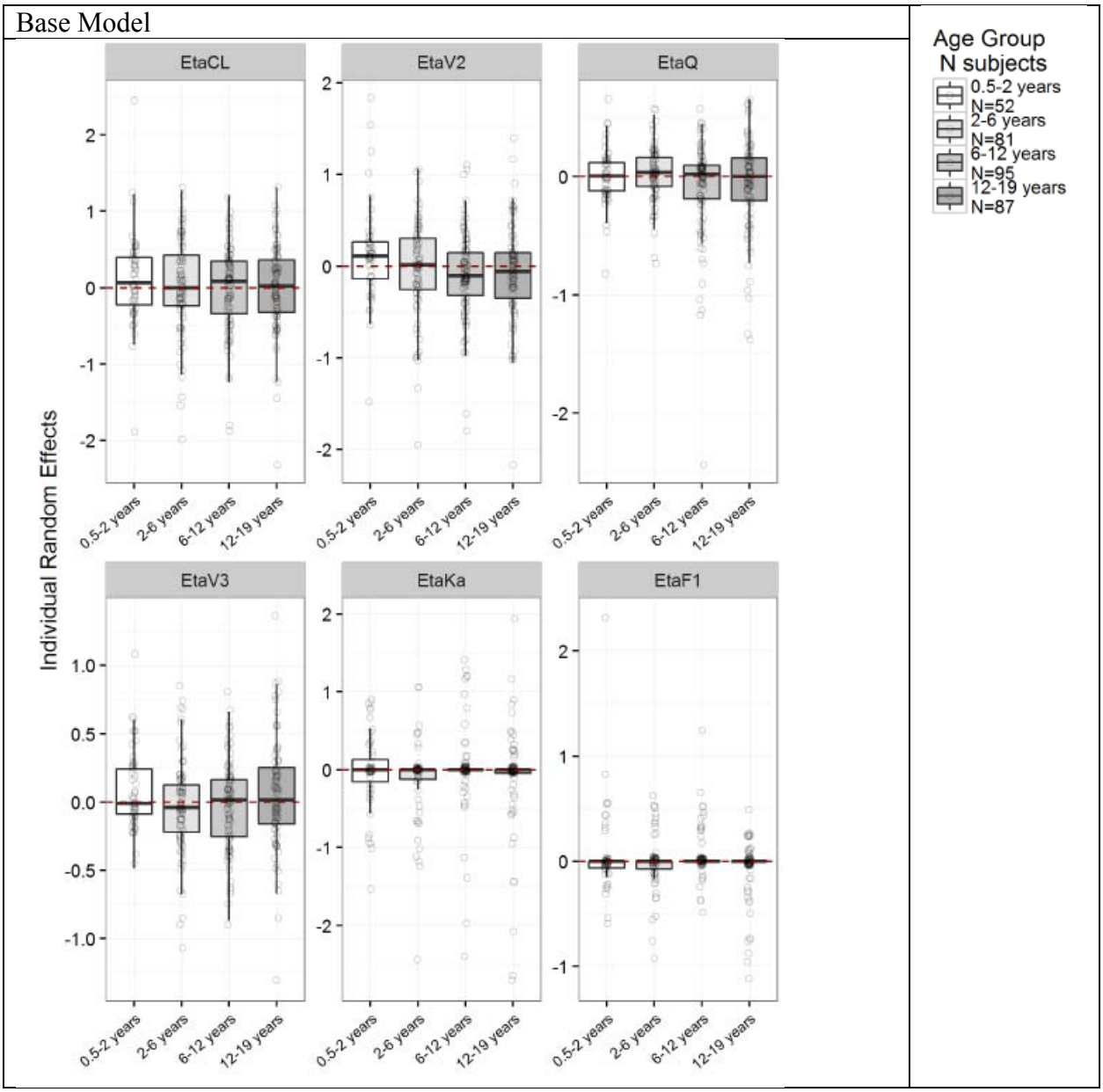
Reviewer's comment: The VPC was conducted following single dose of IV fosaprepitant and compared to the observed data from Study P029, a single-dose dose ranging study. This is acceptable as P029 enrolled all age groups. For all the pediatric studies, only single IV doses of fosaprepitant were used.

4.3.1.4.4 Covariates Effect

The final population PK model included the following covariate effects:

- Age on V2: × (Age/8)-0.205 with 95CI%= (-0.288, -0.122),
- Dose on CL: × (Dose/80)-0.253 with 95CI%= (-0.333, -0.172)
- Formulation on Ka with capsule (P097) for reference: × exp(0.369) for suspension (P134) with 95%CI=(-0.363, 1.10) and × exp(0.821) for suspension for excipients (P148) with 95CI%= (0.0228, 1.62)
- Reduced level of EDTA (P029) on CL: × exp(-0.295) for Study P029 with 95%CI=(-0.421, -0.168)

Figure 17. Relationship between Age and Individual Random Effect – Base vs. Final Population PK Model



Final Model

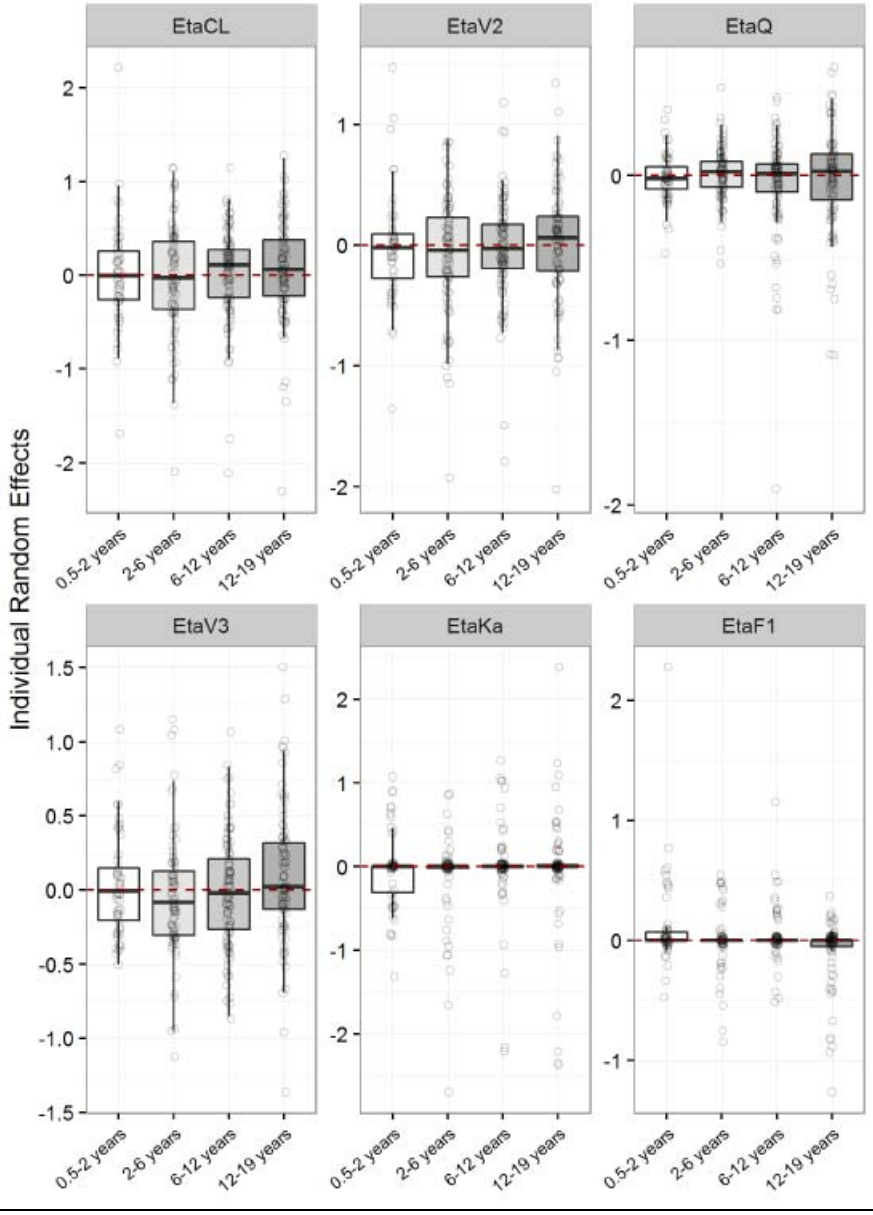
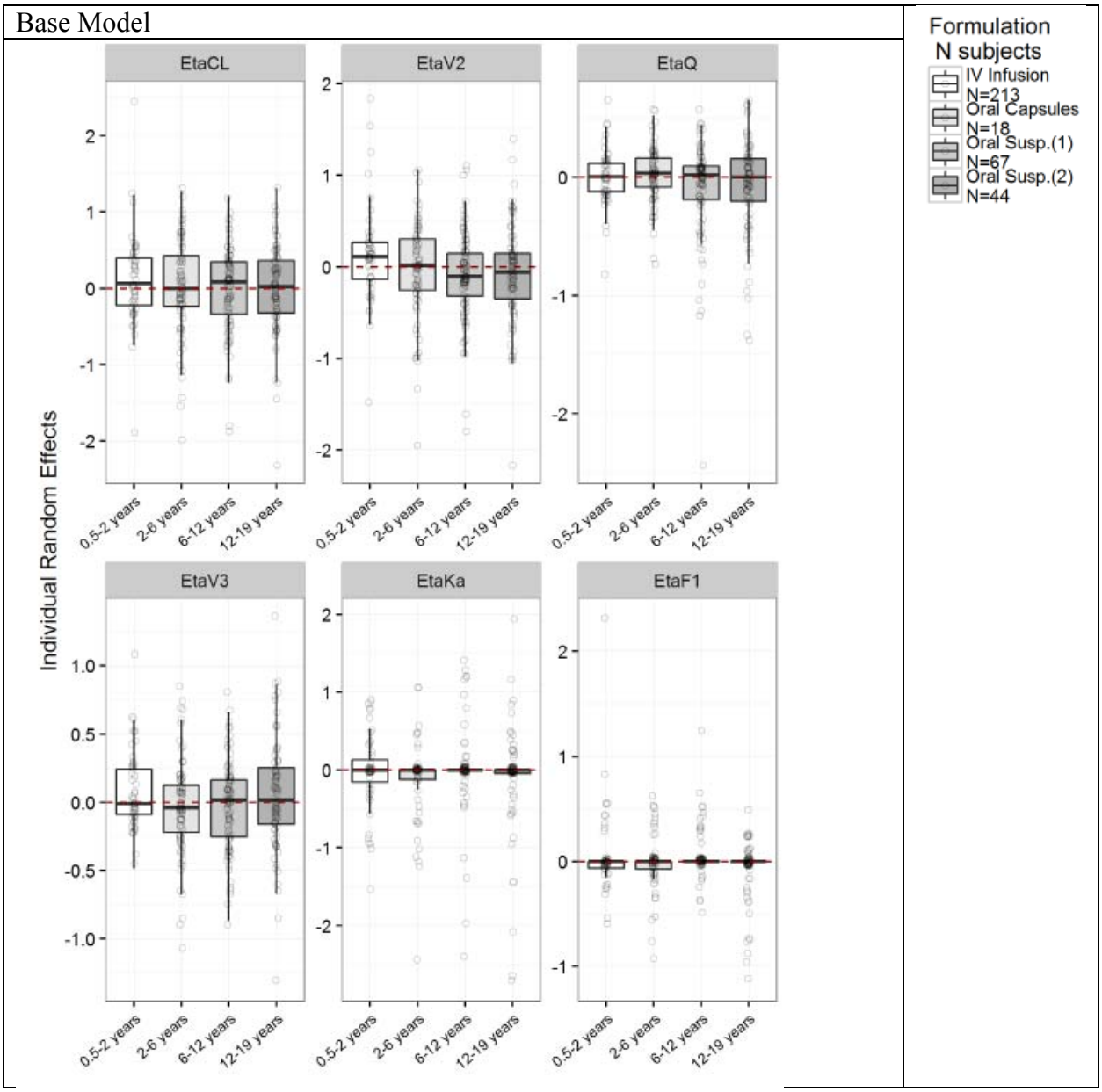

EtaCL
EtaV2
EtaQ
EtaV3
EtaKa
EtaF1
Individual Random Effects
0.5-2 years
2-6 years
6-12 years
12-19 years

Figure 18. Relationship between Formulation and Individual Random Effect – Base vs. Final Population PK Model



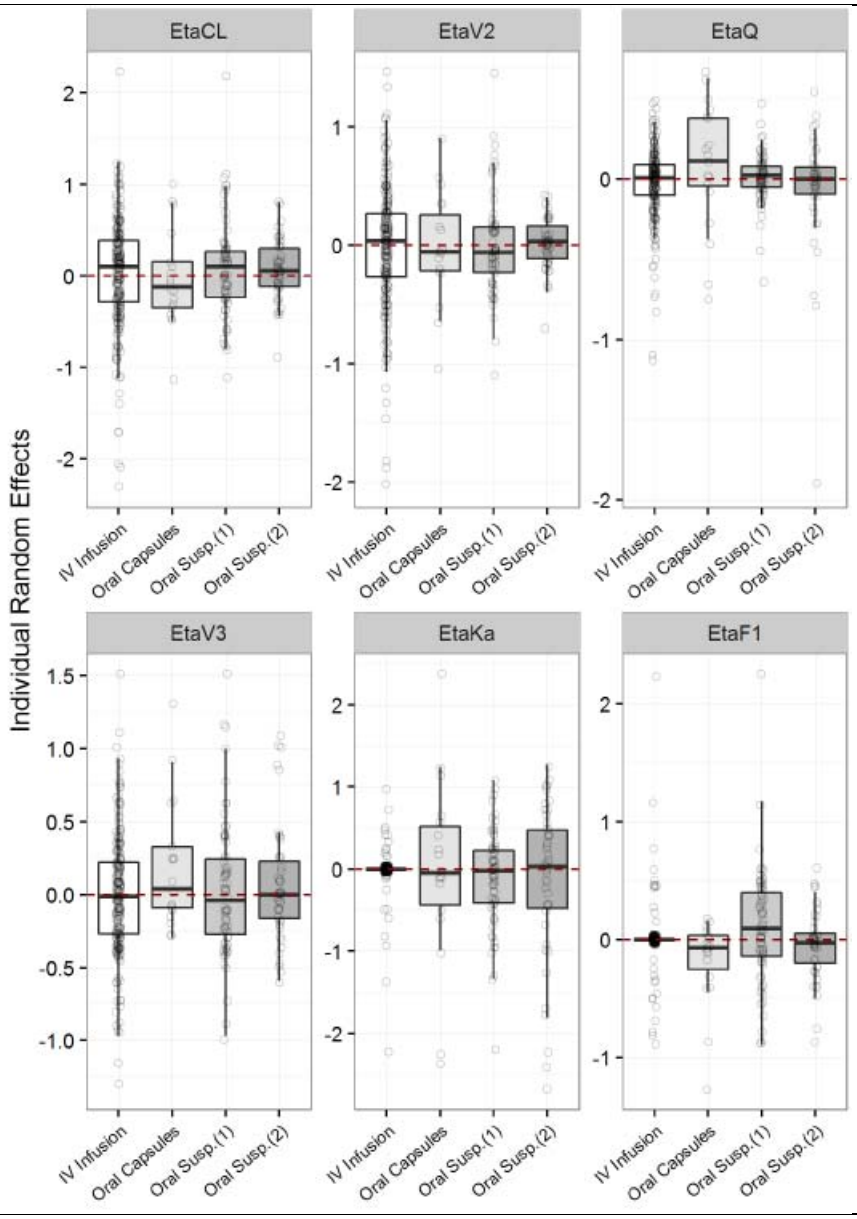
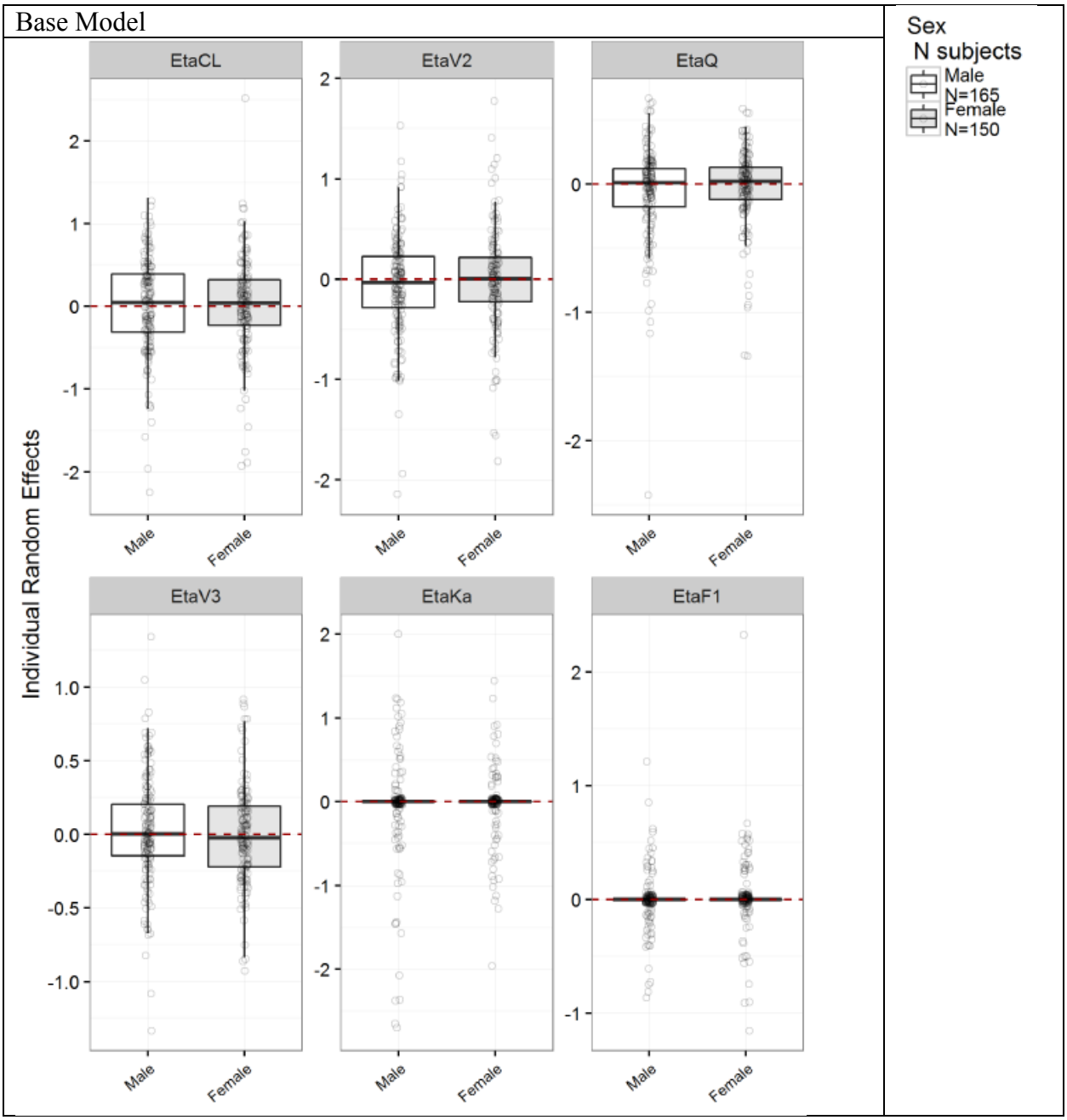
Final Model	
 EtaCL EtaV2 EtaQ EtaV3 EtaKa EtaF1 Individual Random Effects IV Infusion Oral Capsules Oral Susp.(1) Oral Susp.(2)	

Figure 19. Relationship between Sex and Individual Random Effect – Base vs. Final Population PK Model



Final Model

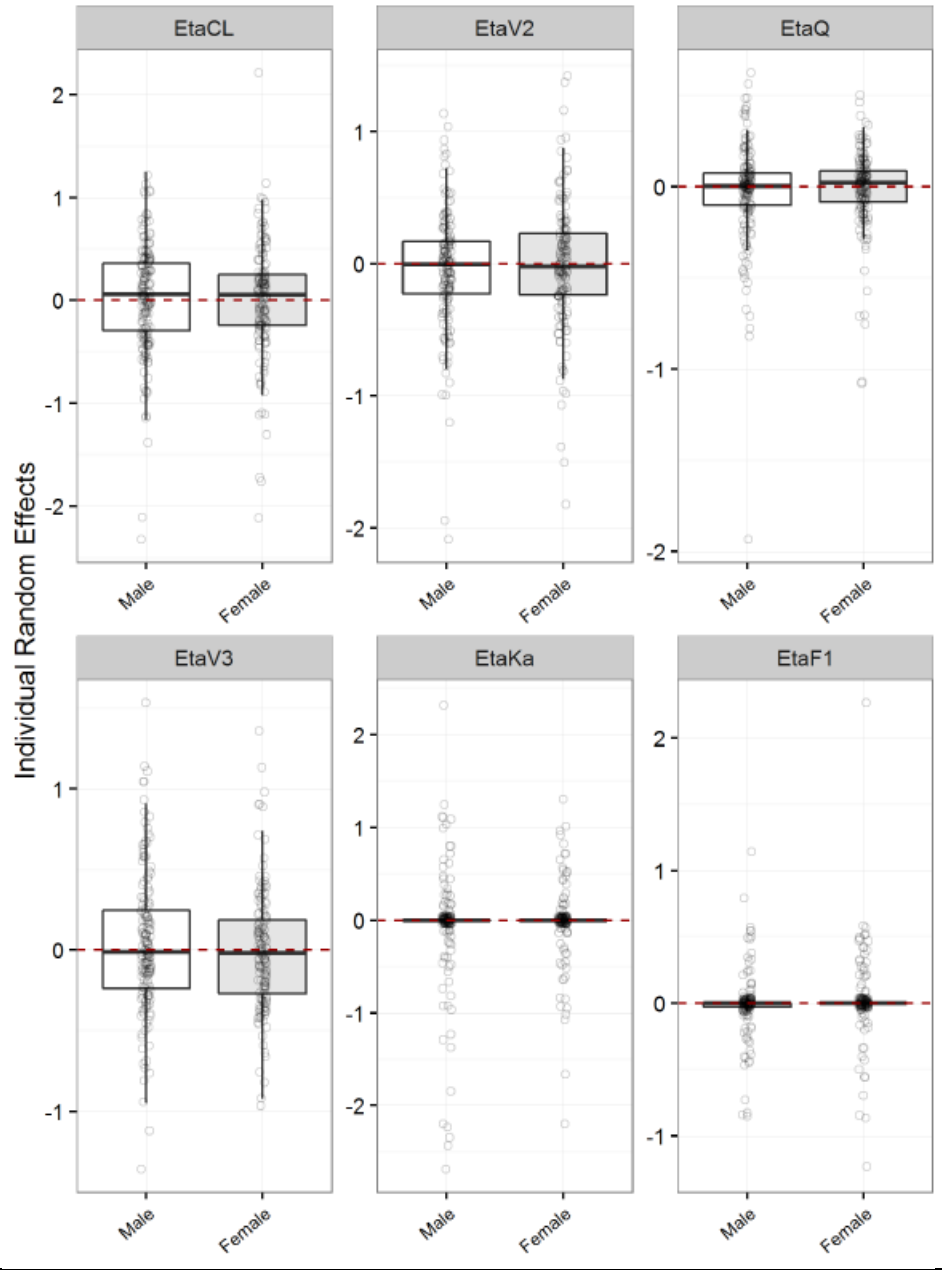
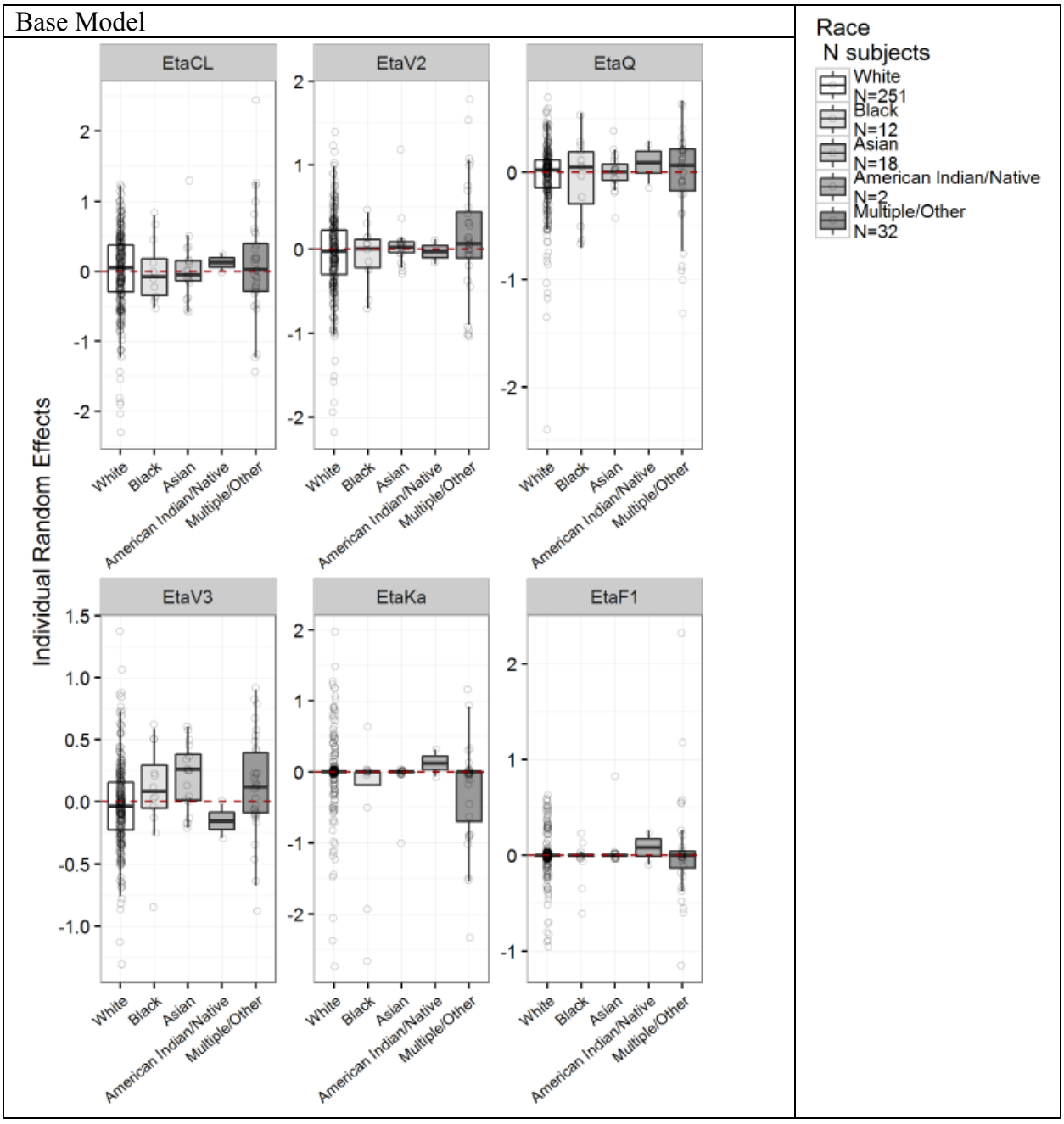


Figure 20. Relationship between Race and Individual Random Effect – Base vs. Final Population PK Model



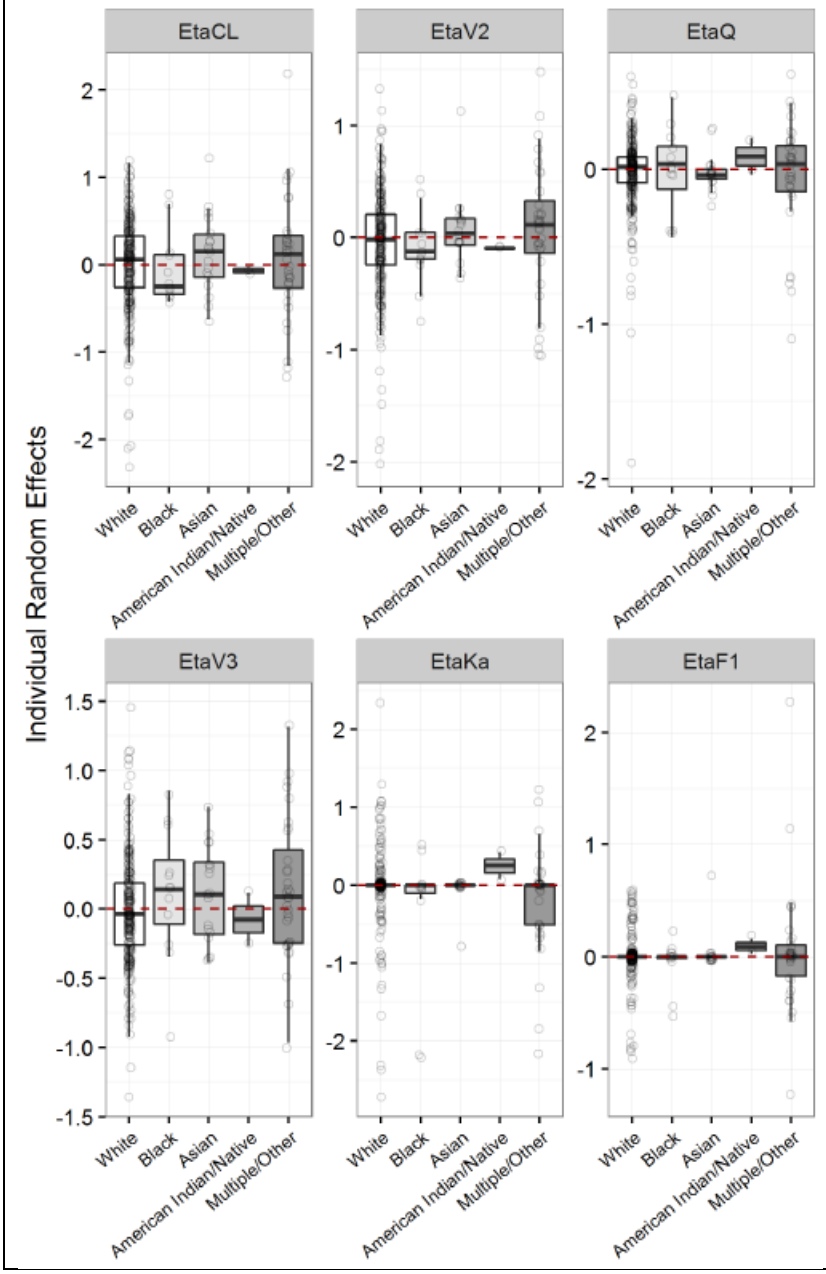
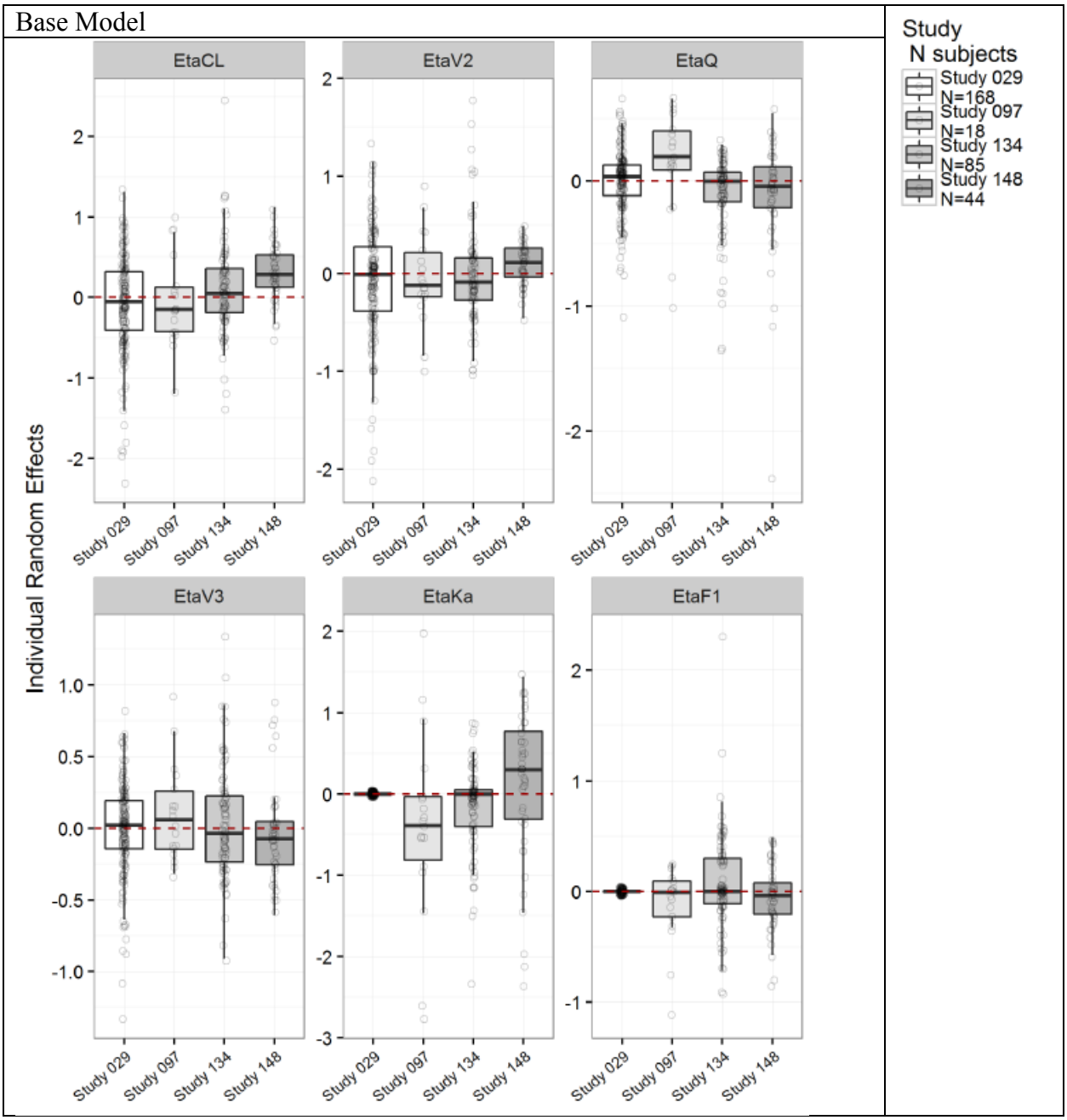
Final Model	
	

Figure 21. Relationship between Study and Individual Random Effect – Base vs. Final Population PK Model



Final Model

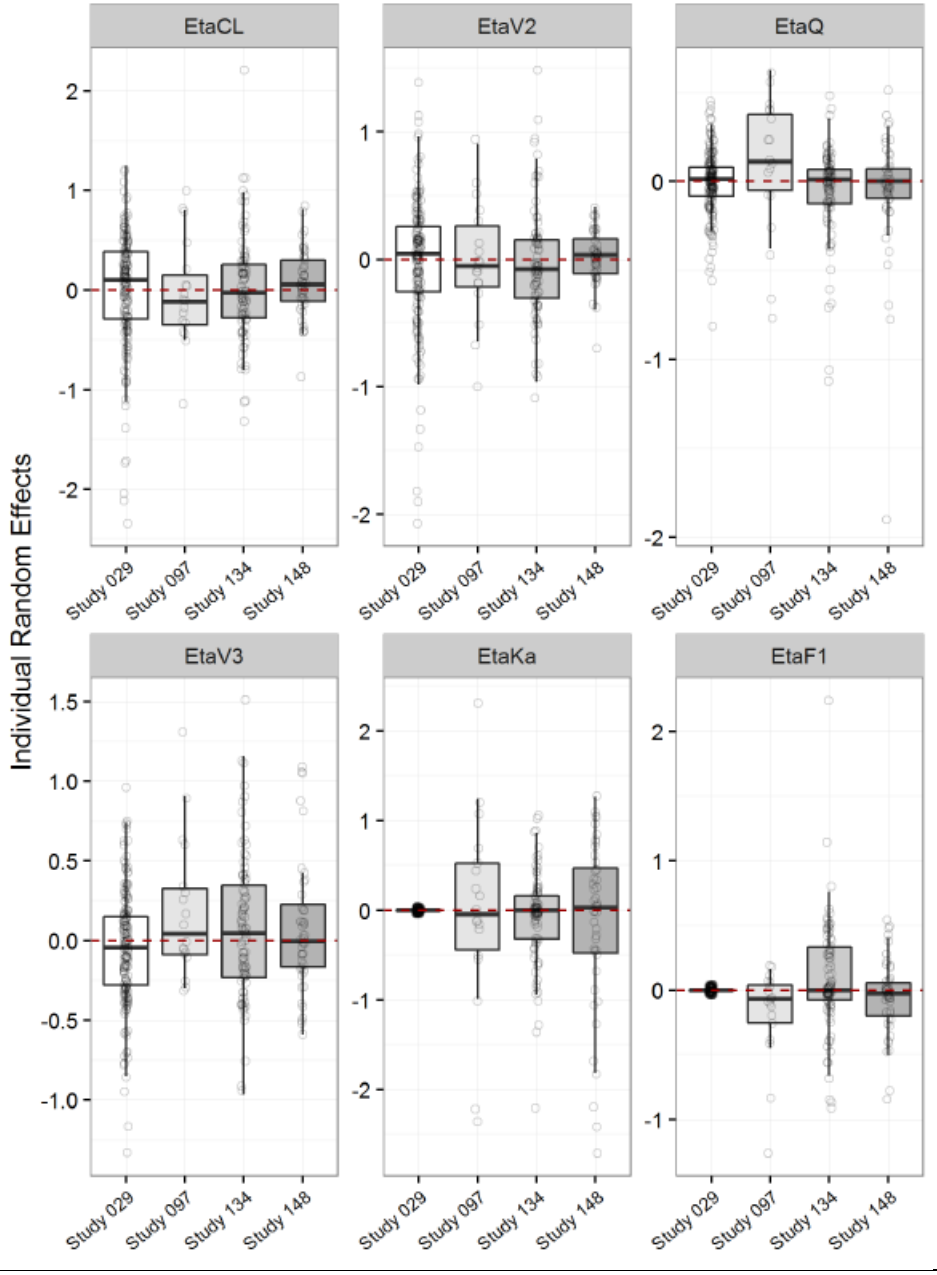
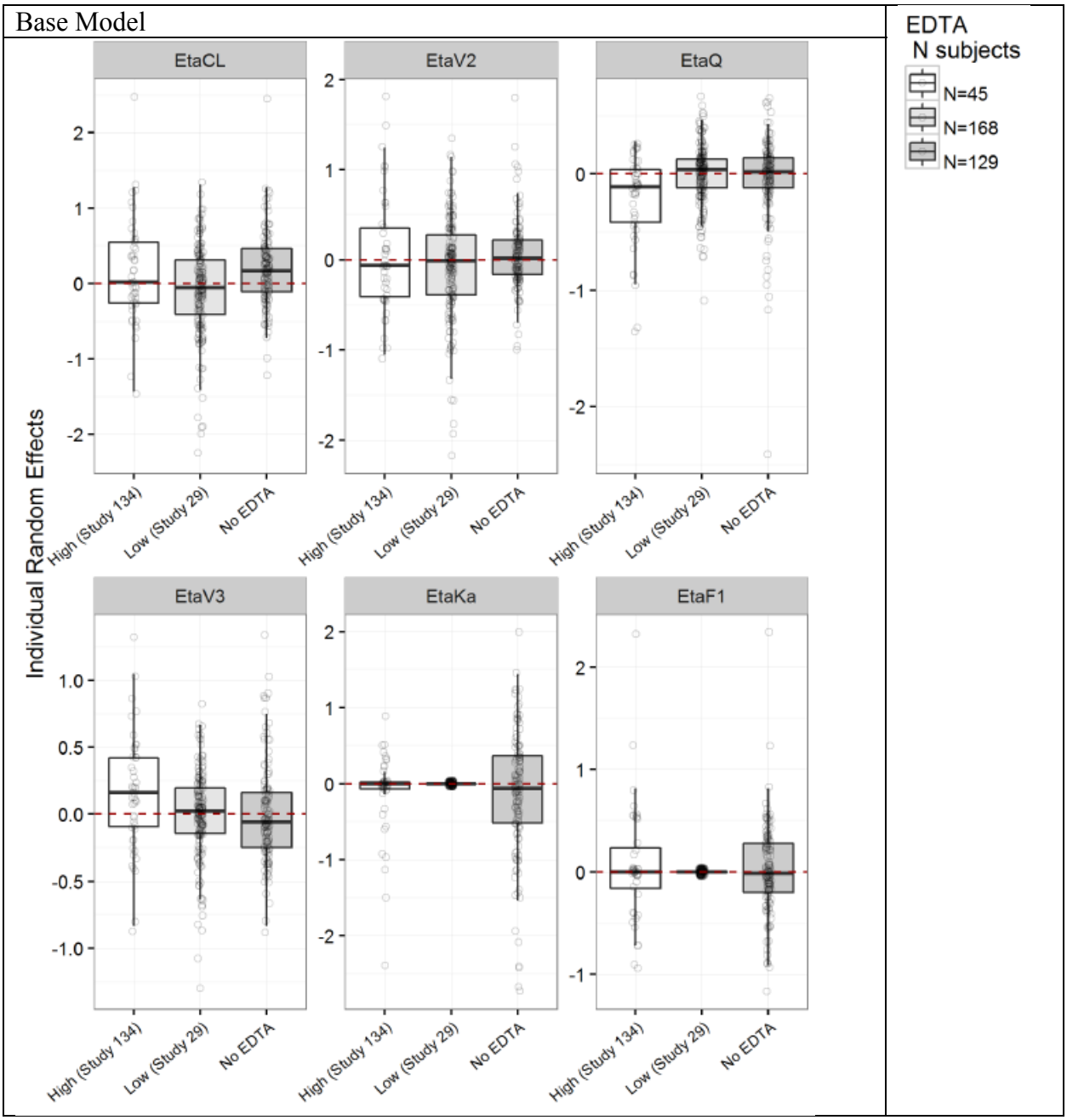
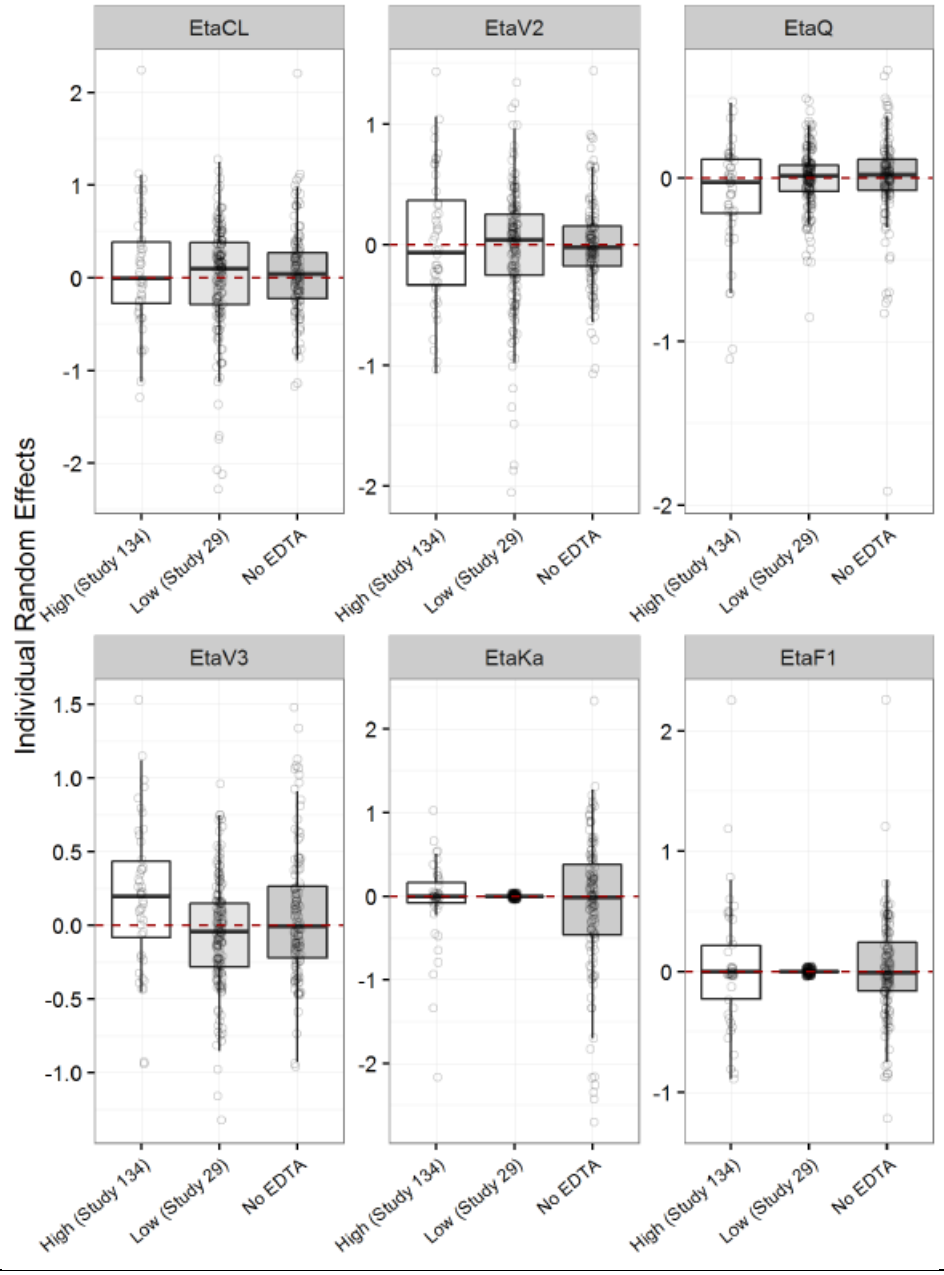


Figure 22. Relationship between Amount of EDTA and Individual Random Effect – Base vs. Final Population PK Model



Final Model



Reviewer's overall assessment: the population PK model was acceptable for the description of aprepitant PK in the product label and simulations for the exposure matching of aprepitant. No additional model development by the reviewer was required.

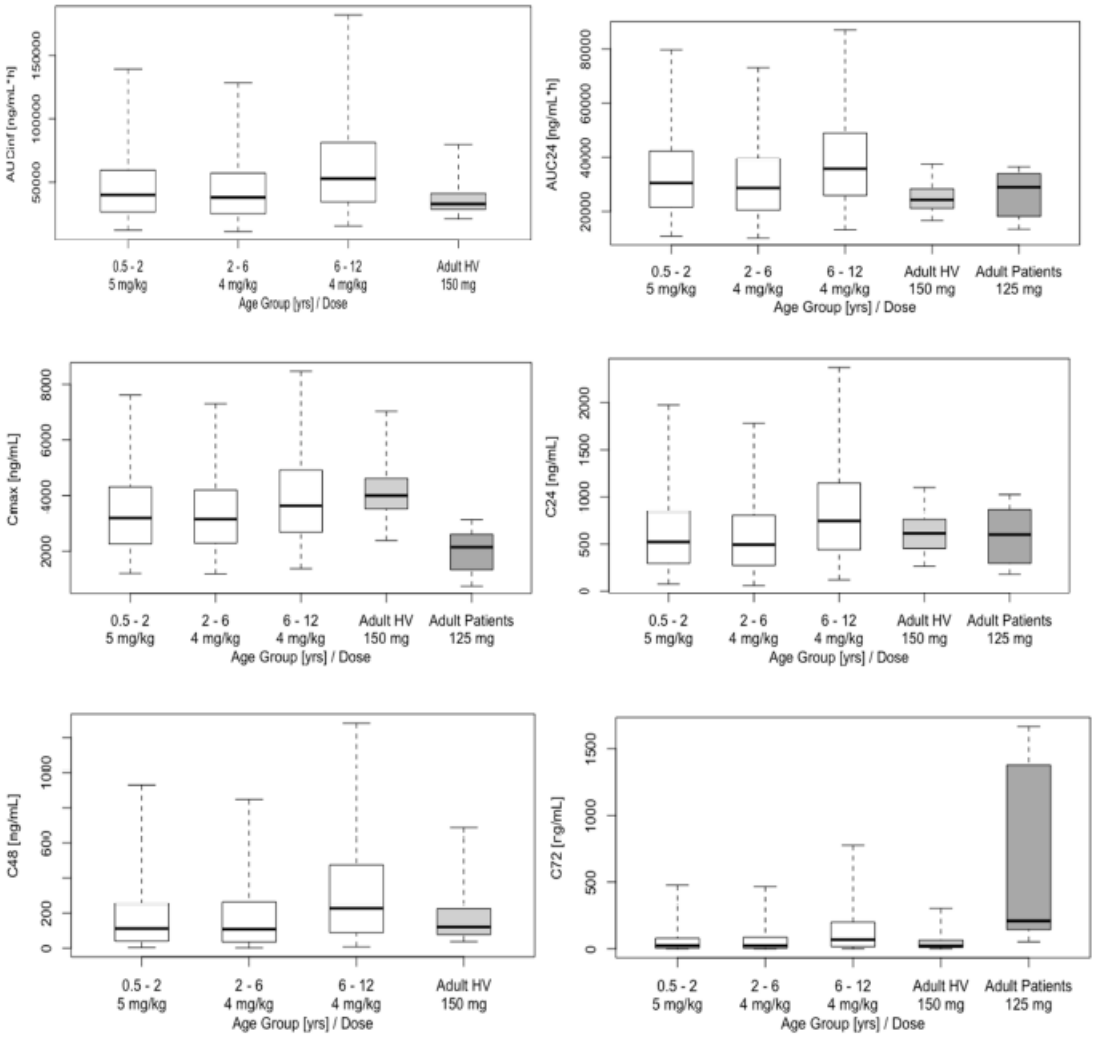
4.3.1.5 Simulation to Support Dose Selection

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/PONV pediatric patients

The results of simulation support the dosing recommendation. Summary plots for the exposure comparisons are presented in Figure 23 and Figure 24.

Single-day regimen

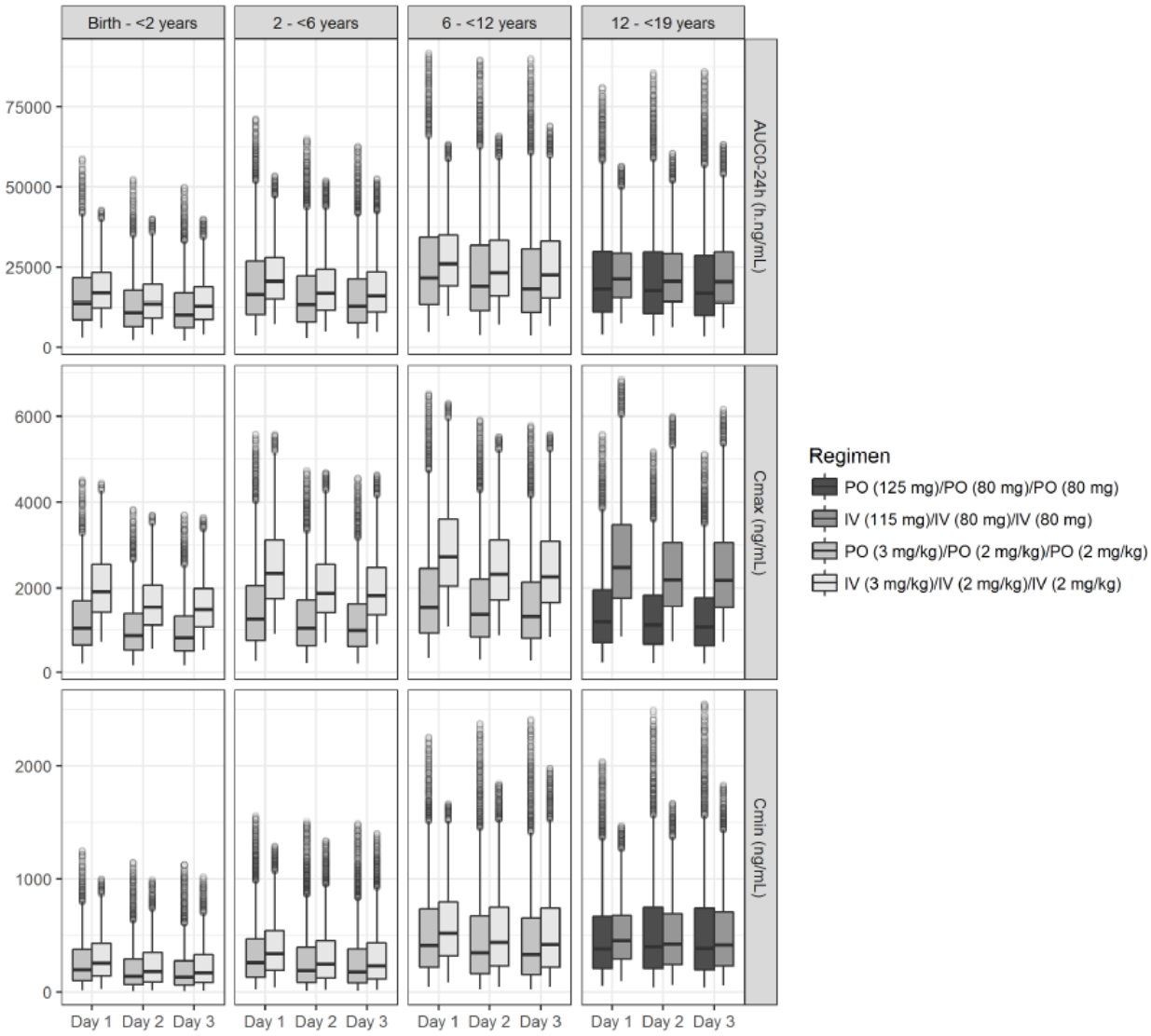
Figure 23. Comparison of Observed 1-day 150 mg IV Fosaprepitant Regimen in Adult Healthy Volunteers, Single Dose 125 mg Oral Aprepitant in Adult Cancer Patients with Model- Simulated Aprepitant PK Parameters (AUCinf, AUC24, Cmax, C24, C48, C72) After Administration of 4 mg/kg in Pediatric Subjects 2 to 12 Years Old and 5 mg/kg in <2 Years Old Subjects (Revised from the Original Figure 2.7.2: 4 without extremes)



Source data: Response to IR on January 12 2018 (SDN570), Figure 2.7.2:4a

Three-day regimen

Figure 24. Comparison of 3-day Oral Aprepitant Regimens in Adolescent (125 mg on Day 1 and 80 mg on Days 2 and 3) and Pediatric Subjects <12 Years Old (3 mg/kg on Day 1 ad 2 mg/kg on Days 2 and 3) with Simulated 3-day IV Fosaprepitant Regimens, 115 mg on Day 1 and 80 mg on Days 2 and 3 in Adolescents and 3 mg/kg and 2 mg/kg on Days 2 and 3 in Pediatric Subjects < 12 Years Old

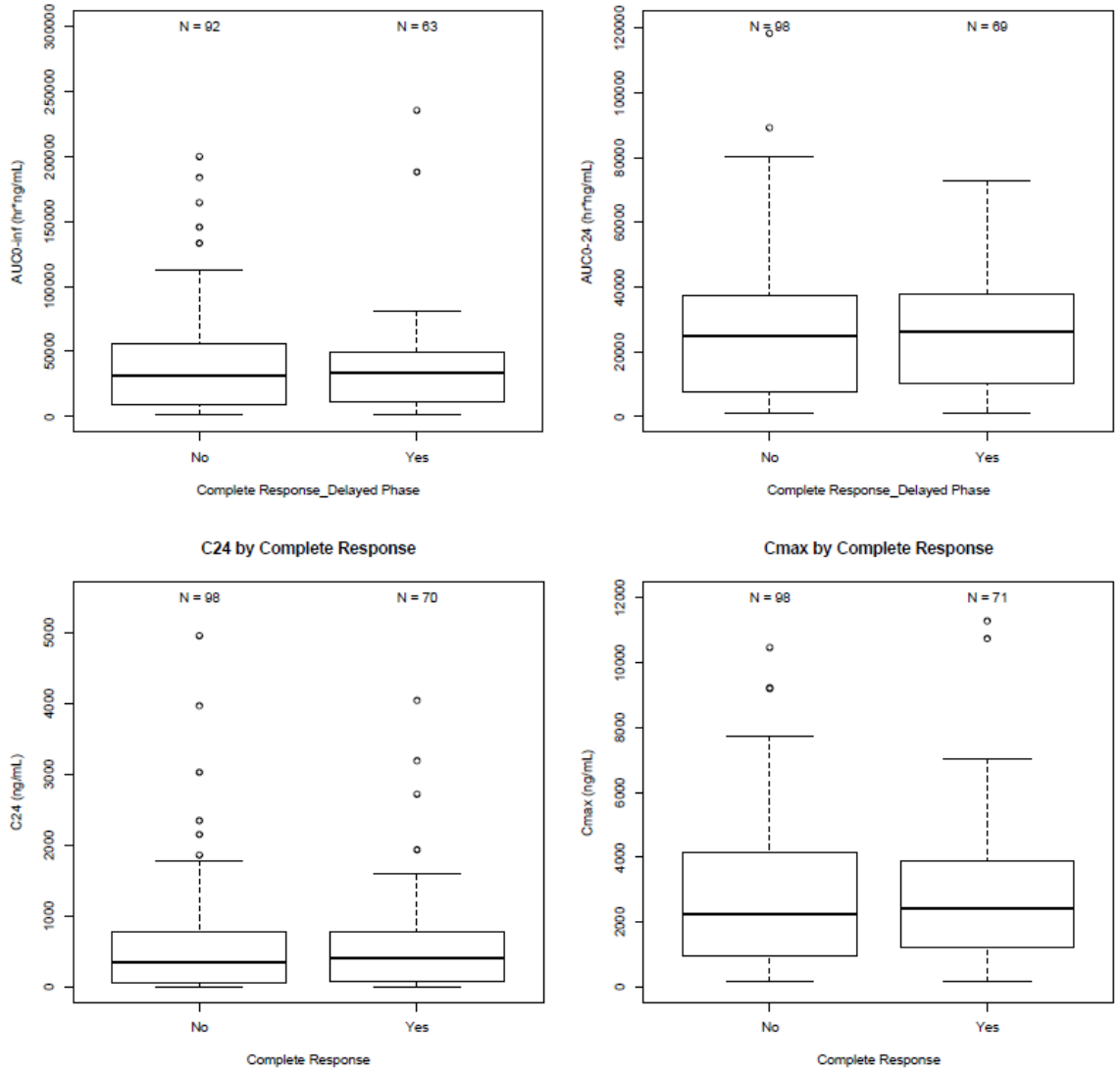


Source data: Section 2.7.2 Summary of Clinical Pharmacology, Figure 2.7.2:5

4.3.1.6 Exposure-Response Analysis for Study P029

Aprepitant exposure (AUC0-inf, AUC0-24, Cmax, and C24) versus the clinical endpoint (yes/no) (**Figure 25**), percent of patients with clinical endpoint (yes only) versus aprepitant exposure (grouped in deciles) (**Figure 26**) and percent of patients with the clinical endpoint (yes/no) by aprepitant exposure (grouped as quartiles) (**Figure 27**) were evaluated.

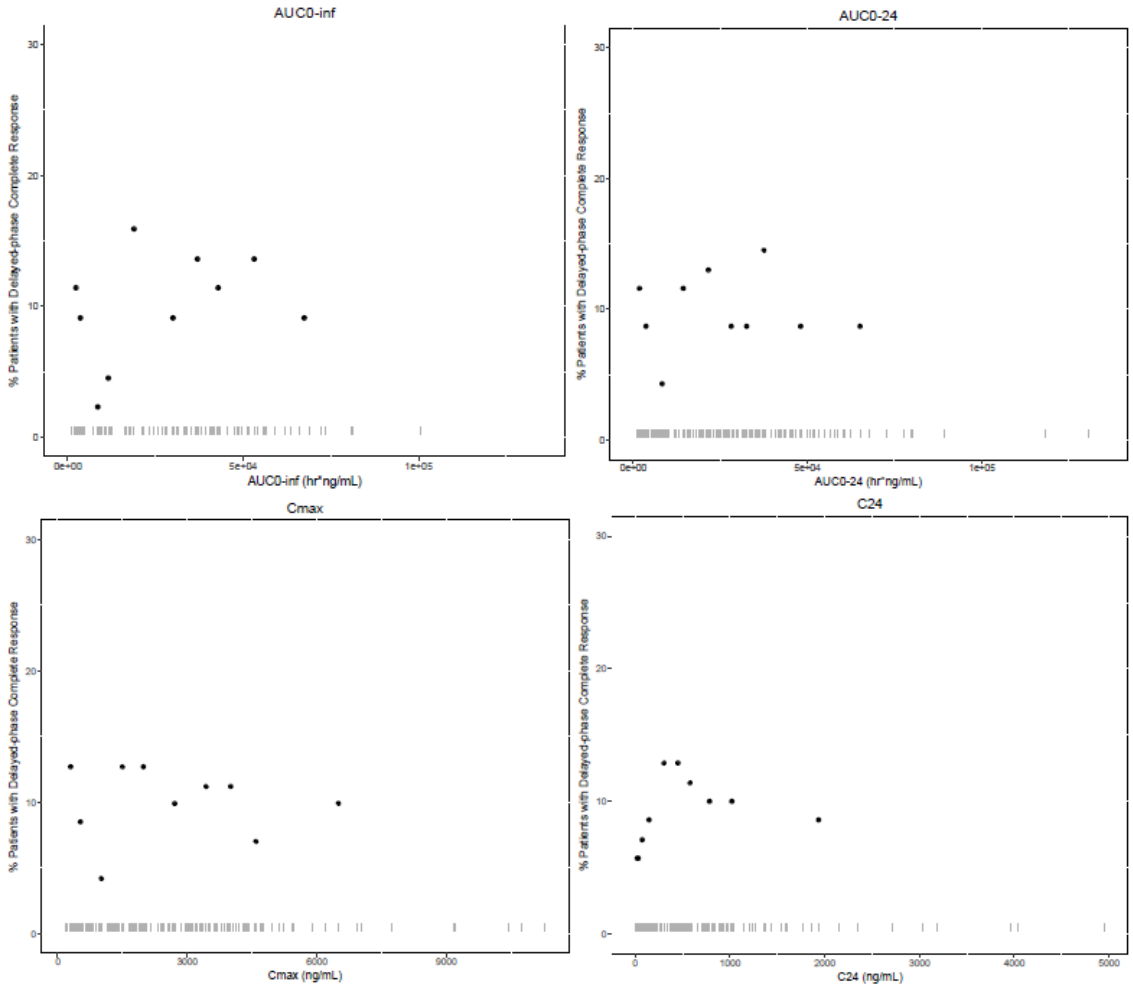
Figure 25. Exploration of Exposure-Response from Protocol 029 Based Upon Aprepitant Exposure (AUC0-inf, AUC0-24, Cmax and C24) versus Complete Response in the Delayed Phase (yes/no)



$AUC_{0\text{-}inf}$= Area under the curve of concentration-time curve from zero to infinity; $AUC_{0\text{-}24}$ =Area under the curve of concentration-time at day 1; C_{max}= Maximum concentration on day 1; C_{24}= Concentration at 24 hours. Boxplots represent interquartile range (box), with the lower whisker denoting values within the first quarter (Q1) - 1.5 * IQR and the upper whisker denoting values within the third quarter (Q3) + 1.5 * IQR and symbols representing values outside of this range of data.

Source data: Response to IR submitted on 2/12/2018, Figure 1

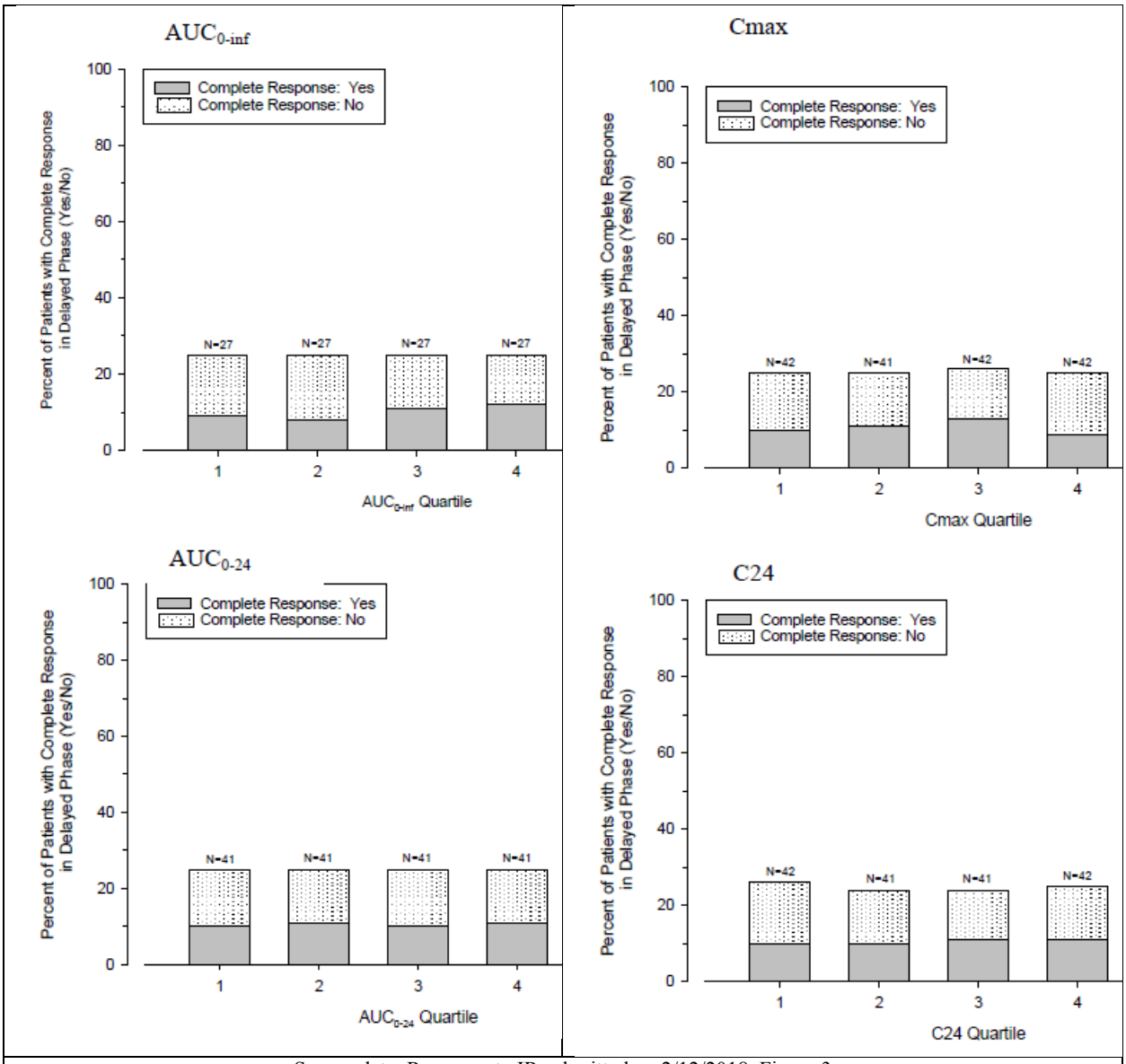
Figure 26. Percent of Patients with Complete Response in the Delayed Phase (yes only) versus Aprepitant Exposure (AUC0-inf, AUC0-24, Cmax and C24, grouped in deciles)



$AUC_{0\text{-}inf}$= Area under the curve of concentration-time curve from zero to infinity; $AUC_{0\text{-}24}$ =Area under the curve of concentration-time at day 1; C_{max}= Maximum concentration on day 1; C_{24}= Concentration at 24 hours. Black dots represent the median of PK parameter values when grouped by deciles. Grey vertical lines denote the entire range of individual PK parameter values.

Source data: Response to IR submitted on 2/12/2018, Figure 2

Figure 27. Percent of Patients with Complete Response in the Delayed Phase (yes/no) versus Aprepitant Exposure (AUC0-inf, AUC0-24, Cmax and C24, grouped in quartiles)



Source data: Response to IR submitted on 2/12/2018, Figure 3

The relationship between Complete Response Rate and single fosaprepitant dose in Cycle 1 from Study P029 are shown in Table 45. It is noteworthy that the study was not powered to measure efficacy, and the open-label amendment (5 mg/kg dose cohort) was not blinded and did not have a control regimen for comparison.

Table 45. Number (%) of Subjects with Complete Response in Cycle 1 by Treatment Regimen Intent to Treat Population

Delayed Phase

Treatment	n/m (%)	Difference (%)†	95% CI for Difference (%)‡
Partially Blinded:			
Fosaprepitant 3mg/kg Regimen	14/42 (33.3)	4.8	(-22.5,25.7)
Fosaprepitant 1.2mg/kg Regimen	11/43 (25.6)	-3.0	(-22.5,24.6)
Fosaprepitant 0.4mg/kg Regimen	17/40 (42.5)	13.9	(-11.7,38.0)
Control Regimen	10/35 (28.6)		
Open-Label:			
Fosaprepitant 5mg/kg Regimen	35/74 (47.3)		

† Fosaprepitant regimen – Control regimen.

‡ Confidence interval (CI) for the difference was calculated using the method proposed by Miettinen and Nurminen, accounting for dose and dexamethasone use (yes/no).

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

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

Partially Blinded:

For Fosaprepitant 3mg/kg Regimen, subjects 12-17 years of age received a fixed 150 mg fosaprepitant dose.

For Fosaprepitant 1.2mg/kg Regimen, subjects 12-17 years of age received a fixed 60 mg fosaprepitant dose.

For Fosaprepitant 0.4mg/kg Regimen, subjects 12-17 years of age received a fixed 20 mg fosaprepitant dose.

Acute Phase

Treatment	n/m (%)	Difference (%)†	95% CI for Difference (%)‡
Partially Blinded:			
Fosaprepitant 3mg/kg Regimen	14/42 (33.3)	4.8	(-22.5,25.7)
Fosaprepitant 1.2mg/kg Regimen	11/43 (25.6)	-3.0	(-22.5,24.6)
Fosaprepitant 0.4mg/kg Regimen	17/40 (42.5)	13.9	(-11.7,38.0)
Control Regimen	10/35 (28.6)		
Open-Label:			
Fosaprepitant 5mg/kg Regimen	35/74 (47.3)		

† Fosaprepitant regimen – Control regimen.

‡ Confidence interval (CI) for the difference was calculated using the method proposed by Miettinen and Nurminen, accounting for dose and dexamethasone use (yes/no).

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

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

Partially Blinded:

For Fosaprepitant 3mg/kg Regimen, subjects 12-17 years of age received a fixed 150 mg fosaprepitant dose.

For Fosaprepitant 1.2mg/kg Regimen, subjects 12-17 years of age received a fixed 60 mg fosaprepitant dose.

For Fosaprepitant 0.4mg/kg Regimen, subjects 12-17 years of age received a fixed 20 mg fosaprepitant dose.

Overall Phase

Treatment	n/m (%)	Difference (%)[†]	95% CI for Difference (%)[‡]
Partially Blinded:			
Fosaprepitant 3mg/kg Regimen	13/42 (31.0)	11.0	(-18.2,29.3)
Fosaprepitant 1.2mg/kg Regimen	8/43 (18.6)	-1.4	(-23.2,21.9)
Fosaprepitant 0.4mg/kg Regimen	14/40 (35.0)	15.0	(-10.7,38.1)
Control Regimen	7/35 (20.0)		
Open-Label:			
Fosaprepitant 5mg/kg Regimen	33/74 (44.6)		

[†] Fosaprepitant regimen – Control regimen.

[‡] Confidence interval (CI) for the difference was calculated using the method proposed by Miettinen and Nurminen, accounting for dose and dexamethasone use (yes/no).

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

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

Partially Blinded:

For Fosaprepitant 3mg/kg Regimen, subjects 12-17 years of age received a fixed 150 mg fosaprepitant dose.

For Fosaprepitant 1.2mg/kg Regimen, subjects 12-17 years of age received a fixed 60 mg fosaprepitant dose.

For Fosaprepitant 0.4mg/kg Regimen, subjects 12-17 years of age received a fixed 20 mg fosaprepitant dose.

Source data: P029 CSR, Tables 11-18, 11-19, and 11-20

The results of subgroup analysis of Complete Response Rate are listed in Table 46. Importantly, pediatric patients in the fosaprepitant treatment groups receiving single-day chemotherapy reported a higher incidence of Complete Response in the delayed phase as compared to children who received multi-day chemotherapy in those same treatment groups. This forms the basis for recommending single-day fosaprepitant regimen to be used in patients receiving single-day chemotherapy.

Table 46. Number (%) of Subjects with Complete Response† in Cycle 1 by Subgroup of Age and Treatment Group Intent to Treat Population

	Fosaprepitant 3mg/kg Regimen n/m (%)	Fosaprepitant 1.2mg/kg Regimen n/m (%)	Fosaprepitant 0.4mg/kg Regimen n/m (%)	Control Regimen n/m (%)	Fosaprepitant 5mg/kg Regimen n/m (%)
Delayed Phase					
Age Group					
birth to <2 years	0/0(-.-)	0/0(-.-)	0/0(-.-)	0/0(-.-)	12/23 (52.2)
2 to <6 years	2/8 (25.0)	3/10 (30.0)	6/10 (60.0)	2/9 (22.2)	16/26 (61.5)
6 to <12 years	5/17 (29.4)	3/16 (18.8)	7/13 (53.8)	4/9 (44.4)	7/25 (28.0)
12 to 17 years	7/17 (41.2)	5/17 (29.4)	4/17 (23.5)	4/17 (23.5)	0/0(-.-)
Chemotherapy Duration in Cycle 1					
One Day of Chemotherapy	2/3 (66.7)	4/6 (66.7)	6/10 (60.0)	1/4 (25.0)	11/18 (61.1)
More Than 1 Day of Chemotherapy	12/39 (30.8)	7/37 (18.9)	11/30 (36.7)	9/31 (29.0)	24/56 (42.9)
Acute Phase					
birth to <2 years	0/0(-.-)	0/0(-.-)	0/0(-.-)	0/0(-.-)	21/23 (91.3)
2 to <6 years	4/8 (50.0)	6/10 (60.0)	10/10 (100.0)	4/9 (44.4)	23/26 (88.5)
6 to <12 years	9/17 (52.9)	9/16 (56.3)	9/13 (69.2)	5/9 (55.6)	16/25 (64.0)
12 to 17 years	14/17 (82.4)	9/17 (52.9)	11/17 (64.7)	5/17 (29.4)	0/0(-.-)
Chemotherapy Duration in Cycle 1					
One Day of Chemotherapy	3/3 (100.0)	2/6 (33.3)	6/10 (60.0)	2/4 (50.0)	14/18 (77.8)
More Than 1 Day of Chemotherapy	24/39 (61.5)	22/37 (59.5)	24/30 (80.0)	12/31 (38.7)	46/56 (82.1)
Overall Phase					
birth to <2 years	0/0(-.-)	0/0(-.-)	0/0(-.-)	0/0(-.-)	12/23 (52.2)
2 to <6 years	2/8 (25.0)	2/10 (20.0)	6/10 (60.0)	1/9 (11.1)	15/26 (57.7)
6 to <12 years	4/17 (23.5)	2/16 (12.5)	5/13 (38.5)	3/9 (33.3)	6/25 (24.0)
12 to 17 years	7/17 (41.2)	4/17 (23.5)	3/17 (17.6)	3/17 (17.6)	0/0(-.-)
Chemotherapy Duration in Cycle 1					
One Day of Chemotherapy	2/3 (66.7)	2/6 (33.3)	3/10 (30.0)	1/4 (25.0)	10/18 (55.6)
More Than 1 Day of Chemotherapy	11/39 (28.2)	6/37 (16.2)	11/30 (36.7)	6/31 (19.4)	23/56 (41.1)

† Complete Response = No vomiting and no rescue therapy.
‡ Overall Phase: 0 to 120 hours following initiation of chemotherapy.
n/m = Number of subjects with desired response/number of subjects included in time point
Partially Blinded:
For Fosaprepitant 3mg/kg Regimen, subjects 12-17 years of age received a fixed 150 mg fosaprepitant dose.
For Fosaprepitant 1.2mg/kg Regimen, subjects 12-17 years of age received a fixed 60 mg fosaprepitant dose.
For Fosaprepitant 0.4mg/kg Regimen, subjects 12-17 years of age received a fixed 20 mg fosaprepitant dose.

Source data: P029 CSR, Tables 11-27, 11-28, and 11-29

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/s/

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