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

Fycompa

perampanel

Procedure no: EMEA/H/C/002434/P46/014

Note

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

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1. Introduction

On 10 August 2015, the MAH submitted a completed paediatric study for Fycompa, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study E2007-G000-232 (Study 232) is part of a clinical development program. The variation application consisting of the full relevant data package (i.e containing several studies) is expected to be submitted by April 2021. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Perampanel was provided as 0.5 mg/mL oral suspension stock and was to be administered as provided or diluted with placebo to appropriate concentrations, as needed. Batch numbers used were: P13015AZA, P13018AZA, P23004AZA, P23007AZA, P14007AZA, P14010AZA, P14013AZA, P19016AZA, P19019AZA, P23013AZA, and P23016AZA

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted final reports for:

- E2007-G000-232
- E2007-G000-232 (Extension Phase)

The two studies are related, but following the MAH's presentation of the data from them separately there is some duplication in the descriptions presented in this report.

2.3.2. Clinical study E2007-G000-232

An Open-Label Pilot Study With an Extension Phase to Evaluate the Pharmacokinetics, and to Generate Preliminary Safety, Tolerability, and Efficacy of Perampanel (E2007) Oral Suspension When Given as an Adjunctive Therapy in Paediatric Subjects From 2 to Less Than 12 Years of Age With Epilepsy.

Methods

Objective(s)

Primary Objective

• To evaluate the pharmacokinetics (PK) of perampanel following oral suspension administration given as an adjunctive therapy in paediatric subjects from 2 to less than 12 years old with epilepsy

Secondary Objectives

• To evaluate the short- and long-term safety and tolerability of perampanel oral suspension in paediatric subjects from 2 to less than 12 years of age

• To evaluate the short- and long-term efficacy of perampanel oral suspension in paediatric subjects with epilepsy

• To evaluate the long-term effect of perampanel oral suspension on growth in children

• To explore the PK/pharmacodynamic (PD) relationship

• To evaluate the palatability of perampanel oral suspension in paediatric subjects from 2 to less than 12 years of age

Study design

This was a multicenter, multiple ascending dose, open-label study with an extension phase conducted to evaluate the PK and to generate preliminary safety, tolerability, and efficacy data for perampanel oral suspension when given as an adjunctive therapy in paediatric subjects from 2 to less than 12 years of age with epilepsy. Only the results of the Core Study are presented in this clinical study report. Subjects were enrolled into 2 cohorts depending upon age at the time of consent/assent: Cohort 1 consisted of subjects from ≥7 to <12 years of age and Cohort 2 consisted of subjects from ≥2 to <7 years of age.

The Core Study consisted of 2 phases: the Pretreatment Phase and the Treatment Phase. The Pretreatment Phase lasted up to 2 weeks in duration, during which subjects were assessed for their eligibility to participate in the study. The Treatment Phase consisted of 3 periods: Titration (7 weeks), Maintenance (4 weeks), and Follow-up (4 weeks; only for those subjects not rolling over into the Extension Phase after completing the Treatment Phase and for those subjects who discontinued from the study).

Treatment Phase

During the Titration and Maintenance Periods of the Treatment Phase, subjects were dosed with perampanel oral suspension. Subjects continued to take their baseline anti-epileptic medication regimen throughout the Treatment Phase. Changes of baseline anti-epileptic drug (AEDs; addition, deletion, or adjustment in dose) were not allowed during the Treatment Phase.

Titration Period

During the 7-week Titration Period, subjects received perampanel oral suspension once daily. Subjects started at a set daily dose of 0.015 mg/kg and had doses up-titrated at 1 week intervals (6 titration steps) to a maximum daily dose of 0.18 mg/kg or until the maximum tolerated dose based on tolerability was reached. At the completion of the Titration Period, subjects began the Maintenance Period of the Treatment Phase.

Maintenance Period/Follow-Up Period

During the 4-week Maintenance Period, subjects continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period. Subjects continued taking this dose level once daily for the duration of the Maintenance Period of the Treatment Phase.

Subjects who did not roll over into the Extension Phase or those who discontinued from the study were required to complete the Follow-up Period 4 weeks after the last dose of treatment, as part of the

Treatment Phase of the Core Study. During this period, subjects did not receive study drug. At the end of the Follow-up Period, subjects returned to the clinical site and underwent all end-of-study procedures.

Blood samples were collected by the dried blood spot (DBS) method and the concentrations of perampanel were quantified by a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) analytical method in sodium heparinized human blood.

Study population /Sample size

This study enrolled male or female subjects aged from 2 to less than 12 years at the time of consent/assent.

Subjects had a diagnosis of epilepsy with any type of seizure according to the International League Against Epilepsy's (ILAE) Classification of Epileptic Seizures. Diagnosis should have been established at least 6 months prior to Visit 1, by clinical history and an electroencephalogram (EEG) that was consistent with epilepsy; normal interictal EEGs were allowed provided that the subject met the other diagnosis criterion (i.e., clinical history). Subjects must have had a brain imaging scan (computed tomography or magnetic resonance imaging) prior to Visit 1 that ruled out a progressive cause of epilepsy and had 1 or more seizure(s) during the 4 weeks prior to Visit 1. Subjects were currently being treated with stable doses of 1 to a maximum of 3 AEDs for at least 4 weeks prior to Visit 1 and throughout the study duration (only 1 perampanel-inducing AED [ie, carbamazepine, oxcarbazepine, phenytoin] out of the maximum of 3 AEDs was allowed in at least one third of the subjects in each cohort and was not to exceed one half of the population of each cohort; the remaining subjects were not to be taking any inducer). Subjects had been on their current concomitant AED regimen for 2 months or more with a stable dose for at least 4 weeks prior to Visit 1.

A sample size of 24 subjects in each cohort was considered a reasonable number to allow an initial exploration of the PK profile of perampanel in this age group. However, a cohort size of 22 subjects in Cohort 2 was accepted per a Paediatric Investigation Plan modification.

Treatments

Perampanel was provided as 0.5 mg/mL oral suspension stock and was to be administered as provided or diluted with placebo to appropriate concentrations, as needed. Dilutions were to be administered orally and daily according to the subject's weight. Dosing was to occur before bedtime.

Batch numbers used were: P13015AZA, P13018AZA, P23004AZA, P23007AZA, P14007AZA, P14010AZA, P14013AZA, P19016AZA, P19019AZA, P23013AZA, and P23016AZA.

The duration of treatment for each subject in the Core Study was as follows:

Pretreatment Phase: up to 2 weeks; Treatment Phase: 11 weeks (7-week Titration + 4-week Maintenance) + a 4-week Follow-up for those not entering the Extension Phase

Outcomes/endpoints

Efficacy

Efficacy was assessed by seizure counts and types as recorded on a subject's diary, and by the Clinical Global Impression (CGI), CGI of Severity (CGIS), and CGI of Change (CGIC).

Pharmacokinetics

Blood concentrations of perampanel were measured via collection of blood samples and subsequent population PK analysis.

Efficacy and selected safety endpoints were correlated against dose and/or exposure.

Safety

Safety was assessed by monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs), regular monitoring of clinical laboratory tests (i.e., haematology, blood chemistry, and urinalysis), regular measurement of vital signs and electrocardiograms (ECGs), the performance of physical and neurological examinations, and the completion of a Photosensitivity Questionnaire. In addition, growth was assessed for this age population by measurement of height and weight, thyroid and insulin-like growth factor-2 (IGF-2) testing.

A suicidality scale questionnaire (Columbia-Suicide Severity Rating Scale [C-SSRS]) was also administered to subjects aged 6 years and older at the time consent/assent.

Other

A Palatability Questionnaire was completed

Statistical Methods

Details of statistical methods and analyses were specified in the statistical analysis plan (SAP).

Analysis Sets:

PK Analysis Set: the PK Analysis Set was the group of subjects with at least 1 PK assessment of perampanel with a documented dosing history.

PK/PD Analysis Set: the PK/PD Analysis set was the group of subjects for whom exposure to perampanel could be derived and who had seizure frequency data.

Safety Analysis Set: the Safety Analysis Set was the group of subjects who received study drug treatment and had at least 1 postdose safety assessment.

Full Analysis Set: the Full Analysis Set (FAS) was the group of subjects who received study drug, had any seizure frequency data during the 2-week Pretreatment Phase plus the 4 weeks prior to the Pretreatment Phase (Visit 1), and during the Treatment Phase.

Interim Analyses:

PK interim analyses were carried out in Aug 2012 (8 subjects), Dec 2012 (18 subjects), and Nov 2013 (38 subjects). These analyses were performed to obtain preliminary data on PK to assist in determining dosing for future paediatric studies.

There were 4 data monitoring committee meetings: Jul 2012 (data cutoff 06 Jun 2012), Nov 2012 (data cutoff 26 Oct 2012), Apr 2013 (data cutoff 01 Mar 2013), and Feb 2014 (data cutoff 10 Jan 2014).

Efficacy Analyses:

This study was designed to assess PK and provide preliminary safety, tolerability, and efficacy data. Given the small sample size and lack of placebo or comparator, it was not possible to draw definitive conclusions regarding the efficacy of perampanel oral suspension for the population in this study. As such, no formal statistical tests were performed. Summary statistics were displayed for all efficacy parameters in the FAS.

The efficacy endpoints were:

• Percent change in 28-day seizure frequency in the Treatment Phase compared to Baseline. The primary analysis of baseline seizure frequency per 28 days was calculated using seizure diary data from the 2-week Pretreatment Phase. A secondary analysis of baseline seizure frequency per 28 days was calculated using seizure diary data from the 2-week Pretreatment Phase plus the seizure history data from 4 weeks prior to Visit 1.

• Responder rate, defined as the proportion of subjects with a 50% decrease in 28-day seizure frequency during the Maintenance Period compared to Baseline, where the baseline seizure frequency per 28 days was calculated as above.

• Seizure-free rate, defined as the proportion of subjects who were seizure-free during the Maintenance Period.

• CGIC at end of treatment (EOT).

Pharmacokinetic Analyses:

Perampanel blood concentrations in this study were summarised at each applicable visit.

A population PK approach was used to characterize the PK of perampanel, with data from this study pooled with data from adolescents with partial-onset seizures (POS) from 1 Phase 2 study (Study 235) and 3 Phase 3 studies (Study 304, Study 305, and Study 306). The effect of covariates (ie, most common concomitant AEDs, demographics) on perampanel PK was evaluated. The PK model was parameterised for apparent clearance (CL/F) and apparent volume of distribution (V/F). The derived exposure parameter steady-state average concentration during a dosing interval (Cav,ss) was calculated from the model using the individual posterior estimates of CL/F and dosing history.

PK/PD Analyses:

No PK/PD analyses were performed for either efficacy or safety due to there being limited data for the different seizure types and due to the small number of subjects who experienced AEs; however, the PK/PD relationship between exposure to perampanel and percent reduction from Baseline in 28-day average seizure frequency during the Maintenance Period was explored graphically.

Safety Analyses:

All safety analyses were performed on the Safety Analysis Set.

Safety data, presented by cohort, were summarised on an “as treated” basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables included treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG results, growth parameters (height, weight, thyroid and IGF-2 parameters), suicidality, and photosensitivity. Study Day 1 for all safety analyses was defined as the date of the first dose of study drug.

Other Analyses:

Data from the Palatability Questionnaire were summarized

Results

Recruitment / Number analysed

A total of 50 out of 63 subjects who were screened continued into the Core Study. All 50 subjects received at least 1 dose of study drug; 22 subjects were aged ≥2 to <7 years (Cohort 2) and 28 subjects were aged ≥7 to <12 years (Cohort 1). The number (percentage) of subjects who completed the Core Study was 20 (90.9%) subjects in Cohort 2 and 22 (78.6%) subjects in Cohort 1.

The FAS (50 subjects) was the primary analysis set used for efficacy analyses; the Safety Analysis Set (50 subjects) was the group of subjects who received study drug treatment and had at least 1 postdose safety assessment. In this study, the FAS and the Safety Analysis Set were identical.

For Study 232, data from 42 pediatric subjects were available from the Maintenance Period for population PK analysis. The final PK dataset included 194 subjects, aged from 2 to 17 years, from Study 232, Study 235, Study 304, Study 305, and Study 306. The graphical PK/PD seizure frequency analysis population for Study 232 alone also consisted of 42 subjects during Maintenance Period. The presence or absence of the most common AEs was derived. Adverse event data at each visit during the Maintenance Period was used; however, as there were no AEs experienced in more than 10 subjects, no evaluation was performed for the PK/PD relationship between Cav,ss and any of the AEs.

Baseline data

The majority of subjects were male (34 [68.0%]) and white (40 [80.0%]). Median age was 5.0 (range: 2 to 6) years in Cohort 2 (≥2 to <7 years) and 9.0 (range: 7 to 11) years in Cohort 1 (≥7 to <12 years).

Pharmacokinetics, Pharmacodynamics, Pharmacogenomics

The PK results from the population PK analysis for this study, pooled with data from adolescents with POS from 1 Phase 2 study (Study 235) and 3 Phase 3 studies (Study 304, Study 305, and Study 306) are consistent with results from previous analyses. Higher perampanel clearance was observed with concomitant cytochrome P450 (CYP) 3A4/5-inducing AEDs; clearance was 1.9-fold higher with concomitant oxcarbazepine or phenytoin and was 2.6-fold higher with concomitant carbamazepine.

The PK/PD relationship between exposure to perampanel and percent reduction from Baseline in 28-day average seizure frequency during the Maintenance Period was not modelled due to the limited number of subjects who experienced each seizure type. Additionally, the PK/PD relationship between exposure to perampanel and most frequent AEs during the Maintenance Period was not explored since only a small number of subjects experienced AEs in the study.

The PK of perampanel was dose- and time-independent and was not significantly affected by age, weight, gender, race (Caucasian versus non-Caucasian), hepatic function markers (ALT and AST), renal function marker (creatinine clearance), formulation and co-administration of other AEDs (valproic acid, lamotrigine, topiramate, and levetiracetam). These findings were also consistent with the previous population-based analyses of perampanel PK in both adults (Report CPMS-E2007-2011-003) and adolescents.

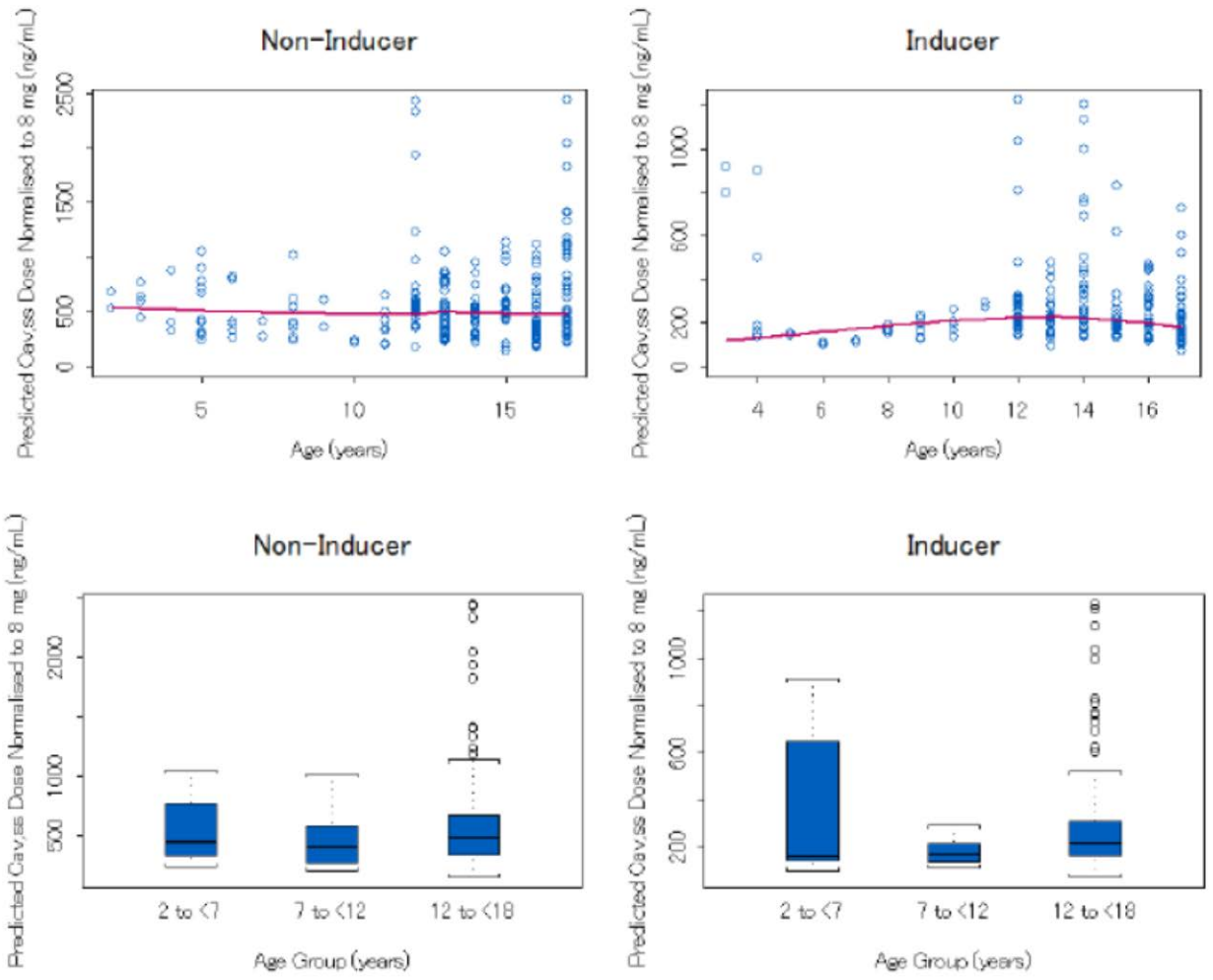

Figure: Relationship Between Model Predicted Dose-Normalized Cav,ss of Perampanel Dose-Normalized to 8 mg and Age. (Cav,ss = steady-state average concentration during a dosing interval.)

Efficacy results

Based on the FAS for efficacy, the analyses of efficacy endpoints indicated that perampanel reduced the occurrence of seizures. Seizure frequency per 28 days decreased during the Treatment Phase relative to Baseline (Pretreatment Phase plus 4 weeks prior to Visit 1); median percent change in seizure frequency per 28 days as compared to baseline for overall seizures was -43.6% in Cohort 2 (≥2 to <7 years) and -33.9% in Cohort 1 (≥7 to <12 years). Responder rate for overall seizures was 72.7% in Cohort 2 and 53.8% in Cohort 1. Of the subjects who completed the Core Study, 9 (21.4%) subjects overall (15.0% in Cohort 2 and 27.3% in Cohort 1) achieved seizure-free status during the Maintenance Period.

The CGIC results showed that at EOT the majority of subjects (63.6% and 53.6% in Cohort 2 and Cohort 1, respectively) were very much improved or much improved compared to Baseline.

Safety results

The median daily dose of perampanel was 0.09 mg/kg during the Titration Period and 0.17 mg/kg during the Maintenance period. Exposure was similar in the 2 cohorts, with the exception that in the Titration Period no subjects in Cohort 2 and 7 (25.0%) subjects in Cohort 1 were in the less than or

equal to 0.03 mg/kg mean daily dose category, and 19 (86.4%) subjects in Cohort 2 and 17 (60.7%) subjects in Cohort 1 were in the greater than 0.06 to 0.12 mg/kg mean daily dose category.

TEAEs occurred in 22 (100%) subjects in Cohort 2 (≥2 to <7 years) and 27 (96.4%) subjects in Cohort 1 (≥7 to <12 years). The most frequently reported (≥10%) TEAEs were pyrexia, somnolence, aggression, cough, dizziness, irritability, upper respiratory tract infection, and vomiting in Cohort 2, and fatigue, irritability, vomiting, pyrexia, increased appetite, somnolence, weight increased, and abdominal pain upper in Cohort 1.

There were no deaths during treatment or within 30 days after the last dose.

SAEs were reported in 13.6% and 17.9% of subjects in Cohort 2 and Cohort 1, respectively; no SAE was reported in more than 1 subject. All subjects recovered from their SAE with no sequelae. None of the subjects discontinued study treatment due to these events, with exception of 1 subject in Cohort 1 who had a severe SAE of abnormal behaviour in the Titration Period.

The percentage of subjects with TEAEs that resulted in discontinuation of study drug was 4.5% in Cohort 2 and 7.1% in Cohort 1. None of the events leading to discontinuation were reported in more than 1 subject.

TEAEs resulting in dose adjustment occurred in 9 (40.9%) subjects in Cohort 2 and 8 (28.6%) subjects in Cohort 1. The TEAEs most commonly resulting in adjustment of study drug dose were fatigue and irritability (reported in 3 [6.0%] and 4 [8.0%] subjects in Cohort 2 and Cohort 1, respectively). The most common dose adjustment due to an AE was dose reduction (in 14 [28.0%] subjects overall). All dose adjustments due to TEAEs occurred during the Titration Period. The pattern of occurrence of TEAEs that resulted in dose reduction, dose interruption, or drug discontinuation by week during the Titration Period was similar in the 2 cohorts, except that during the first 2 weeks no subject in Cohort 2 and 2 subjects in Cohort 1 had such TEAEs. In both cohorts, the incidence increased in the later weeks of the Titration Period and was higher in the group of subjects who were not taking a concomitant perampanel-inducing AED.

There were no clinically important changes in mean laboratory values during the study and no shifts of clinical concern. The incidence of markedly abnormal laboratory values was low and generally comparable in the 2 cohorts. The majority of the subjects who had markedly abnormal values were taking concomitant AEDs such as carbamazepine that are known to cause laboratory abnormalities.

There were no clinically important changes in vital signs or ECG parameters.

The C-SSRS data showed no notable findings relating to suicidality.

The results of the Photosensitivity Questionnaire showed that the majority of subjects had no notable reaction.

The results of the Palatability Questionnaire showed that the majority of subjects/guardians found it easy or very easy for them/their child to take the medicine every day.

2.3.3. Clinical study E2007-G000-232 (Extension Phase)

An Open-Label Pilot Study With an Extension Phase to Evaluate the Pharmacokinetics, and to Generate Preliminary Safety, Tolerability, and Efficacy of Perampanel (E2007) Oral Suspension When Given as an Adjunctive Therapy in Pediatric Subjects From 2 to Less Than 12 Years of Age With Epilepsy.

Methods

Objective(s)

Note: only objectives pertaining to the Extension Phase are listed. The following objectives were all secondary objectives for the study; however, the first bullet point was nominated in the Statistical Analysis Plan (SAP) as the primary objective for the Extension Phase.

Secondary Objectives

• To evaluate the long-term safety and tolerability of perampanel oral suspension in paediatric subjects from 2 to less than 12 years of age

• To evaluate the long-term efficacy of perampanel oral suspension in paediatric subjects with epilepsy

• To evaluate the long-term effect of perampanel oral suspension on growth in children

Study design

This final synoptic report presents all data from the entire study (Core Study plus Extension Phase) for those subjects who continued into the Extension Phase.

This was a multicenter, multiple ascending dose, open-label study with an Extension Phase.

Only the results from subjects who entered the Extension Phase are presented.

The Core Study consisted of 2 phases: the Pretreatment Phase and the Treatment Phase. The Pretreatment Phase lasted up to 2 weeks, during which subjects were assessed for their eligibility to participate in the study. The Treatment Phase consisted of 3 periods: Titration (7 weeks), Maintenance (4 weeks), and Follow-up (4 weeks; only for those subjects not rolling over into the Extension Phase after completing the Treatment Phase and for those subjects who discontinued from the study). Subjects were enrolled into 2 cohorts depending upon age at the time of consent/assent: Cohort 1 consisted of subjects from equal or greater than 7 to less than 12 years of age and Cohort 2 consisted of subjects from equal or greater than 2 to less than 7 years of age.

Extension Phase

All subjects who completed all scheduled visits up to and including the final visit of the Treatment Phase (Visit 8) were eligible to participate in the Extension Phase of the study. The Extension Phase consisted of 2 periods: Maintenance (41 weeks) and Follow-up (4 weeks).

Subjects continued taking perampanel oral suspension once daily, at the dose level achieved at the end of the Treatment Phase. The maximum daily dose level subjects could receive was 0.18 mg/kg; the maximum total daily dose a subject was allowed was 12 mg. For subjects who rolled over into the Extension Phase, the last visit of the Maintenance Period in the Treatment Phase of the Core Study was the first visit of the Extension Phase. During the Extension Phase, changes of concomitant anti-epileptic drugs (AEDs; addition, deletion, or adjustment in dose) were allowed. However, if changes did occur, subjects were to be carefully monitored, especially when switching between an inducer AED and a non-inducer AED.

Study population /Sample size

Male and female subjects aged 2 to less than 12 years of age, were eligible for the Extension Phase of this study if they completed all scheduled visits up to and including Visit 8 in the Treatment Phase of the Core Study and had shown compliance with the inclusion and exclusion criteria for the study.

Subjects were not permitted to participate in another study involving administration of an investigational drug or device for the full duration of the Extension Phase (ie, up to and including the Follow-Up Visit).

Treatments

Maintenance Period

Subjects continued taking perampanel oral suspension once daily, at the dose level achieved at the end of the Treatment Phase. The maximum daily dose level subjects could receive was 0.18 mg/kg. The maximum total daily dose a subject was allowed was 12 mg.

Batch numbers used were: P13015AZA, P13018AZA, P14007AZA, P14010AZA, P14013AZA, P19015AZA, P19016AZA, P19019AZA, P23004AZA P23007AZA, P23013AZA, P23016AZA, and P23019AZA.

Duration of Treatment

Core Study: Pretreatment Phase: up to 2 weeks; Treatment Phase: 11 weeks (7-week Titration + 4-week Maintenance).

Extension Phase: 41-week Maintenance + 4-week Follow-up.

For the Core Study + Extension Phase, the maximum planned total duration of treatment for each subject was 52 weeks; the maximum total duration of the study for each subject was 58 weeks.

Dose adjustment was allowed during the Extension Phase if necessary, per the investigator's clinical judgment. Subjects returned to the clinic for an unscheduled visit for any dose increase; however, dose decreases could be done via telephone.

All dose adjustments during the Extension Phase were done by going 1 dose level up or down.

Subjects who did not tolerate a daily dose of 0.015 mg/kg were discontinued from the study. For more detailed information on the study treatments during the Extension Phase see Appendix 16.1.1 (Clinical Study Protocol, Appendix 3).

Outcomes/endpoints

Efficacy

Efficacy was assessed by seizure counts and types as recorded on a subject's diary, and by the Clinical Global Impression (CGI), CGI of Severity (CGIS), and CGI of Change (CGIC).

Safety

Safety was assessed by monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs), clinical laboratory tests (i.e., haematology, blood chemistry, and urinalysis), vital signs, electrocardiograms (ECGs), medical history, physical and neurological examinations, and a Photosensitivity Questionnaire. In addition, growth was assessed for this age population by measurement of height and weight and thyroid and insulin-like growth factor (IGF) -1 and -2 testing. A suicidality scale questionnaire (Columbia-Suicide Severity Rating Scale [C-SSRS]) was also administered for subjects aged 6 years and older at the time of consent/assent.

Statistical Methods

The following populations were to be used in the statistical analyses for the Extension Phase:

The Safety Analysis Set included all subjects who took at least 1 dose of perampanel and had at least 1 postdose safety assessment during the Extension Phase.

The Full Analysis Set included all subjects who took at least 1 dose of perampanel during the Extension Phase, and had any seizure frequency data during the 2-week Pretreatment Phase plus the 4 weeks prior to Pretreatment Phase (Visit 1) of the Core Study and had any seizure frequency data during the Extension Phase.

Efficacy Analyses

Seizure frequency was based on the number of seizures per 28 days, calculated as (the number of seizures over the time interval multiplied by 28) and divided by the number of days in the interval. Seizure frequency referred to the overall seizure type, unless stated otherwise, obtained by combining across all seizure types.

All efficacy analyses were performed on the Full Analysis Set. Data reported during the overall treatment duration of the entire study were analysed. The overall treatment duration of the entire study was defined as follows:

• For diary data: The duration between the day of first Core Study drug dose and the last day of Extension Phase drug dose, inclusive.

• For CGIC data: The duration after the day of first Core Study drug dose up to 7 days after the last Extension Phase drug dose, inclusive.

Primary Efficacy Analyses

The seizure efficacy variables were:

• Percentage change in seizure frequency per 28 days from baseline by 13-week intervals during the overall treatment duration;

• Responder rate, the proportion of subjects who experienced a 50% or greater reduction in seizure frequency per 28 days, by 13-week intervals during the overall treatment duration;

• Seizure-free status by 13-weeks intervals during the overall treatment duration.

The baseline 28-day seizure frequency for the primary analyses used seizure data from the Core Study 2-week Pretreatment Phase. The seizure efficacy variables were summarized overall and by seizure type.

To assess long-term efficacy, the following summaries of the percentage change, responder rate endpoints and seizure-free status were provided by 13-week intervals (Weeks 1-13, 14-26, 27-39, and 40-52):

• For the overall treatment duration for all subjects. A subject needed at least 1 day of seizure frequency data in a 13-week interval to be included in the summary for the overall treatment duration;

• For the first 13 weeks of the overall treatment duration in subjects with at least 13 weeks of treatment;

• For the first 26 weeks of the overall treatment duration in subjects with at least 26 weeks of treatment;

• For the first 39 weeks of the overall treatment duration in subjects with at least 39 weeks of treatment;

• For the overall perampanel treatment duration in subjects with at least 1 year (52 weeks) of perampanel exposure.

Secondary analyses for the percentage change and responder rate endpoints in seizure frequency used seizure data from the Core Study 2-week Pretreatment Phase plus data from the 4 weeks prior to Pretreatment Phase (Visit 1) to calculate baseline 28-day seizure frequency.

Clinical Global Impression of Change scores were summarized by visit and at end of treatment (EOT). The EOT value was the last non-missing value while on-treatment (ie, after the day of first Core Study drug dose up to 7 days after the last Extension Phase drug dose, inclusive).

Safety Analyses

All safety analyses were performed on the Safety Analysis Set. Safety data were summarized using descriptive statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) for the entire study (Core Study and Extension Phase combined). Safety variables included treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG results, growth parameters (height, weight, thyroid, and IGF-1 and IGF-2 parameters), suicidality (for subjects age 6 years and older at the time of consent/assent), and photosensitivity. Study Day 1 for all safety analyses was defined as the date of the first dose of perampanel (ie, the date of the first dose of study drug from the Core Study).

Results

Recruitment / Number analysed

Of the 42 subjects who completed the Core Study, 41 subjects continued into the Extension Phase; 19 subjects were aged ≥2 to <7 years (Cohort 2) and 22 subjects were aged ≥7 to <12 years (Cohort 1). All subjects who continued into the Extension Phase were included in both the Safety Analysis Set and the Full Analysis Set. Six (31.6%) subjects in Cohort 2 and 8 (36.4%) subjects in Cohort 1 discontinued from the Extension Phase, which was a higher percentage than in the Core Study (2 [9.1%] subjects and 6 [21.4%] subjects, respectively). The duration of treatment was approximately 4 times longer in the Extension Phase than in the Core Study. Of the subjects who discontinued from the Extension Phase, 2 in Cohort 2 and 1 in Cohort 1 were in the inducer group, and 4 in Cohort 2 and 7 in Cohort 1 were in the non-inducer group. The most common primary reason for discontinuation from the Extension Phase was AE (4 [21.1%] subjects in Cohort 2 [gingival recession and oral mucosal discolouration in 1 subject; incoherent, lethargy, and aggression in 1 subject each] and 2 [9.1%] subjects in Cohort 1 [aggression and suicidal ideation in 1 subject; blood alkaline phosphatase increased, total bile acids increased, and urine bilirubin increased in 1 subject each]) followed by “other” (no subjects in Cohort 2 and 3 [13.6%] subjects in Cohort 1 [unable to adhere to study protocol for 2 subjects and principal investigator left the study site for 1 subject]).

Baseline data

There were no remarkable differences between the Baseline characteristics of the Core study population and those subjects who entered the Extension Phase. Demographic and Baseline characteristics were similar in the inducer and non-inducer groups.

Concomitant Medications and Treatment Compliance

In both cohorts, all subjects received at least 1 concomitant medication during the Extension Phase. The most commonly taken individual drugs were ibuprofen, diazepam, levetiracetam, valproic acid, oxcarbazepine, and paracetamol.

Compliance was between 80% and 120% during the Extension Phase for 17/19 (89.5%) subjects in Cohort 2 and 14/22 (63.6%) subjects in Cohort 1.

Efficacy results

Seizure frequency per 28 days decreased relative to Baseline during all 13-week intervals for all the seizure types, with the exception of overall generalised seizures in Cohort 1 during Weeks 1 to 13, which was consistent with results from the Core Study and unclassified seizures in Cohort 1 during Weeks 27 to 39, which included data from only 1 subject. In both cohorts, median seizure frequency for overall seizures was lower during all 13-week intervals than during the Treatment Phase of the Core Study.

For all the seizure types, responder rate was higher in Cohort 2 than in Cohort 1. The seizure-free rate ranged from 13.3% (Weeks 27-39) to 27.3% (Weeks 40-52) of subjects in Cohort 2 and 22.7% (Weeks 1-13) to 36.4% (Weeks 40-52) of subjects in Cohort 1.

Overall, at Baseline 15 (36.6%) subjects were classed as either normal (not at all ill) or mildly ill, 20 (48.8%) subjects were moderately ill, and 6 (14.6%) subjects were either markedly ill or severely ill. The distribution of subjects across these categories was similar between the 2 cohorts, except that in Cohort 2 fewer subjects were either markedly ill or severely ill (1 [5.3%] and no subjects, respectively, compared with 4 [18.2%] and 1 [4.5%] subjects, respectively, in Cohort 1). At EOT, 9 (47.4%) subjects in Cohort 2 and 13 (59.1%) subjects in Cohort 1 were much improved or very much improved, respectively, compared to Baseline. In Cohort 2, 1 (5.3%) subject was much worse compared to Baseline and in Cohort 1, 1 (4.5%) subject was minimally worse compared to Baseline. For 4 (21.1%) subjects in Cohort 2 and 2 (9.1%) subjects in Cohort 1 there was no change compared to Baseline.

Safety results

Extent of Exposure

The mean daily dose of perampanel over the study duration for subjects in the Extension Phase was 0.145 mg/kg; the mean maximum dose received was 0.174 mg/kg.

The mean duration of exposure over the study duration for subjects in the Extension Phase was 50.41 weeks (range: 13.4 – 107.0 weeks).

For 19 (46.3%) subjects in the Extension Phase, exposure over the entire study was longer than 52 weeks. Six of these subjects were dispensed unscheduled resupplies to cover the period until their named patient Investigational New Drug applications could be approved by the US Food and Drug Administration. Four of these 6 subjects were in Cohort 2 (range of exposure period beyond 52 weeks: 90 – 160 days) and 2 were in Cohort 1 (exposure period beyond 52 weeks was 202 and 243 days, respectively). They were passively monitored for safety during this period.

Adverse Events

Overview of Adverse Events

TEAEs included those AEs that occurred from the first day of perampanel administration in the Core Study to 30 days after the last dose of perampanel in the Extension Phase, or that were present before the first day of perampanel administration but worsened in severity during the study.

All subjects had at least 1 TEAE. The incidence of treatment-related TEAEs, severe TEAEs, and treatment-emergent SAEs was similar in the 2 cohorts. The incidence of TEAEs leading to study drug dose adjustment was higher in Cohort 2 than in Cohort 1 (52.6% and 31.8%, respectively).

For both cohorts, the incidence of severe TEAEs and SAEs was higher than in the Core Study (severe TEAEs: 6 [31.6%] subjects and 5 [22.7%] subjects in Cohort 2 and Cohort 1, respectively, in the Extension Phase versus 3 [13.6%] subjects and 3 [10.7%] subjects, respectively, in the Core Study; for SAEs: 6 [31.6%] subjects and 7 [31.8%] subjects in Cohort 2 and Cohort 1, respectively, in the Extension Phase versus 3 [13.6%] subjects and 5 [17.9%] subjects, respectively, in the Core Study). However, taking into consideration the longer mean duration of exposure during the Extension Phase (41.2 weeks versus 10.8 weeks during the Core Study), the frequency of these events was approximately proportionate.

Subject 10230006 in Cohort 2 had a TEAE of fatigue during the Core Study Titration Period that led to study drug dose increase; the event was moderate in severity and possibly related to study drug.

Common Adverse Events

Common TEAEs (≥10% of subjects overall) are consistent both with commonly observed illnesses in this age population and TEAEs observed in adults and adolescents on perampanel treatment. Treatment-emergent AEs that occurred in at least 3 more subjects between cohorts are as follows: aggression (Cohort 2) and abdominal pain upper, fatigue, increased appetite, and weight increased (Cohort 1). A similar pattern of common TEAEs was observed in the inducer and non-inducer groups.

Table: Treatment-Emergent Adverse Events Occurring in at Least 10% of Subjects Overall, by Preferred Term – Safety Analysis Set

MedDRA preferred term	Perampanel		
	Cohort 2 ≥2 to <7 years (N=19) n (%)	Cohort 1 ≥7 to <12 years (N=22) n (%)	Total (N=41) n (%)
Subjects with any TEAE	19 (100)	22 (100)	41 (100)
Pyrexia	8 (42.1)	7 (31.8)	15 (36.6)
Upper Respiratory Tract Infection	5 (26.3)	6 (27.3)	11 (26.8)
Vomiting	4 (21.1)	6 (27.3)	10 (24.4)
Irritability	3 (15.8)	5 (22.7)	8 (19.5)
Fatigue	1 (5.3)	6 (27.3)	7 (17.1)
Ear Infection	3 (15.8)	4 (18.2)	7 (17.1)
Lethargy	4 (21.1)	3 (13.6)	7 (17.1)
Aggression	5 (26.3)	2 (9.1)	7 (17.1)
Nasopharyngitis	3 (15.8)	3 (13.6)	6 (14.6)
Otitis Media	3 (15.8)	3 (13.6)	6 (14.6)
Somnolence	3 (15.8)	3 (13.6)	6 (14.6)
Cough	4 (21.1)	2 (9.1)	6 (14.6)
Abdominal Pain Upper	0	5 (22.7)	5 (12.2)
Increased Appetite	1 (5.3)	4 (18.2)	5 (12.2)
Weight Increased	1 (5.3)	4 (18.2)	5 (12.2)
Headache	2 (10.5)	3 (13.6)	5 (12.2)
Dizziness	3 (15.8)	2 (9.1)	5 (12.2)

MedDRA Version 16.1.
A TEAE was defined as an adverse event with an onset date, or a worsening in severity from Baseline (pretreatment), on or after the first dose of study drug up to 30 days following study drug discontinuation.
A subject with 2 or more adverse events with the same preferred term is counted only once for that preferred term.
MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event.
Source: Table 14.3.1.3.4.

Analysis of Adverse Events

The majority of TEAEs in both cohorts were considered mild or moderate by the investigator; severe TEAEs were reported in 11 (26.8%) subjects overall (6 in Cohort 2 and 5 in Cohort 1). Status epilepticus was the only TEAE rated as severe in more than 1 subject (2 [9.1%] subjects in Cohort 1).

In both cohorts, the majority of TEAEs that occurred were judged by the investigator to be possibly or probably related to the study drug.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No subject died or had AEs that resulted in death during the entire study.

The incidence of SAEs was similar in the 2 cohorts: 6 (31.6%) subjects in Cohort 2 had a total of 9 SAEs and 7 (31.8%) subjects in Cohort 1 had a total of 23 SAEs. Serious AEs that were reported in more than 1 subject included convulsion (2 [10.5%] subjects in Cohort 2 and 1 [4.5%] subjects in Cohort 1), status epilepticus (no subjects in Cohort 2 and 2 [9.1%] subjects in Cohort 1), and mental status changes (2 [10.5%] subjects in Cohort 2 and no subjects in Cohort 1). All subjects recovered from their SAEs with no sequelae; none of the subjects discontinued study treatment due to these events. Four SAEs in 2 subjects in Cohort 2 and 3 SAEs in 2 subjects in Cohort 1 were considered by the investigator to be possibly related to study drug; however, no action was taken with study drug as a result of these events.

Treatment-emergent AEs that resulted in discontinuation occurred in 3 (15.8%) subjects in Cohort 2 and 2 (9.1%) subjects in Cohort 1. The only TEAE (PT) that resulted in discontinuation of more than 1 subject was aggression (1 subject in each cohort).

Treatment-emergent AEs that resulted in dose adjustment of study drug occurred in 10 (52.6%) subjects in Cohort 2 and 7 (31.8%) subjects in Cohort 1. The TEAEs (PT) that resulted in dose adjustment of study drug in more than 5% of subjects overall were lethargy (3 [15.8%] subjects in Cohort 2 and 1 [4.5%] subject in Cohort 1), aggression (2 [10.5%] subjects in Cohort 2 and 1 [4.5%] subject in Cohort 1), and fatigue (1 [5.3%] subject in Cohort 2 and 2 [9.1%] subjects in Cohort 1).

No pregnancies or exposure to study drug through breastfeeding were reported during the study, as would be expected given the age population in the study.

Other Adverse Events of Interest

Adverse events of special interest in this study included: TEAEs suggestive of abuse potential, TEAEs related to alertness or cognition, TEAEs related to hostility or aggression, TEAEs related to psychosis and psychotic disorders, TEAEs related to status epilepticus/convulsions, TEAEs related to Related to Hepatic Lab Abnormalities, TEAEs related to cardiac and ECG results, TEAEs related to rash, TEAEs related to suicidal ideation and behaviour, and TEAEs related to falls.

One subject had a TEAE suggestive of abuse potential: Subject 10030002 in Cohort 1 had an event of accidental overdose during the Core Study Titration Period. At the same time as this TEAE was reported, he also had TEAEs of weight increased, somnolence, attention deficit/hyperactivity disorder, and abnormal behaviour; all except weight increased were considered to be possibly related to study drug.

Treatment-emergent AEs related to alertness or cognition were reported in 9 (47.4%) subjects in Cohort 2 and 5 (22.7%) subjects in Cohort 1. The most frequently reported TEAEs related to alertness or cognition were aggression (5 [26.3%] subjects in Cohort 2 and 2 [9.1%] subjects in Cohort 1) and somnolence (3 [15.8%] subjects in Cohort 2 and 3 [13.6%] subjects in Cohort1).

Two TEAEs related to alertness or cognition in subjects in Cohort 2 were reported as SAEs; both were events of mental status changes and both resolved: Subject 10010007 (during the Core Study Titration Period; the event was severe, not related to study drug, and study drug was interrupted) and Subject 10200002 (during the Extension Phase Maintenance Period; the event was moderate in intensity, possibly related to study drug, and no action was taken with study drug). Two TEAEs related to alertness or cognition that occurred during the Extension Phase Maintenance Period resulted in discontinuation of study drug, both were events of aggression that were moderate in intensity and probably related to study drug: Subject 10200014 in Cohort 2 (the event was reported as recovering/resolving) and Subject 10030001 in Cohort 1 (the event did not resolve). Subject 10030001 also had an event of somnolence during the Core Study Titration Period that resulted in reduction of study drug dose; the event was mild in intensity, possibly related to study drug, and resolved.

Using narrow SMQ terms, TEAEs related to hostility or aggression were reported in 5 (26.3%) subjects in Cohort 2 (all 5 subjects had aggression) and 3 (13.6%) subjects in Cohort 1 (aggression in 2 subjects and anger in 1 subject). Using both narrow and broad SMQ terms, TEAEs related to hostility or aggression were identified in 9 (47.4%) subjects in Cohort 2 and 8 (36.4%) subjects in Cohort 1 (Table 6). The most common TEAEs identified using both narrow and broad SMQ terms were irritability (in 3 [15.8%] subjects in Cohort 2 and 5 [22.7%] subjects in Cohort 1) and aggression (in 5 [26.3%] subjects in Cohort 2 and 2 [9.1%] subjects in Cohort 1). Subject 10200014 in Cohort 2 and Subject

10030001 in Cohort 1 had TEAEs of aggression that led to discontinuation of study drug; these events were also identified as TEAEs related to alertness or cognition and are described above. Two TEAEs related to hostility or aggression resulted in reduction of study drug dose, both were events of irritability that occurred during the Core Study Titration Period and were possibly related to study drug: Subject 10050001 in Cohort 2 (the event was moderate in intensity and resolved) and Subject 10030001 in Cohort 1 (the event was mild in intensity and did not resolve).

Using narrow SMQ terms, TEAEs related to psychosis and psychotic disorders were reported in 1 (5.3%) subject in Cohort 2 (hallucination) and no subjects in Cohort 1. Using both narrow and broad SMQ terms, TEAEs related to psychosis and psychotic disorders were identified in 4 (21.1%) subjects in Cohort 2 and 1 (4.5%) subject in Cohort 1. The most common TEAE identified using both narrow and broad SMQ terms was abnormal behaviour (1 subject in each cohort), which was the only event that was reported in more than 1 subject overall. Treatment-emergent AEs related to status epilepticus/convulsions were reported in 2 (10.5%) subjects in Cohort 2 and 4 (18.2%) subjects in Cohort 1. The TEAEs were: convulsion (2 [10.5%] subjects in Cohort 2 and 1 [4.5%] subject in Cohort 1), status epilepticus (no subjects in Cohort 2 and 2 [9.1%] subjects in Cohort 1), and seizure cluster (no subjects in Cohort 2 and 1 [4.5%] subject in Cohort 1). All events except seizure cluster were SAEs. The SAEs of convulsion in Cohort 2 both occurred during the Extension Phase Maintenance Period, no action was taken with study drug for either event and both events resolved: Subject 10010008 (the event was severe in intensity and not related to study drug) and Subject 10200002 (the event was moderate in intensity and possibly related to study drug). Subject 10140002 in Cohort 1 had 4 SAEs of convulsion, 1 during the Core Study Maintenance Period and 3 during the Extension Phase Maintenance Period. All 4 of these SAEs were moderate in intensity, no action was taken with study drug for any of them, and all 4 resolved. The SAE that occurred during the Core Study Maintenance Period and 1 of the SAEs that occurred during the Extension Phase Maintenance Period were not related to study drug; the remaining SAEs of convulsion in this subject were possibly related to study drug. The SAEs of status epilepticus in 2 subjects in Cohort 1 were both severe, not related to study drug, and both resolved: Subject 10030002 (during the Extension Phase Maintenance Period; no action was taken with study drug) and Subject 10180005 (during the Extension Phase Follow-up Period).

One subject in Cohort 1 (Subject 10160001) had 3 TEAEs (blood alkaline phosphatase increased, total bile acids increased, and urine bilirubin increased) related to hepatic lab abnormalities during the Extension Phase Maintenance Period. All 3 events were nonserious, mild in intensity, possibly related to study drug, and did not resolve.

Treatment-emergent AEs related to cardiac and ECG results were reported in 4 (21.1%) subjects in Cohort 2 and 1 (4.5%) subject in Cohort 1. The most common TEAE related to cardiac and ECG results was mental status changes (in 2 [10.5%] subjects in Cohort 2), which was the only event that was reported in more than 1 subject overall. Both events of mental status changes were SAEs; they were also identified as TEAEs related to alertness or cognition and are described above.

Treatment-emergent AEs related to rash were reported in 3 (15.8%) subjects in Cohort 2 and 1 (4.5%) subject in Cohort 1. Two (10.5%) subjects in Cohort 2 and 1 (4.5%) subject in Cohort 1 had events of rash and 1 [5.3%] subject in Cohort 2 had an event of viral rash. None of these events were serious or resulted in study drug dose modification and none of the subjects reported a positive skin reaction on the Photosensitivity Questionnaire.

One subject in Cohort 2 (Subject 10160002) and 2 subjects in Cohort 1 (Subject 10030001 and Subject 10210002) had TEAEs related to suicidal ideation and behavior (Table 8). None of the events were SAEs.

Two subjects in Cohort 2 (Subject 10010007 and Subject 10200002) and 1 subject in Cohort 1 (Subject 10190003) had TEAEs related to falls; 1 of the subjects in Cohort 2 and the subject in Cohort 1 experienced 2 events. All the events were nonserious and resolved; no action was taken with study drug.

2.3.4. Discussion on clinical aspects

The PK results from the population PK analysis on data from Study 232 pooled with adolescent data from 1 Phase 2 study (Study 235) and 3 Phase 3 studies (Study 304, Study 305, and Study 306) are consistent with results from previous analysis, mainly higher perampanel clearance with concomitant CYP3A4/5-inducing AEDs: 1.9-fold with concomitant oxcarbazepine or phenytoin and 2.6-fold with concomitant carbamazepine. In both non-inducers and inducers, clearance was not affected by either age or bodyweight.

Adjunctive therapy with perampanel oral suspension at daily doses up to 0.18 mg/kg was safe and well tolerated over the entire duration of the study (up to 52 weeks including the extension). The majority of SAEs and other significant events were transient and manageable (the subjects recovered without sequelae) and the safety profile was similar between the 2 age cohorts.

The pattern of common AEs was similar in the inducer and non-inducer groups.

The pattern of occurrence of TEAEs that resulted in dose reduction, dose interruption, or drug discontinuation during the Titration Period was similar in the 2 cohorts, except that during the first 2 weeks no subject in Cohort 2 and 2 subjects in Cohort 1 had such TEAEs. In both cohorts, the incidence increased in the later weeks of the Titration Period and was higher in the group of subjects who were not taking a concomitant perampanelinducing AED.

No safety concerns relating to either suicidality or photosensitivity reactions were identified.

Overall, the safety profile observed in the Extension Phase was similar to that observed during the Core Study.

Preliminary efficacy results from the Core Study showed that adjunctive therapy with perampanel oral suspension at daily doses up to 0.18 mg/kg appeared to be efficacious in controlling seizures in pediatric subjects from 2 to less than 12 years of age with epilepsy; this efficacy was maintained during the Extension Phase of the study.

Of the subjects who completed the Core Study, 9 (21.4%) achieved seizure-free status during the 4-week Maintenance Period. The proportion of subjects who achieved seizure-free status over the 13-week intervals of the study ranged from 22.0% to 31.8%. The CGIC results showed that at EOT the majority of subjects overall were improved compared to Baseline.

No notable effects of perampanel on growth were reported.

No concerns relating to palatability of perampanel suspension were identified.

3. CHMP's overall conclusion and recommendation

The presented information is consistent with the existing knowledge about the compound. There are no new safety signals or unexpected efficacy fluctuations. The PK data is also in line with the expected profile. The population included in the studies does not overlap with the currently licensed target population and there is no new information that would be of importance in control of the off license use either.

The risk benefit balance for Fycompa, therefore, remains unchanged. The submitted data does not introduce any information requiring change of the product information.

These studies are part of PIP and the data will be submitted as part of the development package at the later stage.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled**

4. Additional clarification requested

None

5. Annex - Line listing of all the studies included in the Paediatric Investigation Plan - EMEA-000467-PIP01-08-M06

Table: Clinical Studies in EMEA-000467-PIP01-08-M06

Area	**Number of studies**	**Description☐**
Quality	1	Study 1 Development of an oral liquid formulation (< 0.5mg/ml) and a dosing device suitable for treatment of children of all ages including preterm neonates.
Non-clinical	1	Study 2 33-week oral gavage toxicity study in the juvenile dog.
Clinical	9	Study 3 Pooled subgroup analyses of the efficacy, pharmacokinetics and safety of perampanel in the adolescent population included in three doubleblind, placebo-controlled studies in patients with refractory partial seizures.
		Study 4 Open-label extension to double-blind, placebo-controlled, doseescalation, parallel-group studies to evaluate the efficacy, pharmacokinetics and safety of perampanel as adjunctive therapy in adolescents and adults with refractory partial seizures.
		Study 5 Randomized, double-blind, placebo-controlled, parallel-group study with open-label extension phases to evaluate the effect of perampanel on cognition, safety, tolerability and pharmacokinetics when administered as an adjunctive therapy in adolescents with inadequately controlled partial onset seizures.
		Study 6 Randomized, open-label, crossover study to demonstrate relative bioavailability between a 4 mg oral suspension of perampanel and a 4 mg tablet of perampanel in healthy adult subjects.
		Study 7 Open-label pilot study with an extension phase to evaluate the pharmacokinetics, and to generate preliminary safety, tolerability, and efficacy data of perampanel oral suspension as an adjunctive treatment in paediatric subjects with epilepsy from 2 to less than 12 years of age.

Area	Number of studies	Description□
		Study 8 Exploratory, open-label study with an extension phase to evaluate preliminary efficacy, safety and tolerability of perampanel administered as an adjunctive therapy in paediatric patients (age 1 month to less than 18 years) with childhood epilepsy.
		Study 9 Randomized, double-blind, placebo-controlled, dose-escalation, parallel-group study with an extension phase to evaluate the efficacy, safety and tolerability of perampanel suspension when administered as an adjunctive therapy in paediatric patients (age 2 to less than 12 years) with partial onset seizures.
		Study 10 Open-label, multiple-dose study to explore the safety, tolerability and pharmacokinetics of perampanel as an adjunctive therapy in neonates with seizures, aged from birth to less than 28 days, followed by an open label extension study (up to 1 year).
		Study 11 Open-label pilot study with an extension phase to evaluate the pharmacokinetics, and to generate preliminary safety, tolerability, and efficacy data of perampanel oral suspension as an adjunctive treatment in paediatric subjects with epilepsy from 1 to less than 24 months of age.