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EMA/CHMP/356710/2017
Human Medicines Evaluation Division

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

EMEND

aprepitant

Procedure no: EMEA/H/C/000527/P46/041

Note

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

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1. Introduction

On 16 March 2017, the MAH submitted a completed paediatric study for Emend, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the follow up measure(s).

A short critical expert overview has also been provided.

After the initial AR was finalized, the MAH submitted a correction regarding two tables (Table 11-9 and 11-10) in the study report. This AR includes the assessment of the new corrected study report.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that MK-0869 Trial Protocol 219 titled “A Phase IIb, Partially-Blinded, Randomized, Active Comparator-Controlled Study to Evaluate the Pharmacokinetics/Pharmacodynamics, Safety, and Tolerability of Aprepitant in Pediatric Patients for the Prevention of Post Operative Nausea and Vomiting” is not part of the PIP for aprepitant and was designed to support the U.S. paediatric requirements.

2.2. Information on the pharmaceutical formulation used in the study

The aprepitant PIP covered the PONV as well as the chemotherapy-induced nausea and vomiting (CINV) indications and has already been completed. The paediatric indication for CINV in children from 6 months to 17 years of age received a Commission Decision in 2015 as part of EMEA/H/C/000527/X/049. As part of this procedure also the PONV PIP study, P148 was submitted and the PK data were added to the SmPC, but no paediatric indication was proposed.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- MK-0869 Trial Protocol 219 titled “A Phase IIb, Partially-Blinded, Randomized, Active Comparator-Controlled Study to Evaluate the Pharmacokinetics/Pharmacodynamics, Safety, and Tolerability of Aprepitant in Pediatric Patients for the Prevention of Post Operative Nausea and Vomiting”

2.3.2. Clinical study

MK-0869 Trial Protocol 219 titled "A Phase IIb, Partially-Blinded, Randomized, Active Comparator-Controlled Study to Evaluate the Pharmacokinetics/Pharmacodynamics, Safety, and Tolerability of Aprepitant in Pediatric Patients for the Prevention of Post Operative Nausea and Vomiting"

Description

Methods

Objective(s)

The primary objectives of the trial were **pharmacokinetics** and **safety**, with additional exploratory objectives to explore the efficacy of different doses compared to ondansetron with respect to: **complete response** (no vomiting, no retching and no use of rescue medication) and to **no vomiting** in the 24 hours following end of surgery, but also to compare the PK parameters obtained in paediatric subjects following administration of oral aprepitant to the parameters obtained in adults in study MK-0869 protocol 107.

Study design

The study was a partially blinded, randomised, active comparator-controlled study.

Study population /Sample size

In summary, the trial was conducted in 43 centres in 15 countries and included around 220 patients from birth to 17 years of age.

Subject/Patient Inclusion Criteria (as listed in study protocol)

1. Patient is from birth***** (at least 37 weeks gestation and ≥3 kg of weight) to 17 years of age at the time of randomization.

   Note – for the Czech Republic, only patients 6 months to 17 years of age will be eligible for enrolment.

2. Parent/guardian (legally authorized representative) agrees to the patient's participation as indicated by parent/legal guardian signature on the informed consent form. Patients 12-17 years of age, or as required by local regulation, assents and has the ability to understand the nature and intent of the study including the ability to comply with study procedures, and is willing to keep scheduled study visits. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in the Future Biomedical Research.

3. Patient is scheduled to receive general anaesthesia AND:

   Patients must have at least **one** of the following risk factors for PONV (in addition to receiving general anaesthesia):

   Patient is scheduled to have a surgery with an associated risk of PONV: tonsillectomy, adenoidectomy, strabismus surgery, dental surgery, hydrocelectomy, orchidopexy or herniorraphy.

   -OR-

   Patient is scheduled to have an operative procedure associated with PONV: intraoperative opioid use or anticipated opioid administration within the first 24 following surgery.

4. Patient falls within ASA Physical Status Classification I, II or III. (Appendix 6.1).

5. Female patient who has begun menses has a negative urine pregnancy test prior to randomization. Females of reproductive potential agree to remain abstinent or use a barrier form of contraceptive for at least 14 days prior to, throughout, and for at least 1 month following the last dose of study medication. Females taking oral contraceptive agents must agree to add a barrier form of contraception. For countries where abstinence is not considered an accepted method of birth control, a locally acceptable birth control method must be used.

Subject / Patient Exclusion Criteria

1. Patient is undergoing emergency surgery for a life threatening condition.
2. Patient is scheduled to receive propofol for maintenance of anaesthesia. (Note: propofol is permitted for induction of anaesthesia).
3. Patient is expected to receive opioid antagonists (e.g., naloxone, naltrexone) or benzodiazepine antagonists (e.g., flumazenil).
4. Patient is scheduled to undergo cardiac or neurosurgery.
5. Patient has vomiting caused by any organic aetiology (such as gastric outlet obstruction or small bowel obstruction).
6. Patient has vomited within 24 hours prior to surgery.
7. Patient is pregnant or breast-feeding. (Female patients of child bearing potential are required to have a negative urine pregnancy test prior to entering the study on the morning of surgery).
8. Patient has a nasogastric or oral gastric tube intra- or post-operatively for suctioning gastric contents (Note: nasogastric or oral gastric tube intra- or post-operatively may **ONLY** be used for feeding. Patients should be excluded if a nasogastric or oral gastric tube for suctioning is routinely used for the type of surgery to be performed).
9. Patient has abnormal laboratory values as follows (deviations from these guidelines require discussion with the Merck Clinical Monitor):
    a. Liver Function
        i. AST >1.5 x upper limit of normal for age.
        ii. ALT >1.5 x upper limit of normal for age.
        iii. Bilirubin >1.5 x upper limit of normal for age.
    b. Renal Function
        iv. Creatinine >1.5 x upper limit of normal for age
10. Patient has an active infection (e.g., pneumonia), congestive heart failure, bradyarrythmia, any uncontrolled disease (e.g., diabetic ketoacidosis, gastrointestinal obstruction) except for malignancy, or a history of any illness which in the opinion of the investigator, might confound the results of the study or pose unwarranted risk in administering study drug or concomitant therapy to the patient.
11. Patient is mentally incapacitated or has a significant emotional or psychiatric disorder that in the opinion of the investigator precludes study entry.
12. Patients with a known history of QT prolongation or is taking any medication that is known to lead to QT prolongation.
13. Patient is currently a user of any illicit drugs, including marijuana or has current evidence of alcohol abuse (defined using DSM-IV criteria) as determined by the investigator.
14. Patient has ever participated in a study with aprepitant or fosaprepitant, is currently participating in a study with another NK-1 antagonist, or has taken a non-approved (investigational) drug within the last 4 weeks.
15. Patient is allergic to aprepitant, ondansetron or any 5-HT3 antagonist.
16. Patient is taking the anti-coagulant warfarin.
17. Other Excluded Medications.

Treatments

Patients were randomised to either control regimen of ondansetron intravenously (iv) or aprepitant as oral solution (see table below):

Aprepitant Dose for Each Age Group in Each Dose Arm

Aprepitant Dose Arm	Adult Equivalent Dose	Age-Specific Dose Adjustments				
		12 to 17 years of age	2 to <12 years of age	Birth to <2 years of age		
				4 months to <2 years	1 to <4 months	Birth to <1 month
Dose 1	125 mg	125 mg	3 mg/kg (up to 125 mg)	3 mg/kg	1.5 mg/kg	0.75 mg/kg
Dose 2	40 mg	40 mg	15 mg + 1.1 mg/kg (up to 40 mg)	15 mg + 1.1 mg/kg	7.5 mg + 0.55 mg/kg	3.7 mg + 0.27 mg/kg
Dose 3	10 mg	10 mg	4 mg + 0.27 mg/kg (up to 10 mg)	4 mg + 0.27 mg/kg	2 mg + 0.14 mg/kg	1 mg + 0.069 mg/kg

Outcomes / endpoints

See above

Statistical Methods

Results

Recruitment / Number analysed

Baseline data

Number of subjects in each age category was balanced between treatment groups. There was a slightly smaller proportion female patients (in adults, female gender is a risk factor for PONV) in the comparator group treated with ondansetron, see table below:

	Aprepitant 125 mg		Aprepitant 40 mg		Aprepitant 10 mg		Ondansetron		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	57		55		56		52		220	
Gender										
Male	34	(59.6)	36	(65.5)	28	(50.0)	36	(69.2)	134	(60.9)
Female	23	(40.4)	19	(34.5)	28	(50.0)	16	(30.8)	86	(39.1)
Age (Months)										
Birth to <2 years	14	(24.6)	12	(21.8)	13	(23.2)	11	(21.2)	50	(22.7)
2 years to <6 years	14	(24.6)	14	(25.5)	15	(26.8)	14	(26.9)	57	(25.9)
6 years to <12 years	13	(22.8)	15	(27.3)	14	(25.0)	13	(25.0)	55	(25.0)
12 years to 17 years	16	(28.1)	14	(25.5)	14	(25.0)	14	(26.9)	58	(26.4)
Mean	90.4		87.5		85.1		86.0		87.3	
SD	64.3		64.6		59.7		65.0		63.0	
Median	73.0		78.0		71.0		73.5		74.0	
Range	1 to 214		4 to 212		1 to 195		2 to 214		1 to 214	
Planned Use of Opioids										
N	14	(24.6)	10	(18.2)	13	(23.2)	11	(21.2)	48	(21.8)
Y	43	(75.4)	45	(81.8)	43	(76.8)	41	(78.8)	172	(78.2)

One subject was excluded from this table after being accidentally randomized in IVRS to the 2.5 mg dose arm, which was not evaluated in this study; results for this subject are presented separately.

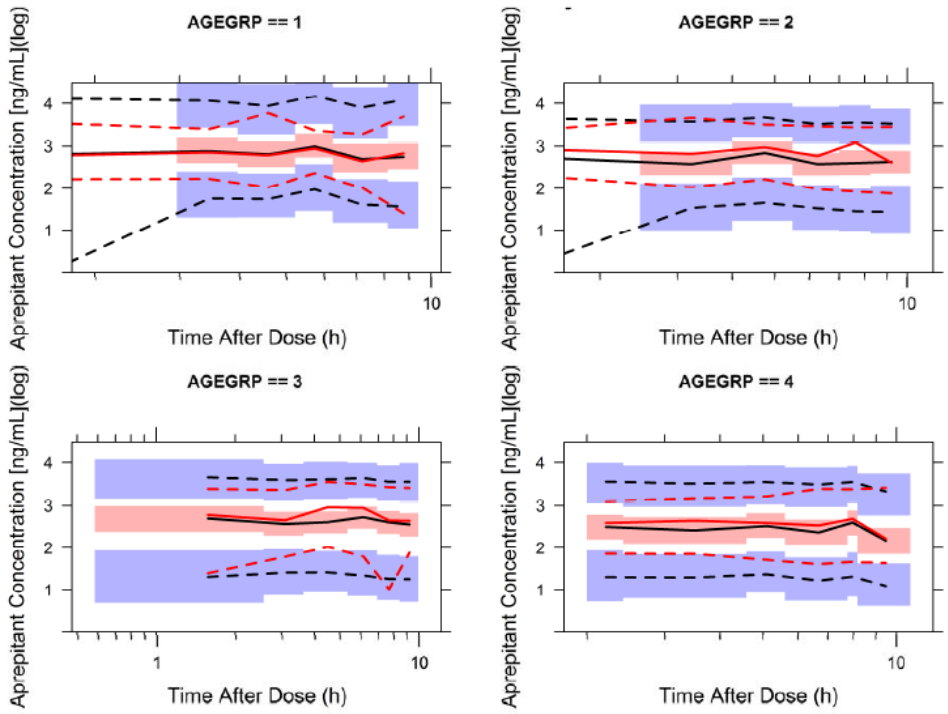
Pharmacokinetics

A popPK (population pharmacokinetic) model of aprepritant has previously been developed based on three completed studies, oral administration of aprepritant (capsule) to adolescent (P097), paediatric patients, 0.5-17 years, receiving either oral aprepitant (suspension) or IV fosaprepitant (P134) and patients from 0.5-17 years reiving oral administration of aprepitant (suspension; P148).

The popPK analysis was assessed in procedure EMEA/H/C/527/X/49/G and the model was concluded to adequately describe the observed data across all age categories and may be considered for simulations.

The model was recently updated including available PK data, not yet reported/submitted, following an iv single dose of fosaprepitant (concomitantly with IV ondansetron) in paediatric cancer patients birth to 17 years of age (P029). The updated model does not include a function for CYP3A4 maturation, which is an important component in children less than 2 years. The appropriateness of the population PK model to perform simulations to derive full PK profiles for subjects in Protocol 219 was evaluated using visual predictive checks (VPCs) on concentration-time profiles of aprepitant, see figure below.

Visual Predictive Check for Oral Aprepitant Administration by Age Group of Pediatric Population



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 ≤17 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% confidence interval of predicted concentrations (50th percentiles are in red and 2.5th and 97.5th percentiles in blue which full and dashed black lines representing the medians of the shared areas).

Summary statistics of predicted plasma PK parameters comparison following a 40 mg oral administration of aprepitant in paediatric and adult subjects are shown in the table below. Pharmacokinetic analyses demonstrated a dose-exposure relationship in the aprepitant treatment groups in all age cohorts across all doses evaluated in this study. As compared with adults, 40-mg aprepitant in paediatrics (<12 years) provides exposures (AUC0-inf and Cmax) that are generally

higher, and increasing with decrease in age, than those observed in adults. Particularly, in the birth to <2-year age group, upper confidence intervals of geometric mean ratios were greater than 2.5 for both AUC0-inf and Cmax values. In contrast, a single 40-mg dose of aprepitant in adolescent subjects 12 to 17 years of age resulted in exposures (AUC0-inf, Cmax) generally comparable with adults.

Plasma Pharmacokinetic Parameter Summary Statistics for Aprepitant Following Administration of 40 mg

PK Parameter	Age Group	N	GM (95% CI)	GMR vs Adult (90% CI)
AUC0-inf (ng•hr/mL)	Birth to <2 Yrs	7	19400 (12900, 29200)	2.40 (1.72, 3.35)
	2 to <6 Yrs	10	13000 (9520, 17700)	1.60 (1.23, 2.09)
	6 to <12 Yrs	11	10900 (9050, 13100)	1.34 (1.13, 1.60)
	12 to 17 Yrs	10	7340 (6200, 8690)	0.91 (0.77, 1.07)
	Adult	12	8090 (7100, 9220)	
Cmax (ng/mL)	Birth to <2 Yrs	7	1150 (716, 1840)	1.68 (1.13, 2.49)
	2 to <6 Yrs	10	946 (745, 1200)	1.38 (1.08, 1.76)
	6 to <12 Yrs	11	743 (608, 908)	1.09 (0.87, 1.36)
	12 to 17 Yrs	10	444 (388, 508)	0.65 (0.54, 0.79)
	Adult	12	684 (558, 839)	

Log transformed PK parameters were analyzed via a linear mixed-effects model containing fixed effect for age (Birth to 2 years, 2 to <6 years, 6 to <12 years, 12 to 17 years and adult).

Historical adult data are MK-0869 PN 107 Treatment C 40 mg oral dose.

Efficacy results

The odds of Complete Response relative to ondansetron were similar in all three aprepitant treatment groups, see table below:

Number of subjects with complete response in the 24 hours following the end of surgery, Intent to treat population (ITT)

Treatment	n/m(%)	Difference[†]	95% CI for Difference[‡]
Aprepitant 125 mg	48/57 (84.2)	3.4	(-11.2, 18.4)
Aprepitant 40 mg	48/55 (87.3)	6.4	(-7.9, 21.1)
Aprepitant 10 mg	48/56 (85.7)	4.9	(-9.5, 19.8)
Ondansetron	42/52 (80.8)		

[†] Aprepitant - Control Regimen (Ondansetron).

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

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

Complete Response: No vomiting, no retching, and no use of rescue medication.

One subject was excluded from this table after being accidentally randomized in IVRS to the 2.5 mg dose arm, which was not evaluated in this study; results for this subject are presented separately.

Source: [P219MK0869: analysis-adsl; adeff]

For the aprepitant dose comparisons and with regard to ondansetron, the observed differences were not clinically meaningful for neither “complete response” nor “no vomiting”. However, the trial was not powered to evaluate efficacy.

Safety results

Adverse events (AE) occurred most frequently in subjects below two years of age. AEs were reported by 39.5% (87/220 subjects) of the total population. AEs were reported for 37% (62/168 subjects) of subjects in the aprepitant group compared to 48,1% (25/52 subjects) in the ondansetron group, and there was no consistent pattern noted within an age category. Two aprepitant-treated subjects experienced AEs that were considered drug-related. One subject in the aprepitant 125-mg treatment group had an AE of electrocardiogram QT prolongation (mild); the investigator assessed this event as possibly related to both aprepitant and ondansetron. One subject in the aprepitant 40-mg treatment group had an AE of tachycardia (moderate), which the investigator assessed as related to ondansetron. However, neither of these two patients with drug-related AEs received ondansetron, both received aprepitant. Nine subjects experienced 10 SAEs. None were considered related to study medication, and all resolved.

2.3.3. Discussion on clinical aspects

Aprepitant was tested at three different dose levels equivalent to 10, 40 and 125 mg in adults and compared to a control regimen with ondansetron. One inclusion criteria was anticipation of intra- or post- operative opioid use. Different types of opioids, and different routes of administration, are more or less emetogenic. This opens for a potential heterogeneous study population which could hamper the comparison between study groups. Exclusion criteria's are deemed reasonable.

There is a small numerical difference in efficacy between the different dosing regimens of aprepitant and ondansetron, but not statistically nor clinically significant (an increase in complete response of approximately 5 percentage points compared to the 80 % achieved by ondansetron).

In the aprepitant arms 2 patients experienced AEs that were considered related to study drug (aprepitant or ondansetron); QT prolongation (mild), and tachycardia (moderated) respectively. These single cases are not on their own sufficient to conclude an ADR in the absence of other supporting circumstances (e.g. positive re-challenge). In two previous non-clinical repeated dose toxicity studies that was filed for the initial application of aprepitant, ECG measurements did not demonstrate any effects on the cardiovascular system, in particular on the QT interval, at exposures up to 80-fold over clinical exposure. Tachycardia has previously been reported in 0.7% - 2% for subjects receiving different doses of aprepitant in a pattern potentially compatible with a dose-response relationship (EPAR 2007-02-14), but is not currently included as ADR in the SmPC.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The corrected study report (correction of tables 11-9 and 11-10) provided by the MAH have been assessed and the corrections provided does not impact the end results of the assessment. Further, it does not entail any changes (compared to the previous version) of this assessment report, apart from this paragraph and the information in the introduction.

A population PK model was used to describe the PK data collected in the P219 study. Due to the use of model-based exposure comparisons between adults and children enforces high demands on the accuracy of the population PK model. However, in this procedure, no formal assessment has been conducted as no full model report has been provided. Hence the reported information does not provide

sufficient support for a change in the SmPC. In general, in paediatrics patients below the age of 12 years higher aprepitant exposures (AUC0-inf and Cmax) were observed following a 40 mg oral administration compared to adults. For adolescent subjects 12 to 17 years of age exposures were comparable to adults.

The data provided in the paediatric study report P219 were not powered for efficacy. Numerically slightly higher response rates were observed for aprepitant compared to ondansetron. Regarding assessment of clinical safety, the study report does not contain new data that provides sufficient support for a change in SmPC.

However, the following safety data should be ***submitted by the MAH within the next PSUSA***: A cumulative review of frequency of tachycardia in different aprepitant dosing groups for adults and children below the age of 18, respectively. SmPC wording should be proposed, if appropriate.

4. Recommendation

☒ Fulfilled:

No regulatory action required.