London, 22 June 2017
EME/340381/2017
Committee for Medicinal Products for Human Use (CHMP)

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/P46/016

Note

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

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1. Introduction

On 21 March 2017, the MAH submitted a completed paediatric study for Fycompa, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation Measure 5.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the study E2007-J000-341 is the remaining part of the clinical development program. The application consisting of the full relevant data package (i.e containing several studies) has already been submitted. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Investigational product: Fycompa®/perampanel (E2007).

Perampanel was available in 2 mg tablets.

Batch number: P34001ZZ

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final report for:

- Study E2007-J000-341

2.3.2. Clinical studies

Clinical study number: E2007-J000-341

An Open-label Extension Study to Evaluate the Safety and Tolerability of Perampanel (E2007) Administered as an Adjunctive Therapy in Epilepsy Subjects

Description

Methods

Objectives

To evaluate the safety and tolerability of perampanel given as an adjunctive therapy in subjects with epilepsy subjects.

Study design

This study consisted of 2 phases:

• Screening – The subject started the study once the Screening assessments were completed and the subject was qualified for participation.

• Treatment – Safety assessments were conducted by the investigator.

Only subjects who were participating in the designated perampanel study as below and who in the opinion of the investigator continued to benefit from treatment with perampanel were eligible for this study. Subjects entered this study on the same dose of perampanel that they were receiving at the end of their participation in the designated perampanel study - Study 332 (with at least 52 weeks of total exposure to perampanel).

Doses of perampanel and concomitant antiepileptic drugs (AEDs) were allowed to be adjusted based on clinical judgment. A minimum perampanel dose of 2 mg per day was required to continue in the study. The maximum daily dose of perampanel permitted was 12 mg per day.

The visit intervals in this study were every 26 weeks.

End of study visit was required to be conducted within 3 months from the launch of perampanel in Japan.

For the subjects who did not switch to commercially available perampanel within 3 months after the launch of perampanel in Japan, Discontinuation Visit was conducted.

Subjects who did not tolerate the minimum dose of 2 mg per day during the study were discontinued from the study.

The investigator was allowed to discontinue the subject from the study at any time for safety or administrative reasons. When the investigator discontinued the study, Discontinuation Visit was conducted.

A Follow-up visit was conducted 4 weeks after Discontinuation Visit in the discontinued subject. Follow-up visit was not required once the investigational drug was switched to commercial product.

Study population /Sample size

Indication: Epilepsy

Main Criteria for Inclusion: Subjects participating in the designated perampanel study (Study 332 with at least 52 weeks of total exposure to perampanel) and who in the opinion of the investigator continued to benefit from treatment with perampanel were eligible for this study.

Enrolled (i.e., signed informed consent): 7 subjects. Treated: 7 subjects.

Treatments

Test treatment: Perampanel was available in 2 mg tablets.

Dose and mode of administration: Subjects started this study with the dose that they were receiving at the end of their participation in the previously participated designated perampanel study. Doses of perampanel were allowed to be adjusted based on clinical judgment. A minimum perampanel dose of 2

mg per day was required to continue in the study. The maximum daily dose of perampanel permitted was 12 mg per day.

Batch number: P34001ZZ

Treatment was continued as long as clinically appropriate according to the judgment of the investigator. However, treatment of subjects was completed when perampanel became commercially available in Japan.

Outcomes/endpoints

Efficacy

Not applicable.

Safety

Safety was assessed by monitoring of adverse events (AEs), withdrawal from treatment, clinical laboratory tests (chemistry), vital signs and weight.

Other

Concomitant medication usage.

Statistical Methods

Analysis Sets

Safety Analysis Set included all subjects who signed informed consent, were eligible for this study, received at least 1 dose of study medication, and have at least 1 post-dose safety assessment in this study.

Interim Analyses

Not applicable.

Efficacy Analyses

Not applicable.

Safety Analyses

All AEs, laboratory parameter, vital signs, and weight were presented in subject data listings. The AE verbatim descriptions (investigator terms from the CRF) were classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events were coded to the MedDRA (Version 19.0) lower level term (LLT) closest to the verbatim term. The number (percentage) of subjects with treatment emergent AEs (TEAEs) was summarised by system organ class (SOC) and preferred term (PT). Summary statistics were presented for laboratory test values, vital signs, and weight.

Other Analyses

Concomitant AEDs were listed.

The number (percentage) of subjects who took concomitant AEDs at baseline (i.e., at the beginning of the Screening Phase of this study was summarized by the AED type (i.e., inducer AED, non-inducer AED) and World Health Organization Drug Dictionary (WHO DD) preferred term.

Sample Size Rationale

The study was open to all subjects participating in the designated perampanel study (Study 332).

Results

Study Conduct and Patient Disposition

A total of 7 subjects who had participated in the designated perampanel study (Study 332) provided informed consent and were enrolled in Study E2007-J000-341 (Study 341). All 7 subjects received at least 1 dose of perampanel and were included in the Safety Analysis Set.

One subject discontinued due to personal choice.

Study Period: 12 May 2015 to 21 Sep 2016

This study was continued until perampanel was commercially available in Japan with respect to the indication or formulation of the designated study (Study E2007-G000-332).

Baseline data

The mean ±SD age was 35.3±19.20 years. Of the 7 subjects, 4 subjects (57.1%) were male, and 3 subjects (42.9%) were female. The median time since onset of epilepsy was 6.6 years (range: 3 to 57 years). All 7 subjects were Japanese with tonic-clonic seizures.

All 7 subjects were taking non-inducer AEDs, while none was taking inducer AEDs. The most common AED taken was valproic acid (71.4%).

Efficacy results

Not applicable.

Safety results

Extent of Exposure

The mean ±SD cumulative duration of exposure to perampanel was 52.73±7.801 weeks for the Safety Analysis Set.

The mean ±SD average daily dose of perampanel during the study was 8.00±2.828 mg for the Safety Analysis Set. The mean ±SD modal dose of perampanel during the study was 8.0±2.83 mg for the Safety Analysis Set. Note that each subject received the same doses during the study although doses of perampanel were allowed to be adjusted based on clinical judgment.

The distribution of the dose received by subjects was 6 mg (4 subjects; 57.1%), 8 mg (1 subject; 14.3%), and 12 mg (2 subjects; 28.6%).

Adverse Events

TEAEs included those AEs for subjects that entered Study 341 that occurred from the first dose of study drug to the last visit of the study, or upto 30 days since the last dose of study drug, whichever comes later, or that were present at pre-treatment (baseline of Study 341) but worsened in severity during the study.

At least 1 TEAE occurred in 6 subjects (85.7%) in the Safety Analysis Set during the study. Table below presents all TEAEs reported during the study by MedDRA SOC and PT for the Safety Analysis Set. The most frequently reported TEAEs were nasopharyngitis (3 subjects; 42.9%).

Table: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set

MedDRA System Organ Class **Preferred Term**	**Perampanel** **(N=7)** **n (%)**
Subjects with any TEAE	6 (85.7)
Infections and infestations	3 (42.9)
Nasopharyngitis	3 (42.9)
Influenza	1 (14.3)
Injury, poisoning and procedural complications	3 (42.9)
Fall	1 (14.3)
Head injury	1 (14.3)
Humerus fracture	1 (14.3)
Metabolism and nutrition disorders	1 (14.3)
Diabetes mellitus	1 (14.3)
Hypercholesterolaemia	1 (14.3)
Hyperuricaemia	1 (14.3)

No treatment-related TEAEs were reported during the study.

All of the TEAEs were considered mild by the investigator, except for 1 moderate TEAE of Fall.

Only 1 moderate TEAE (fall) occurred in 1 subject during the study.

No deaths occurred, and no serious adverse events (SAEs) or TEAEs leading to discontinuation of study drug were reported during the study.

Laboratory Results

There were no clinically important mean and median changes in clinical chemistry laboratory values over time for the Safety Analysis Set. There were no markedly abnormal clinical chemistry laboratory values during the study.

Vital Signs, Physical Findings, and Other Observations Related to Safety

There were no clinically important mean and median changes in vital signs and weight over time for the Safety Analysis Set.

There were no clinically notable vital signs during the study.

Clinically notable reductions in body weight occurred in 1 subject (14.3%), while clinically notable elevations in body weight occurred in 3 subjects (42.9%) during the study; however, there were no TEAEs of weight increased or weight decreased in the Safety Analysis Set.

Discontinuations

Of the 7 subjects treated with perampanel, 1 (14.3%) adult subject discontinued from the study, and the remaining 6 (85.7%) subjects completed the study. The primary reason for discontinuation from the study reported in the 1 subject was subject choice.

2.3.3. Discussion on clinical aspects

Adjunctive treatment with perampanel daily doses up to 12 mg was safe and well tolerated in this study. The adverse events described in Study 341 are consistent with the known safety profile for perampanel as well-tolerated adjunctive treatment of epilepsy in the total population as well as in adolescents and are already included in the reference safety information (Company Core Data Sheet [CCDS] and Summary of Product Characteristics [SmPC]). A review of these adverse events does not suggest new or unexpected information. There were no significant changes in the frequency and severity of previously identified adverse reactions or important/potential risks.

On the basis of a review of the adverse events and TEAEs in Study 341, no additional changes to the CCDS or regional product labelling safety information are considered necessary at this time. The data submitted do not affect the benefit-risk balance for perampanel. Perampanel continues to possess a favourable benefit-risk profile for the treatment of indicated seizure types.

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

4. Additional clarification requested

None

5. Annex. Line listing of all the studies included in the development program

Non-clinical Studies

Study title	Study number	Date of completion	Date of submission of final study report
A 33-week Oral Gavage Toxicity Study in the Juvenile Dog Followed by a 4-week Recovery Period	901979	30 Mar 2011	28 Sep 2011

Clinical Studies

Study title	Study number	Date of completion	Date of submission of final study report
A Randomized, Open-label, Crossover Study to Compare Relative Bioavailability Between a 4 mg Dose of an Oral Suspension of Perampanel and a 4 mg Tablet of Perampanel in Healthy Subjects	E2007-E044-028 (PIP Study 6)	13 Jan 2010	15 Sep 2010
A Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group Study to Evaluate the Efficacy and Safety of E2007 (perampanel) Given as Adjunctive Therapy in Subjects with Refractory Partial Seizures	E2007-G000-306	21 Jul 2010	23 May 2011 (Initial EU MAA)
A Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group Study to Evaluate the Efficacy and Safety of E2007 (perampanel) Given as Adjunctive Therapy in Subjects with Refractory Partial Seizures	E2007-G000-304	11 Nov 2010	23 May 2011 (Initial MAA)
A Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group Study to Evaluate the Efficacy and Safety of E2007 (perampanel) Given as Adjunctive Therapy in Subjects with Refractory Partial Seizures	E2007-G000-305	14 Jan 2011	23 May 2011 (Initial MAA)
Pooled subgroup analyses of the efficacy, pharmacokinetics and safety of perampanel in the adolescent population included in three double-blind, placebo-controlled studies in patients with refractory partial seizures (E2007-G000-304, E2007-G000-305 and E2007-G000-306)	E2007-G000-304, E2007-G000-305, E2007-G000-306 (PIP Study 3)	23 Jun 2011	28 Sep 2011
A Randomized, Double-blind, Placebo-controlled, Parallel-group Study With an Open-label Extension (OLE) Phase to Evaluate the Effect of Perampanel (E2007) on Cognition, Safety, Tolerability and Pharmacokinetics When Administered as an Adjunctive Therapy in Adolescents (12 to less than 18 years of age) With Inadequately Controlled Partial Onset Seizures	E2007-G000-235 (PIP Study 5)	01 Sep 2014	26 Feb 2015
Open-Label Extension Phase of the Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group Studies to Evaluate the Efficacy and Safety of E2007 (perampanel) Given as Adjunctive Therapy in Subjects with Refractory Partial Seizures	E2007-G000-307 (PIP Study 4)	18 Sep 2014	17 Mar 2015
An Open-label Pilot Study with an Extension Phase to Evaluate the Pharmacokinetics (PK), and generate Preliminary Safety, Tolerability and Efficacy of Perampanel (E2007) Oral Suspension when given as Adjunctive Therapy in Pediatric Subjects (age ≥ 2 - < 12 years) With Epilepsy	E2007-G000-232 (PIP Study 7)	13 Feb 2015	10 Aug 2015

Study title	Study number	Date of completion	Date of submission of final study report
A Double-blind, Randomized, Placebo-controlled, Multicenter, Parallel-group Study with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Adjunctive Perampanel in Primary Generalized Tonic-Clonic Seizures	E2007-G000-332	15 Jan 2016	15 Apr 2016
An Open-label Extension Study to Evaluate the Safety and Tolerability of Perampanel (E2007) Administered as an Adjunctive Therapy in Epilepsy Subjects	E2007-J000-341	21 Sep 2016	By 21 Mar 2017
An Open-Label Study With an Extension Phase to Evaluate the Pharmacokinetics of Perampanel (E2007) Oral Suspension When Given as an Adjunctive Therapy in Subjects From 1 Month to Less Than 24 Months of Age With Epilepsy	E2007-G000-238 (PIP Study 11)	By May 2018 (planned)	TBC (6 months after completion)
A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group Study With an Open-Label Extension Phase to Evaluate the Efficacy, Safety, and Tolerability of Perampanel (E2007) Oral Suspension When Administered as an Adjunctive Therapy in Children (ages 2 to < 12 years) with Refractory Partial Onset Seizures	E2007-G000-311 (PIP Study 9)	By Sep 2018 (planned)	TBC (6 months after completion)
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	E2007-G000-236 (PIP Study 8)	By Jan 2019 (planned)	TBC (6 months after completion)
A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial With an Open-Label Extension Phase of Perampanel as Adjunctive Treatment in Subjects at Least 2 years of Age With Inadequately Controlled Seizures Associated With Lennox-Gastaut Syndrome	E2007-G000-338	By Feb 2019 (planned)	TBC (6 months after completion)
A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel-group Study with an Extension Phase to Evaluate the Efficacy, Safety and Tolerability of E2007 (Perampanel) When Administered as an Adjunctive Therapy in Children (age 1 month to < 4 years) With Refractory Partial-onset Seizures	E2007-G000-339	By Sep 2019 (planned)	TBC (6 months after completion)
A Double-blind, Placebo-controlled, Parallel-group Study with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Perampanel (E2007) Administered as an Adjunctive Therapy in Subjects with Refractory Partial Onset Seizures	E2007-J000-335	By 2020(planned)	TBC (6 months after completion)
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)	E2007-G000-237 (PIP Study 10)	By Apr 2021 (planned)	TBC (6 months after completion)