EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Emend / Ivemend

Aprepitant/ fosaprepitant dimeglumine

Procedure no.:

EMEA/H/C/000527/P46/040.1

EMEA/H/C/000743/P46/024.1

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Administrative information

Invented name of the medicinal product:	Emend/Ivemend
INN (or common name) of the active substance(s):	Aprepitant/fosaprepitant
MAH:	Merck Sharp & Dohme Limited
Currently approved Indication(s):	Emend: Prevention of postoperative nausea and vomiting (PONV) in adults, Emend and Ivemend: Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy in adults Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in adults.
Pharmaco-therapeutic group (ATC Code):	A04AD12
Pharmaceutical form(s) and strength(s):	Emend: Hard capsule Ivemend: Powder for solution for infusion
Rapporteur:	Filip Josephson

1. Introduction

On July 2nd 2014, the MAH submitted the paediatric study report P134, (a multicentre, openlabel, 5-part study to evaluate the pharmacokinetics, safety, and tolerability of aprepitant and fosaprepitant dimeglumine in paediatric patients receiving emetogenic chemotherapy), which is part of an agreed PIP, under the scope of Article 46 of Regulation 1901/2006, as amended. The assessment has been concluded with the adoption of a list of questions for which the MAH is hereby providing responses.

2. Assessment of the responses to questions of Rapporteur and MS

2.1. Other Concerns

QUESTION 1

Fosaprepitant was rapidly converted to aprepitant following i.v. infusion, with indication of a slower conversion in in the younger age groups compared to the older children. The MAH is asked to comment on the results and compare with results in adults.

MAH Response:

In general, following IV infusions of fosaprepitant in pediatric patients from 6 months to 12 years (3 mg/kg) and adolescents 12 through 17 years of age (150 mg) fosaprepitant is rapidly converted to aprepitant within 30 minutes from the end of the infusion and consistent with that observed in adults (150 mg). Whilst fosaprepitant concentrations may be observed for a longer duration in patients 6 months to 12 years compared to adolescents and adults and suggesting a slower conversion to aprepitant in this patient cohort, as infusions of 60 minutes were implemented for those 6 months to 12 years of age compared to 30-minute infusions for the older patients, a direct comparison of these profiles must be interpreted with caution. It may also be helpful to consider the following summary of fosaprepitant properties and its conversion to aprepitant as described in the original fosaprepitant submission within the drug development program in healthy young adult subjects and CINV patients.

After intravenous administration (in both animals and humans), fosaprepitant can be recovered in plasma but is converted rapidly (within 30 minutes) to the pharmacologically active entity, aprepitant. The conversion of fosaprepitant to aprepitant has been studied in a variety of preparations including whole blood, human liver preparations, and in fractions from major human organs, including liver, kidney, lung, and ileum. Fosaprepitant was converted to aprepitant at similar rates in all tissues examined. The exact identity of the enzyme(s) involved in the conversion of fosaprepitant to aprepitant remains unknown, but it likely related to the phosphoramidase and/or the phosphatase activities observed in a variety of mammalian tissues. Additionally, since conversion of the prodrug to aprepitant involves hydrolysis of the phosphoramide moiety and can occur in the absence of NADPH, conversion of fosaprepitant to aprepitant is not thought to involve the CYP family of enzymes and is unlikely to differ significantly in patient subpopulations. In support of this, following a fosaprepitant administration, fosaprepitant plasma levels fall near or below the lower limit of quantitation (10 ng/mL) and conversion to aprepitant is nearly complete within 30 minutes after the end of infusion in all adult subjects evaluated in the clinical program. Given that fosaprepitant is no longer quantifiable soon after administration, concentration of fosaprepitant in plasma is not expected to be related to efficacy of the dosage form; rather, the pharmacological activity is expected to be related to aprepitant.

As summarized in CSR P134 Section 11.1.2.1, single dose IV fosaprepitant PK characteristics were investigated in Part I, Step B in adolescents (12-17 years old) at 150 mg, in Part V in younger age groups (0.5- <2 years, 2-< 6 years, 6 - <12 years) at the 150 mg equivalent dose of fosaprepitant (3 mg/kg). Fosaprepitant was infused for 30 minutes in adolescents and 60 minutes in <12 years old pediatric patients.

Tables 1 and 2 display the fosaprepitant PK parameters from the four age groups investigated.

As the basis for comparison to adults, within Part I Panel B of P012L1, following a single 150-mg infusion of fosaprepitant over 15 minutes in healthy young adults, the C15min (end of infusion) mean fosaprepitant value was 7750 ng/mL (SD +/-2400 ng/ml). Again, when comparing this fosaprepitant value in adults to fosaprepitant Cmax values in adolescents and pediatric patients <12 years of age, the difference in infusion times should be noted.

Table 1 Summary of plasma fosaprepitant Cmax and Tmax values following 150 mg IV administration of fosaprepitant (Part I, Step B) over 30 minutes in adolescents

	Tmax (hr)	Cmax (ng/mL)
N	11	11
Mean	0.614	1310
SD	0.251	964
Median	0.500	1020

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; SD: Standard Deviation.

Table 2 Summary of plasma fosaprepitant Cmax and Tmax values following 3 mg/kg IV administration of fosaprepitant over 60 minutes by age group (Part V)

Age Range		Tmax (hr)	Cmax (ng/mL)
6 Months to <2 Years Old	N	7	7
	Mean	1.13	2756
	SD	0.175	3364
	Median	1.00	159
2 to <6 Years Old	N	7	8
	Mean	1.05	3034
	SD	0.089	1718
	Median	1.02	3292
6 to <12 Years Old	N	8	8
	Mean	1.04	1654
	SD	0.088	1995
	Median	1.00	910

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

To further examine the distribution of fosaprepitant Cmax and Tmax values in pediatric patients, summary and individual plasma fosaprepitant Cmax and Tmax values following IV administration of fosaprepitant by pediatric age group are displayed in Table 14-18 (for adolescent patients 12 to 17 yrs.) and in Table 14-44 (for patients 6 months to <12 yrs.) of CSR P134. In addition, individual values and summary statistics for fosaprepitant concentrations per time point following IV administration of fosaprepitant by age group are provided in Table 14-19 (for adolescent patients 12 to 17 yrs.) and in Table 14-45 (for patients 6 months to <12 yrs.) of CSR P134. As noted by the large standard deviations, there was significant variability in the fosaprepitant Cmax values amongst the pediatric

patients with plasma concentrations varying multiple-fold over 15 minutes. Thus, these fosaprepitant Cmax values should be interpreted with caution.

In Part I, Step B, fosaprepitant concentrations in adolescent patients (12 to 17 yrs.) were measurable 30 minutes after the start of infusion and were converted to aprepitant in the majority of the subjects within 15 minutes. However, 2 of the 11 adolescent patients still had quantifiable fosaprepitant plasma concentrations (10.1 and 26.6 ng/mL) at the 1.3-hour PK sampling time point. All subsequent PK sampling time points for fosaprepitant plasma concentrations in adolescent patients were reported as BLOQ (below the limit of quantitation).

In Part V, fosaprepitant concentrations in the younger pediatric patients (6 months to <12 yrs.) were measureable at approximately 60 minutes after the start of infusion and were converted to aprepitant in the majority of the subjects within 15-30 minutes. However, fosaprepitant concentration values were observed for a longer duration in the patients 6 months to <12 years compared to adolescents and adults. For example, at the 2.25-hour PK sampling time point, 3 of the 7 patients 6 months to <2 years old still had quantifiable fosaprepitant concentrations (150, 207, and 13.3 ng/mL); 5 of 8 patients 2 to <6 years old still had quantifiable fosaprepitant concentrations (973, 102, 14.6, 64.7, and 739 ng/mL); and only 1 of 8 patients 6 to <12 years old had a quantifiable fosaprepitant concentration (182 ng/mL) at this same time point. After the 2.25-hour PK sampling time point, all fosaprepitant plasma concentrations in pediatric patients 6 months to <12 years old were reported as BLOQ. While these findings could be suggestive of a slower conversion to aprepitant in this younger patient cohort, these data should be interpreted with caution as fosaprepitant infusion times of 60 minutes were implemented for those patients 6 months to <12 years of age compared to 30-minute infusions for the older patients.

Given that the pharmacological activity observed after IV infusion of fosaprepitant is due to its conversion to the active moiety, aprepitant, the aprepitant exposure following fosaprepitant administration in pediatric patients in P134 was the primary focus for the pharmacokinetic evaluation. Tables 3 - 6 display the aprepitant PK parameters following the administration of IV fosaprepitant within the four pediatric age groups investigated, and also included within each table are mean and SD values for aprepitant AUC0-24hr and Cmax for adult subjects (n=41) from P165 as a means for comparison to the pediatric exposures.

Table 3 (Table 11-2 from CSR)

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

	C_{max} (ng/mL)	T_{max} (hr)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)	HV^{a} (hr)	CL (mL/hr)	AUC_{0-24hr} (hr*ng/mL)	AUC_{0-48hr} (hr*ng/mL)	AUC_{0-72hr} (hr*ng/mL)	AUC_{Inf} (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	1.30	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% = 100sqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log scale.
a. (Apparent) terminal half-life.
b excluded from descriptive statistics since AUC% extrap > 25% of total AUC (AUC0-∞).
c excluded from descriptive statistics since sample result > 2 times higher than the predicted concentration by the best fitted terminal slope without this value.

Table 4 (Table 11-13 from CSR)

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 <2-Year-Old Patients Undergoing Chemotherapy

	C_{max} (ng/ml)	T_{max} (hr)	C_{48hr} (ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)	$t_{1/2}^{\beta}$ (hr)	CL (ml/hr)	$AUC_{0-\infty}$ (hr*ng/ml)	AUC_{0-48hr} (hr*ng/ml)	AUC_{0-72hr} (hr*ng/ml)	AUC_{0-t} (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	130	..[a]	..[a]	7.71	5010	11700	13300	13800	13800
SD	636	0.17	103	..[a]	..[a]	3.10	6230	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	7.34	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	..[a]	..[a]	40.3	125	59.7	58.3	57.7	57.8
HM	1460	1.11	--	--	--	6.24	2560	6120	6640	6750	6470
Pseudo SD	733	0.16	--	--	--	4.96	1330	12900	15000	15000	16600
GM	1580	1.12	--	--	--	7.05	3250	9170	10400	10700	10600
*CV%	44.8	15.01	--	--	--	53.6	113	100	116	118	123
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% = 100*sqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.

β: (Apparent) terminal half-life.

[a]Not reportable since < 50% of the concentration results ≥ Lower Limit of Quantitation (LLOQ).

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.).

In some cases $AUC_{0-\infty}$ results are < AUC_{0-72} results. This can be explained by the fact that $AUC_{0-\infty}$ is calculated based on the last predicted concentration, i.e., concentration at the final observation time estimated using the linear regression performed to estimate λ_z. Whereas AUC_{0-72} is calculated based on interpolation only.

Table 5 (Table 11-14 from CSR)

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 2- to <6-Year-Old Patients Undergoing Chemotherapy

	C_{max} (ng/ml)	T_{max} (hr)	C_{48hr} (ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)	$t_{1/2}^{\beta}$ (hr)	CL (ml/hr)	$AUC_{0-\infty}$ (hr*ng/ml)	AUC_{0-48hr} (hr*ng/ml)	AUC_{0-72hr} (hr*ng/ml)	AUC_{0-t} (hr*ng/ml)
2- to <6-Year-Olds											
N	7	7	7	7	7	7	6	7	7	7	6
AM	2430	1.41	134	..[a]	..[a]	6.44	3460	18300	20600	21100	23400
SD	1100	0.83	139	..[a]	..[a]	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	1.14	22.1	10.9	7000	36000	40000	40200	40200
*CV%	45.3	58.8	102	..[a]	..[a]	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	8850	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
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% = 100*sqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.

β: (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.).

[a]Not reportable since <50% of the concentration results ≥ Lower Limit of Quantitation (LLOQ).

In some cases $AUC_{0-\infty}$ results are < AUC_{0-72} results. This can be explained by the fact that $AUC_{0-\infty}$ is calculated based on the last predicted concentration, i.e., concentration at the final observation time estimated using the linear regression performed to estimate λ_z. Whereas AUC_{0-72} is calculated based on interpolation only.

Table 6 (Table 11-15 from CSR)

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- to <12-Year-Old Patients Undergoing Chemotherapy

	C_{max} (ng/mL)	T_{max} (hr)	C_{max} (ng/mL)	C_{max} (ng/mL)	C_{max} (ng/mL)	t½[#] (hr)	CL (mL/hr)	AUC_{0-inf} (hr*ng/mL)	AUC_{0-last} (hr*ng/mL)	AUC_{0-24hr} (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	--[1]	8.76	3590	19500	23100	24000	24100
SD	641	0.11	240	56.5	--[1]	3.34	1880	6720	9660	10500	11100
Min	1900	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	3830	1.25	751	159	92.5	14.4	7670	34000	44700	47800	49500
*CV%	22.5	10.5	77.8	151	--[1]	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							25103			
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 (<100 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% = 100*sqrt(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.).

[1]Not reportable since >20% 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.

Following a single IV administration of fosaprepitant (3 mg/kg for patients <12 years-old and 150 mg for patients 12 to 17 years-old), the disposition of aprepitant in patients 2 to 17 years is generally comparable to that observed in adults at the fosaprepitant dose level of 150 mg IV; this is not observed with the 6-month to <2-year-old age group. The C24hr levels in patients ages 6 months to <12 years are ~2 to 3 times lower than that of adults and adolescents ages 12 to 17 years.

In summary, following IV infusions of fosaprepitant in pediatric patients from 6 months to 12 years (3 mg/kg) and adolescents 12 through 17 years of age (150 mg) fosaprepitant is rapidly converted to aprepitant within 30 minutes from the end of the infusion and consistent with that observed in adults (150 mg). However, as noted, fosaprepitant plasma concentration values were observed for a longer duration (i.e., beyond 30 minutes after the end of the infusion time) in some patients 6 months to <12 years, which might be suggestive of a slower conversion to aprepitant as compared to adolescents and adults where it was observed that conversion of fosaprepitant to aprepitant is complete or nearly complete within 30 minutes after the end of infusion. However, given the difference in length of infusion times for fosaprepitant and the significant variability in the fosaprepitant plasma concentrations observed among the patients 6 months to <12 years of age, it is unlikely that these observations are clinically relevant.

Assessor's comment:

The Applicant has summarized the data presented in the clinical study report. They state that the enzymes involved in the hydrolysis of fosaprepitant to aprepitant are unknown and that the conversion occur in the absence of NADPH. No discussion has been presented with respect to maturation, with age, of the potential enzymes involved in the metabolism. It is concluded that due to the difference in infusion time between teenagers and smaller children (30 and 60 min, respectively) and the variability in exposure of fosaprepitant it is unlikely that the observations are clinical relevant.

It is agreed that the rate of conversion may be difficult to determine based on the current data. However, the data clearly show that the small children are less exposed to aprepitant than the teenagers and adults following iv infusion of fosaprepitant.

PK of fosprepitant and aprepritant following a 60-min iv infusion of 150 mg or scaled to 3 mg/kg fosprepritant to children aged 6 mon - 17 years

Age	**Dose**	Fosaprepitant	Aprepritant		
		C_{max} (ng/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**AUC_{0-24h}** (ng/ml.h)
6 mon - <2 yrs	3 mg/kg[a]	2756(3364)	1700(636)	1.1(0.2)	11700(6980)
2 - <6 yrs	3 mg/kg[a]	3034(1718)	2430(1100)	1.4(0.8)	18300(11100)
6 – <12 yrs	3 mg/kg[a]	1654(1995)	2850(641)	1.1(0.1)	19500(6720)
12 -17 yrs	150 mg[b]	1310(964)	5870(2770)	0.6(0.3)	30800(7020)
12 -17 yrs	115 mg[c]	–	3240(1280)	0.4(0.3)	–
Adults	150 mg	–	4145(1152)	–	25105(5778)

[a] dose equivalent to 150 mg in adults; [b] 30-min iv infusion; [c] 15-min iv infusion;

The question is considered **resolved** as iv administration in small children is not an actual route of administration in the grouped variation/extension application for paediatric formulation/indication ongoing in parallel to the current procedure.

QUESTION 2

The MAH compares the exposure in the different cohorts with exposure in adults as well as in teenagers, achieved in other studies, with just mentioning single point estimates without any standard deviation etc. or study backgrounds / references. The MAH is asked to provide a clear tabulated / overview, including descriptive statistics and references, on the current results in comparison to relevant exposure in adults.

MAH Response:

In consideration of the Reviewer's request, to further complement the comparisons presented in the CSR (Section 11.1.2) that included point estimates and SD (CSR Tables 11-1 to 11-15 as outlined in Table 7 below), a tabulation of the adult protocols from which fosaprepitant/aprepitant exposures were compared to the pediatric exposures following the various regimens investigated in the different parts of P134 is presented in Table 7.

Table 7 Summary of adult studies and regimens which were used to compare fosaprepitant and aprepitant exposure in the various regimens investigated in pediatric patients within P134

P134 Part, Step	Regimen	Adult Reference*	Adult Regimen	Comparisons of Results (mean and SD) in P134
Part I, Step A	115 mg SD IV fosaprepitant on Day 1 followed by 80 mg oral aprepitant on Days 2 and 3 in adolescents	P012L1	115 mg SD IV fosaprepitant	Table 11-1
Part I, Step B	150 mg SD IV fosaprepitant in adolescents	P165	150 mg SD IV fosaprepitant	Table 11-2
Part II, Step A	Equivalent 80 mg SD oral aprepitant in <12 years old age groups	Not applicable†		
Part II, Step B	Equivalent 125 mg SD oral aprepitant in <12 years old age groups	P067	125 mg SD oral aprepitant on Day 1, 80 mg SD oral aprepitant on Days 2 and 3	Tables 11-7, 11-8,11-9
Part IV	3 /2/2 mg/kg SD oral aprepitant on Day 1, 2 and 3 in <12 years old age groups	P067	125 mg SD oral aprepitant on Day 1, 80 mg SD oral aprepitant on Days 2 and 3	Tables 11-10, 11-11, 11-12
Part V	3 mg/kg SD IV fosaprepitant in < 12 years old age groups	P165	150 mg SD IV fosaprepitant	Tables 11-13, 11-14, 11-15

† Not applicable because an adult exposure from single dose 80 mg aprepitant was not necessary for comparison to the pediatric exposure from an equivalent dose of aprepitant within Step A of Part II prior to proceeding to Step B of Part II wherein the equivalent dose of aprepitant in pediatric patients to 125 mg single dose in adults was evaluated. The equivalent of 80 mg SD oral aprepitant regimen in Part II, Step A was first administered to evaluate safety and tolerability of the drug prior to proceeding with the equivalent of 125 mg SD oral aprepitant in Part II, Step B.

*CSRs were previously submitted to the agency

Assessor's comment:

The Applicant has tabulated dosing regimens/studies for adult references together with the different dosing regimens/groups in the current study. However, no clear overview on comparison of exposure in the different treatment groups has been presented.

Issue resolved, as data are presented/summarized in the grouped variation/extension application for paediatric formulation/indication ongoing in parallel (EMEA/H/C/527/X/49/G) to the current procedure.

QUESTION 3

The MAH should present and discuss the systemic exposure of aprepitant in the different age groups, including also adults, considering treated or not co-medicated with a corticosteroid.

MAH Response:

Previously, in adults, it was demonstrated that neither standard nor modified regimens of dexamethasone resulted in meaningful reductions in aprepitant exposure at clinically relevant doses (125 mg/80 mg). Based upon common biotransformation pathways in pediatrics and adults, and coupled with largely comparable aprepitant exposures between pediatric patients and adults, no relevant drug-drug interaction between dexamethasone and aprepitant was anticipated.

The Sponsor assumes that in consideration of reports that corticosteroids have the potential to induce drug metabolizing enzymes and given that aprepitant is a substrate of CYP3A and therefore has the potential to be a victim of CYP3A inhibition or induction, the Reviewer is seeking to further understand the potential for reduced aprepitant exposure when coadministered with corticosteroids in the pediatric setting. Based upon the clinical setting of CINV and the inclusion/exclusion criteria of P134, the focus of this review is based upon dexamethasone co-administration, rather than corticosteroids in general.

Dexamethasone is an inducer as well as a substrate of CYP3A4. In support of the original, adult indication, the effect of dexamethasone on the pharmacokinetics of aprepitant was evaluated in a Phase I study (P041) conducted in healthy young adult subjects, and the study results were reported in the original WMA submission for EMEND®. Protocol 041 examined the pharmacokinetics of aprepitant given as each of 3 dosing regimens: 375 mg on Day 1 with 250 mg/day on Days 2 through 5, 125 mg on Day 1 with 80 mg/day on Days 2 through 5, or 40 mg on Day 1 with 25 mg/day on Days 2 through 5. These were designated as the 375 mg/250 mg, 125 mg/80 mg, or 40 mg/25 mg aprepitant regimens. Each of these regimens were given alone, and also administered concomitantly with dexamethasone and ondansetron (see Table 8). The dexamethasone and ondansetron were administered either as a standard antiemetic regimen or dexamethasone (20 mg on Day 1 and 8 mg/day on Days 2 to 5) with ondansetron (32 mg IV on Day 1) or as a modified regimen in which the dexamethasone doses were lower (dexamethasone 12 mg on Day 1 and 4 mg/day on Days 2 to 5) with ondansetron (32 mg IV on Day 1). These were referred to as the standard dexamethasone regimen and the modified dexamethasone regimen, respectively.

All doses of aprepitant and dexamethasone were administered orally once daily in the morning. Aprepitant was administered 15 to 60 minutes after a light breakfast. Thirty minutes after administration of aprepitant, subjects received a single oral dose of dexamethasone and began the ondansetron infusion, which lasted 15 minutes. On Days 2 to 5, subjects received a single oral dose of dexamethasone immediately following administration of aprepitant.

Table 8 Treatment Regimens in Protocol 041

Treatment Regimen	Day 1	Days 2 to 5
Treatment A (375 mg/250 mg aprepitant and standard dexamethasone regimen)	Aprepitant (375 mg P.O.), dexamethasone (20 mg P.O.), and ondansetron (32 mg IV)	Aprepitant (250 mg/day P.O.) and dexamethasone (8 mg/day P.O.)
Treatment B (Standard dexamethasone regimen alone)	Dexamethasone (20 mg P.O.) and ondansetron (32 mg IV)	Dexamethasone (8 mg/day P.O.)
Treatment C (375 mg/250 mg aprepitant alone)	Aprepitant (375 mg P.O.)	Aprepitant (250 mg/day P.O.)
Treatment D (125 mg/80 mg aprepitant alone)	Aprepitant (125 mg P.O.)	Aprepitant (80 mg/day P.O.)
Treatment E (Standard dexamethasone regimen alone)	Dexamethasone (20 mg P.O.) and ondansetron (32 mg IV)	Dexamethasone (8 mg/day P.O.)
Treatment F (125 mg/80 mg aprepitant and standard dexamethasone regimen)	Aprepitant (125 mg P.O.), dexamethasone (20 mg P.O.), and ondansetron (32 mg IV)	Aprepitant (80 mg/day P.O.) and dexamethasone (8 mg/day P.O.)
Treatment G (125 mg/80 mg aprepitant and modified dexamethasone regimen)	Aprepitant (125 mg P.O.), dexamethasone (12 mg P.O.), and ondansetron (32 mg IV)	Aprepitant (80 mg/day P.O.) and dexamethasone (4 mg/day P.O.)
Treatment H (40 mg/25 mg aprepitant and standard dexamethasone regimen)	Aprepitant (40 mg P.O.), dexamethasone (20 mg P.O.), and ondansetron (32 mg IV)	Aprepitant (25 mg/day P.O.) and dexamethasone (8 mg/day P.O.)
P.O. = Taken orally. IV = Intravenous.		

Dexamethasone when given as the standard or modified regimens did not affect the AUC0-24 hr of aprepitant on Days 1 and 5 when given as the 125 mg/80 mg regimen (Treatment F versus Treatment D, and Treatment G versus Treatment D) (Table 9; Figure 1). Dexamethasone, when given as the standard regimen for CINV, did not affect the Day 1 AUC0-24 hr of aprepitant when given as the 375 mg/250 mg aprepitant regimen (Treatment A versus Treatment C), while the Day 5 AUC0-24 hr of aprepitant was decreased by 25% (Table 2). The effect of dexamethasone on the 40 mg/25 mg aprepitant regimen was not assessed in this study.

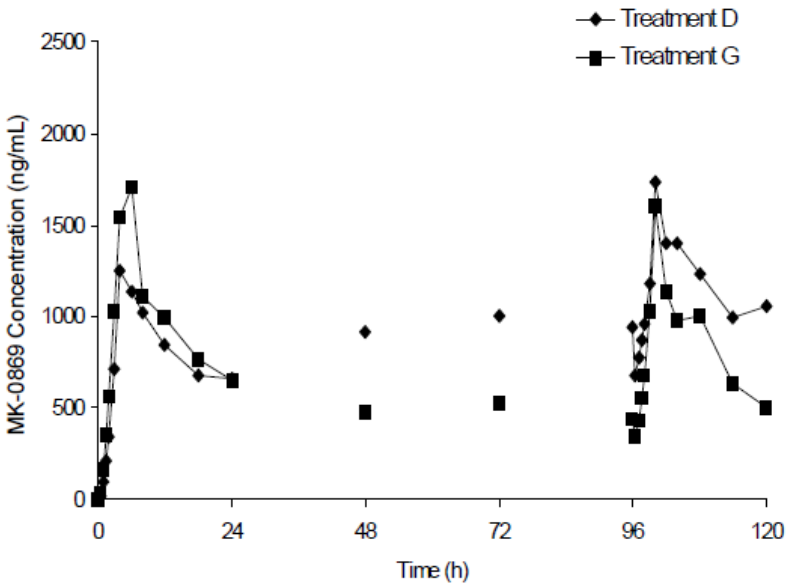
Thus, although dexamethasone has the potential to induce CYP3A4, no clinically relevant reductions in aprepitant exposures were observed at clinically relevant aprepitant doses (125 mg/80 mg) with a 25% reduction observed at the highest aprepitant doses (375 mg/250 mg) used in the study.

Table 9 Summary Statistics for the Geometric Mean AUC0-24 hr and Geometric Mean Ratios and 90% Confidence Interval for Aprepitant in Protocol 041

Effects on Aprepitant $AUC_{0\text{-}24\,hr}$ (ng-h/mL)						
Day	Treatment Regimen Aprepitant $AUC_{0\text{-}24\,hr}$[†]	Reference Regimen Aprepitant $AUC_{0\text{-}24\,hr}$[†]	Ratio[†]	p-Value	90% CI	Hypothesized Interval
1	375 mg/250 mg aprepitant with standard dexamethasone regimen (A) 63,512.3	375 mg/250 mg aprepitant alone (C) 56,941.0	A/C 1.12	0.085	(1.01, 1.24)	(0.5, 2.0)
5	375 mg/250 mg aprepitant with standard dexamethasone regimen (A) 103,291.2	375 mg/250 mg aprepitant alone (C) 137,634.6	A/C 0.75	0.011	(0.63, 0.89)	--
1	125 mg/80 mg aprepitant with standard dexamethasone regimen (F) 24,309.0	125 mg/80 mg aprepitant alone (D) 18,714.5	F/D 1.30	< 0.01	(1.15, 1.46)	(0.67, 1.5)
5	125 mg/80 mg aprepitant with standard dexamethasone regimen (F) 22,531.3	125 mg/80 mg aprepitant alone (D) 23,004.8	F/D 0.98	> 0.25	(0.85, 1.14)	(0.5, 2.0)
1	125 mg/80 mg aprepitant with modified dexamethasone regimen (G) 22,934.3	125 mg/80 mg aprepitant alone (D) 18,714.5	G/D 1.23	< 0.01	(1.09, 1.38)	(0.67, 1.5)
5	125 mg/80 mg aprepitant with modified dexamethasone regimen (G) 19,488.2	125 mg/80 mg aprepitant alone (D) 23,004.8	G/D 0.85	0.058	(0.73, 0.98)	(0.5, 2.0)

[†] Least squares geometric mean. For the amendment, estimates for treatment ratios were based on both paired and unpaired observations for those treatments.
CI = Confidence interval.

Figure 1 Mean Plasma Concentration Profiles of Aprepitant on Days 1 to 5 Following 125 mg/80 mg Aprepitant (Treatment D) and 125 mg/80 mg Aprepitant With the Modified Dexamethasone Regimen (Treatment G)



Time relative to initial aprepitant dosing
Treatment D: Day 1: 125 mg aprepitant P.O.
Days 2 to 5: 80 mg/day aprepitant P.O.
Treatment G: Day 1: 125 mg aprepitant P.O. + 12 mg dexamethasone P.O. + 32 mg ondansetron IV.
Days 2 to 5: 80 mg/day aprepitant P.O. + 4 mg/day dexamethasone P.O.
P.O. = Taken orally.
IV = Intravenous.
MK-0869 = Aprepitant.

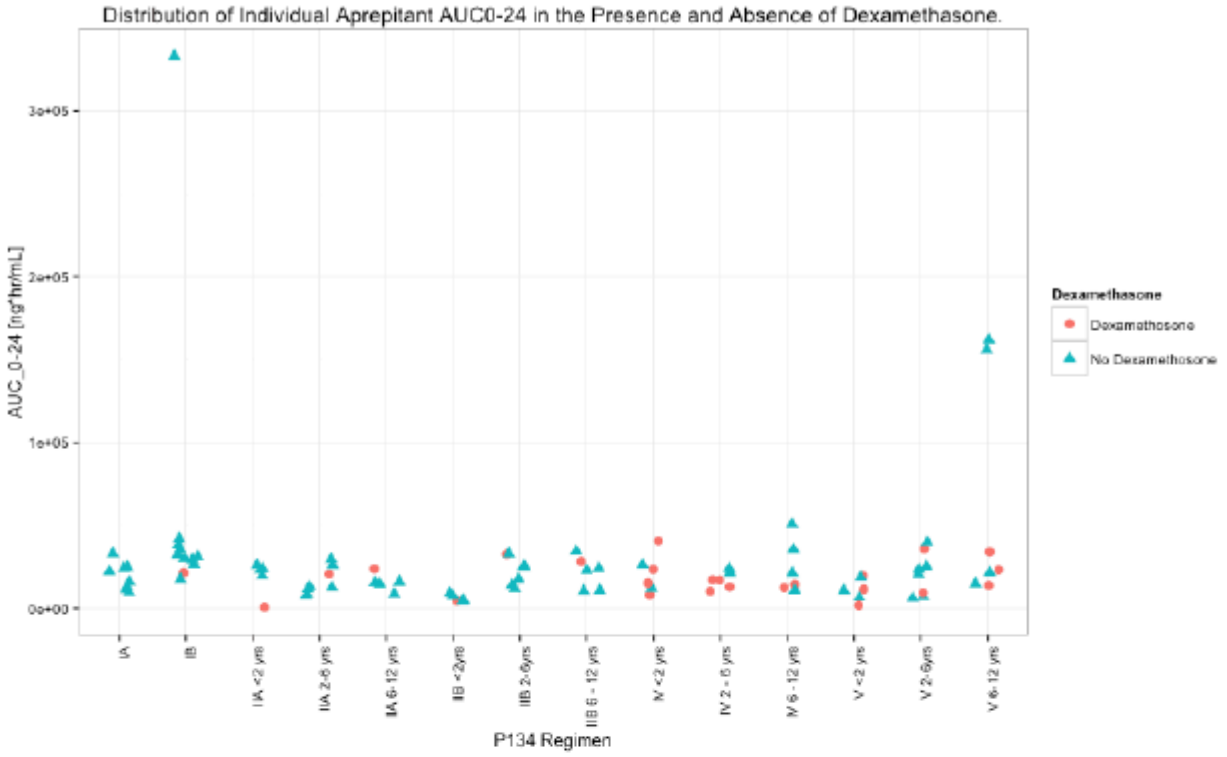
The finding from P041 that dexamethasone does not have an inductive effect with the aprepitant (125 mg/80 mg) CINV regimen as observed in adults are not expected to be different in the pediatric population based upon common biotransformation pathways between pediatric and adult patients.

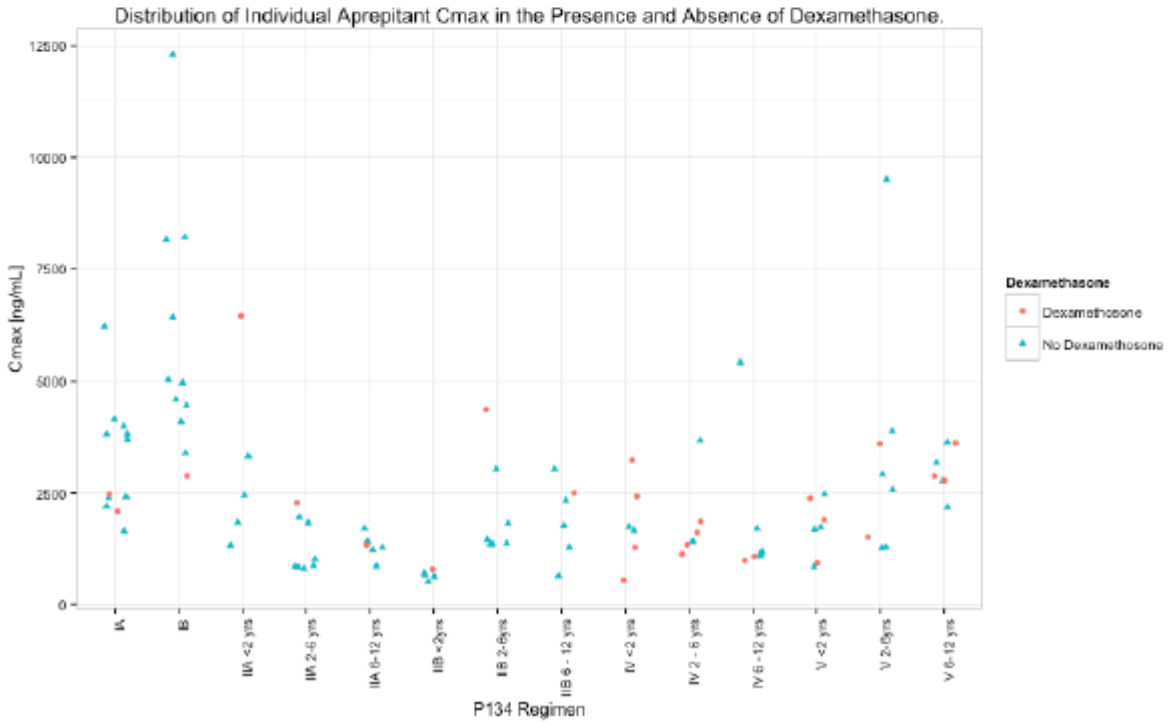
Within P134, the number of pediatric patients with aprepitant PK data when receiving either fosaprepitant or aprepitant alone or with concomitantly administered dexamethasone are small (N = 27 with dexamethasone and N=74 without dexamethasone), and the study was not designed or powered to evaluate the effect of dexamethasone on the pharmacokinetics of aprepitant using inferential statistical analysis. However, a graphical comparison of the aprepitant exposures observed in P134 in the presence or absence of dexamethasone is possible (see Table 10 and Figure 2).

Table 10 Number of Pediatric Subjects within P134 by Study Part Receiving Aprepitant with and without Dexamethasone

P134	Number of Subjects Receiving Aprepitant and Fosaprepitant With Dexamethasone	Number of Subjects Receiving Aprepitant and Fosaprepitant Without Dexamethasone
Part I, Step A	2	10
Part I, Step B	1	10
Part II, Step A, 0.5 - 2yr	1	4
Part II, Step A, 2 - 6 yr	1	7
Part II, Step A, 6- - 12 yr	1	5
Part II, Step B, 0.5 - 2 yr	1	4
Part II, Step B, 2 - 6 yr	1	6
Part II, Step B, 6- - 12 yr	1	5
Part IV, 0.5 - 2 yr	4	2
Part IV, 2 - 6 yr	4	2
Part IV, 6 - 12 yr	2	5
Part V, 0.5 - 2 yr	3	4
Part V, 2 - 6 yr	2	6
Part V, 6 - 12 yr	3	4

Figure 2 Distribution of Individual Aprepitant Exposures (Upper Panel: AUC0-24 and Lower Panel: Cmax) in the Presence and Absence of Dexamethasone





Based on the earlier finding in adults in P041 that dexamethasone did not have an inductive effect on aprepitant pharmacokinetics following the aprepitant 125/80/80-mg CINV regimen, and from the graphical comparison of the aprepitant exposure observed in the pediatric patients within the various parts/regimens of P134, coadministration of dexamethasone with the aprepitant CINV regimen in pediatric patients does not result in a clinically relevant impact on aprepitant pharmacokinetics.

Assessor's comment:

Aprepitant is recommended to be co-administered with dexamethasone and ondansetron. Aprepitant is characterized as a CYP3A substrate and dexamethasone is known to induce CYP3A.

The DDI study between aprepitant and dexamethasone in adults showed a 25% decrease in exposure of aprepitant when aprepitant was co-administered at a higher dose (375 mg/250 mg) than the therapeutic dose (125mg/80 mg). The duration of treatment of CINV is three days. At therapeutic dosing for three days a trend to lower exposure of aprepitant was seen when co-administered with dexamethasone, however, not statistically significant and deemed not clinical relevant. The SPC 4.5 says co-treatment with strong CYP3A inducers should be avoided.

The graphical presentation of exposure of aprepitant in the current study in children does not indicate any differences between treatment alone or together with dexamethasone on Day 1. No exposure data on Day 2 and 3 have been presented, however, no clinical relevant decreases in exposure of aprepitant are expected.

Issue resolved.

QUESTION 4

The MAH's intentions for the future based on this study are expressed differently in different parts of the submission. Is a new indication and/or new formulation intended, or is a type II variation concerning SmPC sections 4.2, 4.8 and 5.1 intended

MAH Response:

EMEND

On December 04th, 2014, the MAH submitted a line extension grouped with two type II variations (EMEA/H/C/000527/X/0049/G) in order to license a 125mg powder for oral suspension for the use in paediatric patients with an age of 6 months to 11 years, and to expand the indication of the 125mg and 80mg capsules from adult to adolescents ages 12 to 17 years for prevention of CINV. Under the scope of this type II variation amending SmPC section 4.1 in order to extend the indication of the 80mg and 125mg capsules strengths to adolescents, a recommendation to the posology (SmPC section 4.2) has been made, and the SmPC section 4.8 concerning undesirable effects as well as the clinical sections of the product label (SmPC section 5.1 to 5.3) has been completed with newly generated paediatric clinical trial results and conclusions from juvenile animal studies, respectively.

IVEMEND

Study protocol P 134 is part of an ongoing paediatric development program, to support an extension of the indication of 150mg IVEMEND® from adults to paediatric patients with an age of 6 months to 17 years for prevention of CINV. In Protocol 134, one dosage level of fosaprepitant, selected to match the exposures previously observed to be safe/efficacious in adults, was evaluated.

Assessor's comment:

The Emend line extension grouped with two type II variations (EMEA/H/C/000527/X/0049/G) has now been submitted and the preliminary assessment report in the first round has been circulated on 13th of March 2015.

Issue resolved.

QUESTION 5

For easier comparison and presentation in the next AR, the MAH is requested to provide a summary table of all AEs in all parts and steps of the study presented side by side.

MAH Response:

As per the request, enclosed are the Adverse Event summaries displayed side by side. Please note, due to the multiple parts, two tables were created for ease of review, Table 11, which includes fosaprepitant Parts I and V along with ondansetron Part III, and Table 12, which includes aprepitant Parts II and IV along with ondansetron Part III.

Table 11 Adverse Event Summary <Parts I, III and V>

	Fosaprepitant (115 mg) Regimen (Step A)		Fosaprepitant (150 mg) Regimen (Step B)		Ondansetron (Part III)		Fosaprepitant Regimen (Part V)	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	12		11		19		23	
with one or more adverse events	11	(91.7)	6	(54.5)	15	(78.9)	17	(73.9)
with no adverse event	1	(8.3)	5	(45.5)	4	(21.1)	6	(26.1)
with drug-related† adverse events	0	(0.0)	0	(0.0)	1	(5.3)	2	(8.7)
with serious adverse events	4	(33.3)	1	(9.1)	5	(26.3)	9	(39.1)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.3)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.3)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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

‡ Study medication withdrawn.

Step A Day 1: fosaprepitant 115 mg + ondansetron; Days 2 and 3: aprepitant 80 mg + ondansetron.

Step B Day 1: fosaprepitant 150 mg + ondansetron.

Part V: Day 1 - fosaprepitant 3 mg/kg + ondansetron.

Table 12 Adverse Event Summary <Parts II, III and IV>

	Aprepitant (80 mg eq.) Regimen (Step A)		Aprepitant (125 mg eq.) Regimen (Step B)		Ondansetron (Part III)		Aprepitant Regimen (Part IV)	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	19		19		19		20	
with one or more adverse events	18	(94.7)	16	(84.2)	15	(78.9)	13	(65.0)
with no adverse event	1	(5.3)	3	(15.8)	4	(21.1)	7	(35.0)
with drug-related† adverse events	0	(0.0)	0	(0.0)	1	(5.3)	1	(5.0)
with serious adverse events	7	(36.8)	4	(21.1)	5	(26.3)	2	(10.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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

‡ Study medication withdrawn.

Step A Day 1: aprepitant 47 mg/m^2 + ondansetron for 6 months to 12 years of age.

Step B Day 1: aprepitant 74 mg/m^2 + ondansetron for >2 to 12 years of age; aprepitant 1.3 mg/kg + ondansetron for 6 months to 2 years of age.

Part IV: Day 1 - aprepitant 3 mg/kg + ondansetron; Days 2-3 - aprepitant 2 mg/kg + ondansetron.

Assessor's comment:

The question's intention was to detail all AEs by PT, however this was misunderstood. It is again noted that AEs and SAEs considered by investigators to be (possibly) related to study drug were very few in Study P134. In view of the more extensive safety data now available from the recently submitted randomised phase 3 study P208, the issue is no longer pursued.

Not further pursued.

QUESTION 6

Individual laboratory data were not provided. The MAH should investigate if any subjects fulfil Hy's law laboratory criteria, and if so further analyse the case with regard clinical Hy's law criteria.

MAH Response:

The MAH monitored for drug induced liver injury, which included the Hy's Law laboratory criteria (an elevated AST or ALT lab value greater than or equal to 3X the upper limit of normal, an elevated total bilirubin lab value greater than or equal to 2X the upper limit of normal, and at the same time, an alkaline phosphatase lab value less than 2X the upper limit of normal). Hy's Law laboratory criteria was considered an "event of clinical interest" in Protocol 134, which required sites to report the laboratory findings within 24 hours of onset, and there were specific recommendations for follow-up assessments should a case occur. However, during the course of the study, there were no cases of Hy's Law reported in all 5 Parts. This was reported in Protocol 134 Clinical Study Report Section 12.3.2.5.1, "Laboratory Findings That Met Predetermined Criteria" in the following tables:

- Table 12-42 on page 323 for Part I (fosaprepitant in patients 12 to 17 years of age),

- Table 12-43 on page 324 for Part II (aprepitant single dose in patients 6 months to <12 years of age),
- Table 12-44 on page 326 for Parts III, IV, and V (aprepitant 3-day regimen, ondansetron alone, and fosaprepitant in subjects 6 months to 12 years of age).

Assessor's comment:

There were no Hy´s laws cases in P134.

Issue resolved.

QUESTION 7

Individual QTc data were not provided. Post-treatment (Day 6-8) mean QTcB (but not QTcF) was prolonged in patients aged 6 months to< 2 years receiving the single-dose fosaprepitant in Part V, to mean 508.6 msec (based on 5 subjects), compared with 410 at baseline (7 subjects) and 436 msec (1 subject) on treatment day 1. Similar successive increases in mean QTcB from baseline visit through Day 1 to post-treatment visits were observed for the other two age groups in study Part V, with post-treatment QTcB 460 msec in 6 subjects 2-<6 years old, and 459 msec in 7 subjects aged 6-<12 years. The MAH should comment, including a discussion on concomitant medications and their QTc prolonging potential in relevant individual cases.

MAH Response:

In the Protocol 134 database, one subject in the 6 months to <2 years age group (AN 50266) had a recorded post-treatment QTcB interval of 907 msec, versus a baseline of 429 msec. It was also noted that this patient had an unusually shortened RR-interval of 102 msec which is not consistent with the recorded heart rate of 129 bpm. Although these data were not censored in the original analyses, given the inconsistencies of these measurements and potential miss-calculation of intervals, the data were re-analyzed after removal of this patient. Excluding AN 50266 resulted in a reduction in mean QTcB for the Part V, 6 month to <2 year age group from 510 to 409 msec, which is consistent with the baseline value in this age group (407 msec). Table 13 below summarizes QTcB data for Protocol 134 Parts III, IV and V for all age groups, excluding AN 50266.

Table 13 Summary Statistics for 12-Lead Electrocardiogram (ECG) by Age Group <Parts III, IV and V, Excluding the Outlier Subject 50266>

ECG Parameter (Units)	Visit	Treatment Group	Age Group	N†	Mean	SD
QTc Interval Bazett (msec)	Baseline	Ondansetron (Part III)	6 months to <2 years	6	447.7	73.55
			2 to <6 years	6	414.3	19.25
			6 to <12 years	7	423.7	36.24
		Aprepitant Regimen (Part IV)	6 months to <2 years	7	398.4	18.88
			2 to <6 years	6	417.3	25.45
			6 to <12 years	7	423.3	21.68
		Fosaprepitant Regimen (Part V)	6 months to <2 years	6	407.3	25.57
			2 to <6 years	8	420.6	18.06
			6 to <12 years	7	436.6	23.32
	Treatment Visit (Day 1)††	Ondansetron (Part III)	6 months to <2 years	1	427.0	.
			2 to <6 years	2	415.5	16.26
		Aprepitant Regimen (Part IV)	6 months to <2 years	1	458.0	.
			2 to <6 years	2	462.5	26.16
		Fosaprepitant Regimen (Part V)	6 months to <2 years	1	436.0	.
			2 to <6 years	1	454.0	.
	Post-treatment Visit (Days 6-8)	Ondansetron (Part III)	6 months to <2 years	5	416.6	43.62
			2 to <6 years	3	424.3	23.97
			6 to <12 years	5	436.6	27.29
		Aprepitant Regimen (Part IV)	6 months to <2 years	5	407.6	16.06
			2 to <6 years	4	448.5	31.93
			6 to <12 years	7	429.1	21.70
		Fosaprepitant Regimen (Part V)	6 months to <2 years	4	409.0	10.30
			2 to <6 years	6	460.0	40.43
			6 to <12 years	7	459.1	86.53

† =Number of treated subjects with specific electrocardiogram results.

SD = Standard deviation.

††: A follow up 12 lead ECG will be obtained 2 hours after the initial dose of ondansetron in subjects with baseline electrolyte abnormalities including hypokalemia and/or hypomagnesaemia.

Part IV: Day1 – aprepitant 3 mg/kg + ondansetron; Days 2-3 – aprepitant 2 mg/kg + ondansetron.

Part V: Day 1 – fosaprepitant 3 mg/kg + ondansetron.

In addition to AN 50266, 12 additional patients in P134 were observed to have an increase from baseline in QTcB, and an absolute post-treatment QTcB > 460 msec, a threshold that has been cited as a significant prolongation in pediatrics [Ref. 5.4: 042YJY]. Four of these cases were unlikely to be related to aprepitant/fosaprepitant, either because no aprepitant/fosaprepitant was administered (i.e., patients from the ondansetron arm in Part III, n=2), or the baseline measurement was itself elevated such the actual change from baseline was small (n=2). In the remaining 8 cases, the increases observed in the QTcB values were likely confounded by specific medications that are known to cause potential QT prolongation such as anthracycline and platinum based chemotherapies [Ref. 5.4: 042Z4N]. In addition, all patients in Protocol 134 received ondansetron (either alone or concomitantly with aprepitant/fosaprepitant), which carries specific precautions regarding the potential for QTc prolongation in its prescribing information. The MAH has also conducted a thorough QTc study (Protocol 016) in healthy adults receiving a supratherapeutic dose of 200-mg fosaprepitant, and the results of this study demonstrated that fosaprepitant did not identify any prolongation in QTc intervals. Therefore, based on the understanding that chemotherapeutic and antiemetic agents can potentiate prolongations in QTc intervals, and that a fosaprepitant QTc study revealed no potential to prolong the QTc interval, the MAH does not believe the sporadic QTcB increases observed in Protocol 134 are likely attributable to aprepitant/fosaprepitant.

Assessor's comment:

The MAH assessment of the QT data in P134 is accepted. The data are confounded by chemotherapies effect on QTc. The presence of a thorough QTc study (P016) in adults without signals for QTc prolongation is reassuring.

Issue resolved.

QUESTION 8

With regard to the MAH's conclusions based on the exploratory efficacy analyses, the definition and use of the word "effective" could be discussed.

a. **Do internationally accepted definitions exist for efficacy of antiemetics? Can the MAH justify its claims based on such guidelines?**

b. **E.g. is the achievement of 60% of patients with no vomiting (i.e. 40% with vomiting) in the delayed phase (as in study Part IV) to be considered effective? The MAH should discuss and justify the use of the term effective in each of their efficacy conclusions (i.e. even in the absence of support from accepted definitions).**

MAH Response:

The MAH is not aware of any internationally acceptable definition of efficacy in CINV.

Protocol 134 was not intended to be a confirmatory efficacy study to support an indication for CINV; rather, it was conducted to determine the appropriate dosing regimen of aprepitant and fosaprepitant in pediatrics for CINV by assessing PK parameters, and monitoring safety and tolerability in an open label fashion. Efficacy assessments of No Vomiting and Complete Response were explored by comparing the aprepitant and fosaprepitant regimens to ondansetron.

EMEND

The 3-day aprepitant regimen in Part IV (3 mg/kg aprepitant in a Powder for solution [PFS] on Day 1 and 2 mg/kg PFS on Days 2 to 3) demonstrated better control of vomiting than ondansetron which was the main exploratory efficacy assessment (Protocol 134 CSR Table 11-21(page 201)]. Additional assessments included evaluating the number of emetic episodes and Complete Response, which demonstrated fewer emetic episodes overall and a more favorable response rate in the acute, delayed and overall phases in the aprepitant regimen compared to ondansetron (Protocol 134 CSR Tables 11-24 [page 204] and 11-27 [page 207]). Therefore since the aprepitant regimen provided better control of CINV than ondansetron, it appears that the aprepitant regimen was more "effective" than ondansetron in this small pediatric population. This was an initial study in the pediatric population leading to a large, double-blind efficacy study (Protocol 208) which evaluated the aprepitant regimen for the prevention of CINV. The data from Protocol 208 demonstrated that the aprepitant regimen was superior to the control regimen (ondansetron) as assessed by a higher percentage of patients achieving Complete Response and No Vomiting in the acute, delayed, and overall phases. The aprepitant product information for the prevention of CINV in pediatric patients 6 months to <17 years of age will be updated based on the results of a separate pediatric Phase III study (Protocol 208, submitted on December 04th, 2014, as a line extension grouped with two type II variations (EMEA/H/C/000527/X/0049/G) in order to license a 125mg powder for oral suspension for the use in paediatric patients with an age of 6 months to 11 years, and to expand the indication of the 125mg and 80mg capsules from adult to adolescents ages 12 to 17 years for prevention of CINV).

IVEMEND

The fosaprepitant regimens include the following: in Part I, patients 12 to 17 years of age received a 3-day regimen of 115 mg IV fosaprepitant on Day 1 followed by oral aprepitant 80 mg on Days 2 to 3 (Step A) and a single day regimen of 150 mg IV fosaprepitant on Day 1 (Step B); and in Part V, patients 6 months to < 12 years of age received a single day regimen of 150 mg IV fosaprepitant on Day 1.

All fosaprepitant regimens were effective in controlling vomiting in the acute phase. The fosaprepitant 150-mg single-dose regimen (Part I Step B) was effective in all 3 phases in adolescents. However, the fosaprepitant 3 mg/kg (150-mg equivalent) single-dose regimen (Part V) in children <12 years of age was only effective in controlling vomiting in the acute phase. Similar to the approach in the aprepitant regimen addressed above, the same assessment for the evaluation of exploratory "efficacy" can be applied to the fosaprepitant regimens in Protocol 134. The results of this Phase I study supports the clinical program evaluating the appropriate dose of fosaprepitant in an ongoing Phase IIB PK/PD study as well as a planned Phase III pivotal efficacy study assessing the prevention of CINV in pediatric patients' birth to 17 years of age.

Assessor's comment:

a) No internationally acceptable definition of efficacy in CINV has been identified.

b) The question was raised based on the wording of the efficacy conclusions in the CSR of P134 in combination with the, at the time, unclear intentions of the MAH with regard to the use of the data. Thus the question concerned the potential intended claims based on the data in view of the MAH wordings. With the recent submission of the Line extension based on the pivotal randomised phase 3 study P208, with P134 as supportive, the issue is no longer relevant.

Issue resolved.

QUESTION 9

It could also be questioned what efficacy conclusions, if any, can be drawn based on exploratory analyses from a study population of around 20 patients. The MAH is advised to carefully consider their wording in the upcoming change of the product information.

MAH Response:

Please refer to Response #8 and #4.

Assessor's comment:

Please refer to the assessment of Q4 and Q8.

Issue resolved.

QUESTION 10

The MAH should present and discuss efficacy results (e.g. percentage with no vomiting or other comparable outcome) observed in the paediatric patients of the present study compared with the efficacy results in adults at corresponding doses and exposures, including a thorough discussion on any discrepancies and their potential mechanisms. This should be presented in a clear and concise manner, preferably in tabular format with paediatric and adult data side by side.

MAH Response:

EMEND

As requested, Tables 14 and 15 display the side-by side efficacy results following administration of a 3-day regimen of aprepitant in pediatric patients (patients 6 months to 12 years of age administered either highly [HEC] or moderately [MEC] emetogenic chemotherapy in Protocol 134) compared to adults (Protocols 052/054 [HEC] and 071 [MEC]) .

Table 14 Number (%) of Subjects with Complete Response by Phase Protocols 052, 054, 71, and 134 Parts III and IV

	Protocols 052/054 Combined		Protocol 071		Protocol 134 Parts III and IV	
	Aprepitant Regimen (N=521)	Standard Therapy (N=524)	Aprepitant Regimen (N=433)	Standard Therapy (N=424)	Part IV Aprepitant Regimen (N=20)	Part III Ondansetron Regimen (N=19)
Phase	%	%	%	%	%	%
Overall Phase	67.7	47.8	50.8	42.5	45.0	10.5
Acute Phase	86.8	73.2	75.7	69.0	80.0	26.3
Delayed Phase	71.5	51.2	55.4	49.1	60.0	15.8

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

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

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

Aprepitant Regimen in Protocols 052/054: aprepitant 125 mg PO, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, aprepitant 80 mg PO and dexamethasone 8 mg PO on Days 2 and 3, dexamethasone 8 mg PO on Day 4.
Aprepitant Regimen in Protocol 071: aprepitant 125 mg P.O., ondansetron 8 mg P.O. twice daily, and dexamethasone 12 mg P.O. on Day 1 and aprepitant 80 mg P.O. once daily on Days 2 to 3.
Aprepitant Regimen Protocol 134 Part IV: Day 1 - aprepitant 3 mg/kg + ondansetron; Days 2-3 - aprepitant 2 mg/kg + ondansetron.

Table 15 Number (%) of Subjects with No Vomiting by Phase Protocols 052, 054, 071, and 134 Parts III and IV

	Protocols 052/054 Combined		Protocol 071		Protocol 134 Part III and IV	
	Aprepitant Regimen (N=521)	Standard Therapy (N=524)	Aprepitant Regimen (N=432)	Standard Therapy (N=424)	Part IV Aprepitant Regimen (N=20)	Part III Ondansetron Regimen (N=19)
Phase	%	%	%	%	%	%
Overall Phase	71.9	44.9	75.7	58.7	45.0	10.5
Acute Phase	86.6	69.6	87.5	77.3	80.0	26.3
Delayed Phase	76.2	47.8	80.8	69.1	60.0	15.8

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

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

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

Aprepitant Regimen in Protocols 052/054: aprepitant 125 mg PO, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, aprepitant 80 mg PO and dexamethasone 8 mg PO on Days 2 and 3, dexamethasone 8 mg PO on Day 4.
Aprepitant Regimen in Protocol 071: aprepitant 125 mg P.O., ondansetron 8 mg P.O. twice daily, and dexamethasone 12 mg P.O. on Day 1 and aprepitant 80 mg P.O. once daily on Days 2 to 3.
Aprepitant Regimen Protocol 134 Part IV: Day 1 - aprepitant 3 mg/kg + ondansetron; Days 2-3 - aprepitant 2 mg/kg + ondansetron

As noted in the tables, in the adult and pediatric studies, aprepitant was administered as part of a 3-day oral regimen in which the dose in pediatric patients was selected to match the exposure previously observed in adults. Ondansetron was administered across the aprepitant and standard of care arms in both the adult and pediatric studies, however in the pediatric studies the use of dexamethasone was not required and was administered at the discretion of the investigator. While the response rates in Protocol 134 are higher in the aprepitant regimen versus the standard-of-care control regimen, the overall efficacy of Complete Response and No Vomiting rates were lower (most notably in the overall and delayed phases) than those seen in studies of adults receiving MEC or HEC. As discussed by Gore et al. [Ref. 5.4: 03QZZ2], possible reasons for this may be different emetogenicity of chemotherapies, higher chemotherapy dosages, and different combinations of chemotherapeutic agents between the two populations. Additionally, differences in the use of dexamethasone, required in the adult studies and only administered at the discretion of the investigator in Protocol 134, could also have an impact on overall response rates. In Protocol 134, the reductions in nausea and vomiting implied by the Complete Response and No Vomiting rates observed with the aprepitant regimen compared to ondansetron, while lower than those reported in adults, still represent an improvement over standard of care in the paediatric/adolescent patient population, where there is medical need for better prevention of nausea and vomiting.

IVEMEND

As requested, Tables 16 and 17 display the side-by side efficacy results following administration of a single day regimen of fosaprepitant in pediatric patients (6 months to 17 years of age administered either highly [HEC] or moderately [MEC] emetogenic chemotherapy in Protocol 134) compared to adults from Protocol 17 (HEC).

As noted in the tables, in the adult and paediatric studies, fosaprepitant was administered as part of a single day intravenous regimen in which the dose in pediatric patients was selected to match the exposure previously observed in adults. Ondansetron was administered across the fosaprepitant and standard of care arms in both the adult and paediatric studies; however in the paediatric studies the use of dexamethasone was not required and was administered at the discretion of the investigator.

Similar to the aprepitant regimen, the response rates in Part I, including patients 12 to 17 years of age, are higher in the fosaprepitant regimen compared to the ondansetron (control) regimen for Complete Response and No Vomiting. However, when compared to the adult HEC study, the response rates were similar in the delayed phase, higher in the overall phase, and lower in the acute phase. Part V, including patients 6 months to < 12 years of age, revealed that the Complete Response and No Vomiting rates were higher than the ondansetron (control) regimen and comparable to the adult HEC data in the overall phase, while the acute and delayed phase were lower than both the ondansetron and adult HEC response rates. It is notable that the decreased efficacy observed for the delayed phase appears to correlate well with the very low plasma levels observed at delayed time points (e.g., C48hr, C72hr) in the same age groups. Previous studies in adults have suggested that central nervous system (CNS) receptor occupancies >80-85% (as measured by positron emission tomography [PET]) are required for maximal efficacy in CINV; the plasma levels of about 10 ng/mL and about 100 ng/mL will produce NK1 receptor occupancies of about 50 and 90%, respectively. Since the plasma levels at delayed time points in children are below this threshold, these data suggest that response to NK1 blockade in children is similar to that in adults, and that similar CNS receptor occupancy levels may be required to achieve maximal efficacy in children. The data further suggest that it is unlikely that single oral or IV doses are likely to overcome the low plasma exposures observed at delayed time points, and that hence, multiple-day regimens (such as that studied in Part IV of the current study) will be needed for optimal prevention of CINV, particularly in the delayed phase.

Table 16 Number (%) of Subjects with Complete Response by Phase Protocol 017 and 134 Parts I, III, and V

	Protocol 017		Protocol 134 Part I, III, and V		
	Fosaprepitant Regimen (N=1147)	Aprepitant Regimen (N=1175)	Part I (Step B) Fosaprepitant 150 mg Regimen 12 to 17 years (N=11)	Part III Ondansetron Regimen (N=19)	Part V Fosaprepitant 150 mg Regimen 6 months to < 12 years (N=22)
Phase	%	%	%	%	%
Overall Phase	71.9	72.3	72.7	10.5	18.2
Acute Phase	89.0	88.0	90.97	26.3	72.7
Delayed Phase	74.3	74.2	72.7	15.8	18.2

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

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

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

Fosaprepitant Regimen: Fosaprepitant 150 mg, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, dexamethasone 8 mg PO on Day 2, and dexamethasone 16 mg PO on Days 3 and 4.
Aprepitant Regimen: Aprepitant 125 mg PO, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, aprepitant 80 mg PO and dexamethasone 8 mg PO on Days 2 and 3, dexamethasone 8 mg PO on Day 4.
Fosaprepitant (Part I): fosaprepitant 150mg + ondansetron

Fosaprepitant (Part V): fosaprepitant 3mg/kg + ondansetron

Table 17 Number (%) of Subjects with No Vomiting by Phase Protocol 017, and 134 Parts I, III, and V

	Protocol 017		Protocol 134 Part I and V		
	Fosaprepitant Regimen (N=1147	Aprepitant Regimen (N=1175)	Part I (Step B) Fosaprepitant 150 mg Regimen 12 to 17 years (N=11)	Part III Ondansetron Regimen (N=19)	Part V Fosaprepitant 150 mg Regimen 6 months to < 12 years (N=22)
Phase	%	%	%	%	%
Overall Phase	72.9	74.6	72.7	10.5	18.2
Acute Phase	89.4	89.0	90.9	26.3	72.2
Delayed Phase	75.6	76.4	72.7	15.8	18.2

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

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

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

Fosaprepitant Regimen: Fosaprepitant 150 mg, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, dexamethasone 8 mg PO on Day 2, and dexamethasone 16 mg PO on Days 3 and 4.
Aprepitant Regimen: Aprepitant 125 mg PO, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, aprepitant 80 mg PO and dexamethasone 8 mg PO on Days 2 and 3, dexamethasone 8 mg PO on Day 4.
Fosaprepitant (Part I): fosaprepitant 150mg + ondansetron

Fosaprepitant (Part V): fosaprepitant 3mg/kg + ondansetron

Assessor's comment:

Emend

The MAH's assessment is overall agreed. Thus, the overall efficacy of Complete Response and No Vomiting rates were lower than those seen in studies of adults. This could potentially be related to confounding factors such as a lower use of concomitant corticosteroid (dexamethasone), differences in the emetogenicity, doses and combinations of the chemotherapies used. However, PK data submitted in the recent line extension, including data from Study P134, indicated lower exposure (AUC) in all paediatric groups than what has previously been observed in adults, with the lowest mean AUC seen in the group aged 6-11 years, which also had the lowest response rate in the pivotal trial. Overall, children <12 years had lower Cmin values than adults. Thus, the somewhat lower efficacy observed in children compared with adults at corresponding doses could also be related to a lower exposure achieved in children.
This issue is further pursued in the currently ongoing line extension procedure EMEA/H/C/527/X/49/G.

Ivemend

The MAHs assessment is overall agreed. The suboptimal response in the delayed phase in children can be plausibly linked to the observed corresponding plasma levels below that needed to produce the required level of CNS receptor occupancy for optimal antiemetic effect (based on data in adults).

Issue resolved.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The final report of study Protocol 134 (P134) was submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The study is part of an agreed PIP of aprepitant (EMA decision P/0008/2014 adopted on 22 January 2014) to support an extension application for an age appropriate paediatric formulation (powder for suspension) and a label update with information for paediatric use.

Protocol 134 consisted of 5 Parts and enrolled a total of 91 paediatric who were 6 months to 17 years old, had a documented malignancy, and were undergoing moderately – highly emetogenic chemotherapy. Different regimens of Emend (aprepitant), Ivemend (fosaprepitant) and combinations of both were studied in different age sets. Part III of the study served as "control arm" with ondansetron (5-HT3 inhibitor).

The overall efficacy of Emend in P134 with regard to Complete Response and No Vomiting rates were lower than those seen in studies of adults at corresponding doses. This could partly be related to confounding factors such as a less frequent use of concomitant corticosteroid for antiemetic purposes, as well as potential differences in the emetogenicity, doses and combinations of the chemotherapies used. In addition, PK data submitted in the recent line extension, including data from Study P134, indicated lower exposure (AUC) in all paediatric groups than what has previously been observed in adults, with the lowest mean AUC seen in the group aged 6-11 years, which also had the lowest response rate in the pivotal trial. Overall, children <12 years had lower C_{min} values than adults. Thus, the somewhat lower efficacy observed in children compared with adults at corresponding doses could

also be related to the lower exposure achieved in children. This issue is further pursued in the currently ongoing line extension procedure EMEA/H/C/527/X/49/G.

With regard to Ivemend, the suboptimal response in the delayed phase in children can be plausibly linked to the observed plasma levels at corresponding time points below those needed to produce the required level of CNS receptor occupancy for optimal antiemetic effect (based on data in adults).

Recommendation

☒ **Fulfilled**