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Human Medicines Division

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/P46/025

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	18 Jul 2022	18 Jul 2022	☐
☐	CHMP Rapporteur Assessment Report	22 Aug 2022	22 Aug 2022	☐
☐	CHMP members comments	05 Sep 2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	08 Sep 2022	n/a	☐
☐	CHMP adoption of conclusions:	15 Sep 2022	15 Sep 2022	☐
☐	Submission	04 October 2022	04 October 2022	☐
☐	Re-start	17 October 2022	17 October 2022	☐
☐	CHMP Rapporteur Assessment Report	21 Nov 2022	21 Nov 2022	☐
☐	CHMP members comments	05 Dec 2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	08 Dec 2022	n/a	☐
☒	CHMP adoption of conclusions:	15 Dec 2022	15 Dec 2022	☐

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Introduction
On 16 June 2022, the MAH submitted a completed paediatric study for Fycompa oral suspension, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Perampanel is a highly selective non-competitive AMPA-type glutamate receptor antagonist. In the EU, Fycompa (perampanel), following the extension of indication in the paediatric population (EMEA/H/C/002434/II/0047), is indicated for the adjunctive treatment of:

- partial-onset seizures (POS) with or without secondarily generalised seizures in patients from 4 years of age and older.

- primary generalised tonic-clonic (PGTC) seizures in patients from 7 years of age and older with idiopathic generalised epilepsy (IGE).

Perampanel has also been approved as monotherapy or adjunctive therapy in paediatric patients with POS aged 4 years and older in the US as of September 2018. The International Birth Date is 23 July 2012 in the EU (via the centralized procedure). Perampanel is marketed under the trade name Fycompa and is available as 2-, 4-, 6-, 8-, 10-, and 12-mg tablets and 0.5 mg/ml oral suspension.

EISAI is hereby submitting final study results and report related to paediatric population for Study E2007-G000-338 (referred to as Study 338). This study 338 was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study (Core Study) followed by an Extension Phase (Extension A and Extension B) of perampanel as adjunctive therapy in subjects 2 years of age and older with inadequately controlled seizures associated with Lennox-Gastaut Syndrome (LGS). The study enrolled 70 subjects (planned 142 subjects, (71 placebo, 71 perampanel)) of which 34 were treated with perampanel in the study, 22 of whom were less than 18 years of age. A total of 61 subjects completed the Core Study (29 perampanel, of whom 20 were less than 18 years of age), and 58 of them entered Extension A (40 were less than 18 years of age). A total of 32 subjects completed Extension A, (23 were less than 18 years of age); and 13 of them entered Extension B (9 were less than 18 years of age).

The primary objective of the study was to demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in reducing the incidence of drop seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS.

The submission of these final data is being made to the European Medicines Agency to fulfil the obligation to present data from any MAH-sponsored study in a paediatric population.

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

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that Post-authorisation measure - Submission of paediatric study pursuant to article 46 of Regulation (EC) No 1901/2006 is a stand-alone study.

1.2. Information on the pharmaceutical formulation used in the study

The investigational medicinal product tested in Study 338 was Fycompa as 2-mg oral tablets and 0.5 mg/ml oral suspension. Perampanel was orally administered once daily before bedtime.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for study 338, 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 LGS.

1.3.2. Clinical study

Description

The study was a phase 3, 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 LGS. A total of 74 sites were selected, of which 40 sites enrolled subjects as follows: US (16), India (6), Japan (7), Belgium (5), Australia (3), South Korea (2), and Czech Republic (1).

The study consisted of 3 phases: Prerandomization, Randomization, and Extension. The Core Study consisted of the Prerandomization and Randomization Phases.

- *Core Study*

• Prerandomization Phase (Screening and Baseline Periods): 4 to 8 weeks

The Prerandomization Phase will consist of a 4- to 8-week Screening/Baseline Period during which subjects were assessed for overall eligibility to participate in the study, including seizure activity. Baseline seizure count were assessed using all diary data before randomization (at least 4 weeks prospectively). Following successful completion of this period, subjects were randomized to receive perampanel or placebo in a 1:1 ratio.

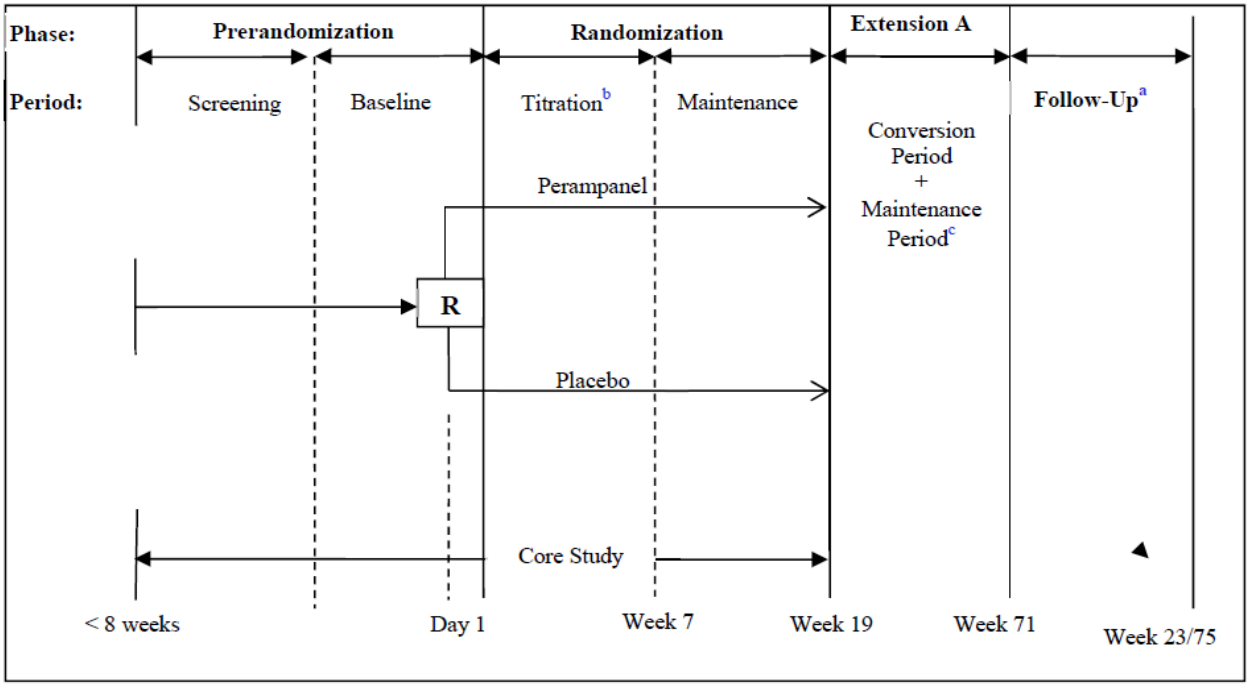
• Randomization Phase: Titration Period = 6 weeks, Maintenance Period = 12 weeks (for a total of 18 weeks) followed by a 4-week Follow-up Period (for those subjects not entering into Extension A)

- *Extension phases*

Extension A: Conversion Period = 6 weeks (subjects who received perampanel during the Core Study continued to receive perampanel in a blinded manner at the same dose received during the Core Maintenance Period. Subjects who received placebo during the Core Study began treatment with perampanel in a blinded manner), Maintenance Period = 46 weeks (for a total of 52 weeks) followed by a 4-week Follow-up Period (for those not entering into Extension B). During the Extension A Maintenance Period, subjects could be titrated up to 12 mg/day (except in Japan, where the maximum allowed dose remained at 8 mg/day), in 2-week intervals as per the investigator's discretion. Addition, deletion, and dose changes to the concomitant AEDs were then allowed.

Extension B: Until perampanel is available commercially for the treatment of LGS, or accessible via extended access program (if activated in the country in which a subject resides), or until the study was terminated by the sponsor.

An overview of the study design is presented in Figure 1:



R = randomization.

a: Subjects who do not continue in Extension A or those who prematurely discontinue from the study will return to the study site for Follow-up visits 1 week and 4 weeks after the last study drug administration.

b: Subjects will be up-titrated to optimize efficacy while maintaining good tolerability, up to a maximum dose of 8 mg/day. Once titrated, all subjects will be kept at a stable dose for at least 2 weeks (to reach steady-state) before the start of the Maintenance Period. The dose of study drug during the Maintenance Period will be the last dose achieved at the end of the Titration Period.

c: After the double-blind Conversion Period of Extension A, subjects can be titrated (except in Japan, where the maximum allowed dose remains at 8 mg/day) up to 12 mg/day in 2-week intervals, as per the investigator's discretion.

CHMP's comment:

Subjects who completed all scheduled visits of the 18-week Core Study were eligible to participate in the 52-week open label Extension A (6-week Double-blind Conversion Period followed by a 46-week Open-label Maintenance Period). The total treatment duration in Extension A was 52 weeks aimed at assessing long-term safety and efficacy of perampanel treatment in LGS subjects. Subjects who lived in Japan or another country where an extended access program was not implemented and who completed Extension A, were eligible to continue perampanel treatment in Extension B. Participation in Extension B continued as long as clinically appropriate according to the judgment of the investigator or until an extended access program was activated or perampanel was commercially available.

This study was terminated by the sponsor before completion due to challenges with subject recruitment that was further impacted by the COVID-19 pandemic. Study discontinuation was not related to any safety concern. The submission of the results of this study are more than 6 months after the end of this study due to some delays in finalising the data sets for the EEG report, which delayed the subsequent data analysis.

Methods

Study participants

- *Core Study*

The Core Study enrolled male or female subjects who were at least 2 years old at the time of consent/assent and had a minimum body weight of 8 kg. Subjects were to be less than 11 years old at the onset of LGS.

Subjects were to have a diagnosis of LGS as evidenced by more than one type of generalized seizures, including drop seizures (atonic, tonic, or myoclonic) for at least 6 months before screening and an electroencephalogram (EEG) reporting diagnostic criteria for LGS at some point in their history (abnormal background activity accompanied by slow, spike and wave pattern <2.5 Hz).

Subjects were to be receiving 1 to 4 concomitant AEDs at a stable dose for at least 30 days before screening, and subjects must have experienced an average of at least 2 drop seizures per week in the 4-week Baseline Period preceding randomization.

- *Extension Phases*

Extension A: Subjects who were considered reliable, available for the study duration, and willing to comply with study procedures, and who completed all scheduled visits up to and including Week 19 (Visit 7) of the Core Study were eligible to participate in Extension A.

Extension B: To be eligible for Extension B, a subject was to reside in Japan or in a country where an extended access program could not be implemented or had not yet been implemented. Subjects must have completed Extension A, and in the opinion of the investigator, would continue to benefit from treatment with perampanel.

Treatments

The investigational medicinal product tested in Study 338 was Fycompa as 2-mg oral tablets and 0.5 mg/ml oral suspension. Perampanel was orally administered once daily before bedtime. Oral tablets were recommended for dosing subjects ≥12 years of age and oral suspension for subjects <12 years of age. However, the most appropriate formulation was to be selected based on the subject's condition and at the discretion of the investigator and was to be used for a given subject throughout the course of the study.

Objective(s)

- Primary objective

The primary objective of the study was to demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in reducing the incidence of drop seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS.

- Secondary objectives

The secondary objectives were:

1. To demonstrate that perampanel given as adjunctive anti-epileptic treatment was superior to placebo in reducing the incidence of all seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS

2. To demonstrate that perampanel given as adjunctive anti-epileptic treatment was superior to placebo in the 50%, 75%, and 100% responder rates for drop seizures during 12 weeks of the Maintenance Period in subjects with inadequately controlled seizures associated with LGS

3. To demonstrate that perampanel given as adjunctive anti-epileptic treatment was superior to placebo in the 50%, 75%, and 100% responder rates for total seizures during 12 weeks of the Maintenance Period in subjects with inadequately controlled seizures associated with LGS

4. To demonstrate that perampanel given as adjunctive anti-epileptic treatment was superior to placebo in reducing the incidence of non-drop seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS

5. To evaluate the 50%, 75%, and 100% responder rates in non-drop seizure frequency during 12 weeks of the Maintenance Period in subjects with inadequately controlled seizures associated with LGS

6. To evaluate physicians' global evaluation of subjects' overall changes in symptoms

7. To evaluate the safety of perampanel relative to placebo as adjunctive therapy in subjects with inadequately controlled seizures associated with LGS during both the Core Study and the Extension Phase

8. To evaluate the pharmacokinetics (PK) and the pharmacokinetic/pharmacodynamics (PK/PD) relationships of perampanel as adjunctive therapy in subjects with inadequately controlled seizures associated with LGS.

CHMP's comment:

The primary objective of the study was to demonstrate that perampanel given as adjunctive anti-epileptic treatment was superior to placebo in reducing the incidence of drop seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS. The key secondary objectives (objectives 1, 2 and 3) were to demonstrate that perampanel was superior to placebo in reducing total seizure frequency and in achieving a 50% or greater reduction in drop and total seizure frequency.

The primary and some of the secondary objectives are commonly used and relevant objectives in phase 3 studies aimed at demonstrating the efficacy and safety of an antiepileptic drug versus placebo, as described in the guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (26 July 2018 CHMP/EWP/566/98 Rev.3). Some further exploratory objectives were anticipated. These are however not described in detail in this report as regards to their relevance, all the more that the study was terminated earlier.

The Applicant pointed out that due to the early termination of the study resulting in a reduced sample size, and given the variability in treatment response, population PK analysis and population PK/PD modelling planned for this study were not conducted.

Outcomes/endpoints

- *Primary Endpoint*

The primary efficacy endpoint was the median percent change in drop seizure frequency per 28 days during double-blind treatment (Titration Period and Maintenance Period) relative to the Prerandomization Phase.

- *Key Secondary Endpoints*

1. Median percent change in total seizure frequency per 28 days during double-blind treatment relative to the Prerandomization Phase

2. The 50% responder rate in the Maintenance Period of the double-blind treatment relative to the Prerandomization Phase for drop seizures

3. The 50% responder rate in the Maintenance Period of the double-blind treatment relative to the Prerandomization Phase for total seizures.

- *Other Secondary Endpoints*:

4. Median percent change in non-drop seizure frequency per 28 days during double-blind treatment (Titration Period and Maintenance Period) relative to the Prerandomization Phase

5. Proportion of subjects with 75%, and 100% responder rates for drop, non-drop, and total seizures in the Maintenance Period relative to the Prerandomization Phase

6. Proportion of subjects with 50% responder rate in the Maintenance Period of the double-blind treatment relative to the Prerandomization Phase for non-drop seizures

7. Physicians' global evaluation of the subject's overall changes in symptoms (using a 7-point Likert scale with 1=very much improved and 7=very much worse) at the end of the double-blind treatment

8. Incidence of AEs and SAEs, changes in clinical laboratory values, and vital signs

9. Model-derived average perampanel concentrations at steady state (Cav,ss) during the Maintenance Period of the Core Study. (Due to the early termination of the study resulting in a reduced sample size, and given the variability in treatment response, population PK analysis and population PK/PD modeling planned for this study were not conducted).

CHMP's comment:

The primary and secondary endpoints are commonly used and relevant endpoints in phase 3 studies aimed at demonstrating the efficacy and safety of an antiepileptic drug versus placebo, as described in the guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (26 July 2018 CHMP/EWP/566/98 Rev.3). The 50% responder rate is usually the primary endpoint in the EU procedures and the percent change in seizure frequency per 28 days the secondary endpoint. This is the opposite in the US. Therefore, for studies intended to be conducted in both areas (US and EU), the most important is that both criteria develop similarly and match together.

Some exploratory endpoints were anticipated. These are however not described in detail in this report as regards to their relevance, all the more that the study was terminated earlier.

Sample size / Randomisation and blinding (masking)

The sample size determination was based on the primary endpoint percent change from baseline in drop seizures as follows:

Placebo rates in drop seizures in the rufinamide and clobazam clinical trials were +1.4%, and -12.1%, respectively. In the active treatment arm, rufinamide had a median decrease of 42.5% in drop seizures and clobazam had mean decreases of 41.2%, 49.4%, and 68.3% for the low, medium, and high doses, respectively. A standard deviation of ~63% was observed for both rufinamide and for the medium dose of clobazam for drop seizures. It is assumed that comparable results will be seen in this trial for the placebo and perampanel treatment arms for drop seizures.

A sample size of 71 subjects in each treatment arm in the FAS will have 94% power to detect a treatment difference in median percentage seizure frequency change in drop seizures per 28 days of 40% (common SD of 63%) between placebo and perampanel based on a Wilcoxon rank-sum test at the 0.05 two-sided significance level.

Study drugs were administered on a double-blind basis. During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff were blinded to the treatment codes. Randomization data were kept strictly confidential, filed securely by an appropriate group with the sponsor or contract research organization (CRO) and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per standard operating procedure (SOP).

CHMP's comment:

Approximately 142 subjects were planned to be randomized (71 placebo, 71 perampanel). The sample size calculation was described in the protocol with the primary endpoint of median percent change from baseline tested at a 0.05 significance level. Since the study ended earlier with a resulting reduction in sample size, the study had lower power to detect a statistically significant difference between treatment groups. This prevented from drawing any robust conclusion of the conducted study. In these circumstances, the sample size determination is not more valid.

The randomization and blinding procedure are well described in the protocol as well as the urgent unblinding procedure when mandatory for safety reasons.

Statistical Methods

All statistical analyses were performed after the study was completed and the database was locked.

The analysis sets are defined as follows:

- *Core Study*

The Safety Analysis Set was the group of subjects who received at least one dose of study drug and had at least one post dose safety assessment.

The Full Analysis Set (FAS) was the group of randomized subjects who received at least one dose of study drug and had at least one post-dose seizure measurement.

The Per Protocol (PP) Analysis Set was the group of subjects who sufficiently complied with the protocol.

The Intention to Treat Set (ITT) was the group of randomized subjects who received at least one dose of study drug.

- *Extension Phase*

In general, the scope of endpoints and analyses included the entirety of perampanel exposure (Core and Extension [Extension refers Extension A and Extension B, as applicable]).

The Safety Analysis Set was the group of subjects who entered into Extension A and received at least one dose of perampanel and had at least one post-perampanel safety assessment. Subjects who continued into Extension B were included in this Safety Analysis Set. There was no separate Safety Analysis Set for Extension B alone.

The FAS was the group of subjects who entered into Extension A and received at least one dose of perampanel and had at least one post-perampanel seizure measurement.

Results

Participant flow / Recruitment

- Core Study

The subject disposition from the core study is displayed in Table 1 below:

Table 1 Subject Disposition and Primary Reason for Discontinuation From the Core Study – All Randomized Subjects

	Placebo (N=36) n (%)	Perampanel (N=34) n (%)
Randomized, n	36	34
Not treated, n	0	0
Treated, n (%)	36 (100)	34 (100)
Completed Core Study, n (%)	32 (88.9)	29 (85.3)
Discontinued from Core Study, n (%)	4 (11.1)	5 (14.7)
Primary reason for discontinuation[a], n (%)		
Adverse event[b]	0	3 (8.8)
Lost to follow-up	1 (2.8)	0
Subject choice	1 (2.8)	0
Inadequate therapeutic effect	1 (2.8)	0
Withdrawal of consent	1 (2.8)	1 (2.9)
Pregnancy	0	0
Study terminated by sponsor	0	1 (2.9)
Other	0	0

CRF = case report form
Percentages are based on the number of subjects randomized and treated in the relevant treatment group.
a: As reported on the Subject Disposition Core Study CRF.
b: Corresponding adverse event(s) leading to withdrawal from the study/study drug were reported on the Adverse Event CRF.
Source: Table 14.1.1.3.

A total of 101 subjects were screened for entry into the study. Of these 101 subjects, there were 30 screening failures and 70 subjects were randomized: 34 subjects were randomized to perampanel and 36 subjects were randomized to placebo. One subject passed screening but was not randomized due to the termination of the study by the sponsor.

By age subgroup, 35 subjects were children (16 perampanel, 19 placebo), 13 subjects were adolescents (6 perampanel, 7 placebo) and 22 subjects were adults (12 perampanel, 10 placebo).

A total of 29 (85.3%) subjects in the perampanel group (including 16 children and 4 adolescents) and 32 (88.9%) subjects in the placebo group (including 16 children and 6 adolescents) completed the Core Study.

A total of 5 (14.7%) subjects in the perampanel group and 4 (11.1%) subjects in the placebo group discontinued from the Core Study. The number (%) of subjects who discontinued from the Core Study and reasons for discontinuation by age subgroup was as follows:

- Children: No subjects in the perampanel group, and 3 (15.8%) subjects in the placebo group discontinued from the Core Study due to lost to follow-up, inadequate therapeutic effect, or withdrawal of consent (1 [5.3%] subject each).
- Adolescents: 2 (33.3%) subjects in the perampanel group discontinued from the Core Study due to adverse event and withdrawal of consent (1 [16.7%] subject each), and 1 (14.3%) subject in the placebo group discontinued from the Core Study due to subject choice.

- Adults: 3 (25.0%) subjects in the perampanel group discontinued from the Core Study due to adverse event (2 [16.7%] subjects) and study terminated by sponsor (1 [8.3%] subject), and no subjects in the placebo group discontinued from the Core Study.

CHMP's comment:

Nearly 70% (48 subjects) of the population in the core study are children or adolescents. Twenty two adults were also included in the study, although this is a P46 paediatric procedure. This fact has already been observed previously for other P46 procedures with perampanel. It is considered preferable to focus only on paediatric population within the framework of P46 procedures in order not to dilute the information and collect more accurate and specific data.

- Extension Phase

Extension A: A total of 61 subjects (29 in the perampanel group and 32 in the placebo group) completed the Core Study. And 58 subjects (including 30 children and 10 adolescents) entered into Extension A. Of these, 32 (55.2%) subjects (including 18 children and 5 adolescents) completed Extension A. Overall 26 (44.8%) subjects (including 12 children and 5 adolescents) discontinued from Extension A. The most common reason for discontinuation was study termination by the sponsor (3 [10.0%] children and 2 [20.0%] adolescents).

Extension B: Of the 32 subjects who completed Extension A, 13 subjects (including 5 children and 4 adolescents) entered into Extension B. Of these, 1 subject (in the children subgroup) completed Extension B. Four (80.0%) children and 4 (100%) adolescents discontinued from Extension B, mostly due to study termination by the sponsor (3 [60.0%] children and 3 [75.0%] adolescents). Additionally, 1 (7.7%) subject each discontinued due to AE, subject choice, inadequate therapeutic effect, or other reasons.

CHMP's comment:

Apart from the high discontinuation rate after extension A (for a duration of 52 weeks), with a rate of 44.8%, depicting that nearly 1 in 2 patients discontinue the study, the earlier than anticipated study termination by the Sponsor led to the fact that only 1 subject actually completed the extension B.

Baseline data

- Core Study

The demographic and other baseline characteristics in the core study from the Safety Analysis Set are displayed in Table 2 below:

Table 2 Demographic and Baseline Characteristics in the Core Study – Safety Analysis Set

Category	Placebo (N=36)	Perampanel (N=34)	Combined Total (N=70)
Age (year)[a]			
n	36	34	70
Mean (SD)	13.3 (7.80)	14.7 (10.37)	14.0 (9.10)
Median	11.0	12.5	11.5
Min, Max	2,35	2,39	2,39
Age group, n (%)			
2 to <12 years	19 (52.8)	16 (47.1)	35 (50.0)
12 to <18 years	7 (19.4)	6 (17.6)	13 (18.6)
18 to <65 years	10 (27.8)	12 (35.3)	22 (31.4)
>=65 years	0	0	0
Sex, n (%)			
Male	23 (63.9)	17 (50.0)	40 (57.1)
Female	13 (36.1)	17 (50.0)	30 (42.9)
Race, n (%)			
White	15 (41.7)	16 (47.1)	31 (44.3)
Black or African American	4 (11.1)	2 (5.9)	6 (8.6)
Japanese	11 (30.6)	8 (23.5)	19 (27.1)
Other Asian	2 (5.6)	5 (14.7)	7 (10.0)
Native Hawaiian or Other Pacific Islander	1 (2.8)	0	1 (1.4)
Other	3 (8.3)	3 (8.8)	6 (8.6)
Ethnicity, n (%)			
Hispanic or Latino	5 (13.9)	4 (11.8)	9 (12.9)
Not Hispanic or Latino	31 (86.1)	30 (88.2)	61 (87.1)

CHMP's comment:

The perampanel and placebo groups were comparable in demographic and baseline characteristics. Overall, the mean (SD) age was 14.0 (9.10) years (ranging from 2 to 39 years). A total of 35 (50.0%) subjects were children, 13 (18.6%) subjects were adolescents, and 22 (31.4%) subjects were adults. There were no elderly subjects enrolled in this study.

Most subjects were white (44.3%) or Japanese (27.1%). Most subjects were not Hispanic or Latino (87.1%). Slightly more males (40 [57.1%] subjects) than females (30 [42.9%] subjects) were in the study.

The epilepsy-specific medical history in the core study from the Safety Analysis Set are displayed in Table 3 below:

Table 3 Epilepsy-Specific Medical History in the Core Study – Safety Analysis Set

Category	Placebo (N=36) n (%)	Perampanel (N=34) n (%)	Combined Total (N=70) n (%)
Time since diagnosis (years)[a]			
n	36	34	70
Mean (SD)	8.93 (6.884)	9.22 (8.447)	9.07 (7.628)
Median	7.38	6.41	7.34
Min, Max	0.0,33.1	0.0,30.5	0.0,33.1
Etiology			
Unknown	21 (58.3)	19 (55.9)	40 (57.1)
Head injury/cranial trauma	0	2 (5.9)	2 (2.9)
CNS infection	2 (5.6)	1 (2.9)	3 (4.3)
Structural brain anomalies or malformations	4 (11.1)	3 (8.8)	7 (10.0)
Vascular brain anomalies	1 (2.8)	0	1 (1.4)
Perinatal events	2 (5.6)	2 (5.9)	4 (5.7)
Genetic	4 (11.1)	2 (5.9)	6 (8.6)
Family history of epilepsy	0	1 (2.9)	1 (1.4)
Other	2 (5.6)	4 (11.8)	6 (8.6)
Suspected Localization of Epileptogenic Region			
Idiopathic	10 (27.8)	7 (20.6)	17 (24.3)
Symptomatic	19 (52.8)	18 (52.9)	37 (52.9)
Temporal lobe	6 (16.7)	10 (29.4)	16 (22.9)
Frontal lobe	9 (25.0)	10 (29.4)	19 (27.1)
Parietal lobe	5 (13.9)	6 (17.6)	11 (15.7)
Occipital lobe	4 (11.1)	5 (14.7)	9 (12.9)
Other	12 (33.3)	8 (23.5)	20 (28.6)
Missing	7	9	16
Seizure type (history)			
Tonic-Atonic	35 (97.2)	33 (97.1)	68 (97.1)
Myoclonic with fall	9 (25.0)	12 (35.3)	21 (30.0)
Myoclonic without fall	15 (41.7)	15 (44.1)	30 (42.9)
Partial	9 (25.0)	13 (38.2)	22 (31.4)
Absence	6 (16.7)	5 (14.7)	11 (15.7)
Atypical Absence	13 (36.1)	17 (50.0)	30 (42.9)
Clonic	1 (2.8)	4 (11.8)	5 (7.1)
PGTC	15 (41.7)	17 (50.0)	32 (45.7)
Other	7 (19.4)	11 (32.4)	18 (25.7)

CHMP's comment:

The perampanel and placebo groups were comparable with regard to epilepsy-specific medical history. The overall median (minimum, maximum) time since diagnosis of epilepsy was 7.34 (0.0, 33.1) years. The suspected localization of the epileptogenic region was symptomatic in 37 (52.9%) subjects and idiopathic in 17 (24.3%) subjects. The most common seizure types (based on epilepsy-specific medical history) were tonic and/or atonic seizures (68 [97.1%] subjects), myoclonic seizures with and without fall (21 [30.0%] and 30 [42.9%] subjects, respectively), primary generalized tonic clonic (PGTC) seizures (32 [45.7%] subjects), and atypical absence seizures (30 [42.9%] subjects).

By age subgroup, the median (minimum, maximum) time since diagnosis of epilepsy was shortest in children (4.25 [0.0, 11.4] years) compared with adolescents (8.77 [0.1, 17.0] years) and adults (16.70 [0.3, 33.1] years).

In all age subgroups, the most commonly reported seizure types were tonic and/or atonic seizures (97.1% for children, 92.3% for adolescents and 100% for adults).

Anti-Epileptic Drugs (AED) at Baseline:

Overall, all but 1 subject (69 [98.6%] subjects) were reported to be receiving at least one AED at baseline. For the 1 subject (an adolescent) without a reported AED at baseline, the subject was in fact receiving an AED, but the start date of AED was recorded incorrectly in the database. Most subjects received 2 or 3 AEDs at baseline (19 [27.1%] or 40 [57.1%] subjects, respectively), whatever the age groups. Nearly all subjects in this study were taking only non-inducer type AEDs (68 [97.1%] subjects). The most common baseline AEDs were clobazam (35 [50.0%] subjects), lamotrigine (22 [31.4%] subjects), rufinamide (20 [28.6%] subjects), topiramate (18 [25.7%] subjects), valproate sodium (17 [24.3%] subjects), and levetiracetam (16 [22.9%] subjects).

CHMP's comment:

The subjects received the recommended and authorized treatments for the treatment of seizures in LGS. Inducer type AED are usually not recommended in that case since it could promote or aggravate the occurrence of some seizures. In all age subgroups, nearly all subjects were taking only non-inducer type AEDs (100% for children, 92.3% for adolescents and 95.5% for and adults). Overall, the most common baseline AEDs were similar across age groups.

- Extension phase

A summary of the demographic and baseline characteristics and the baseline epilepsy-specific medical history of subjects who entered into the Extension is provided in the following tables:

Table 14.1.4.1.1
Demographic and Baseline Characteristics by Age Group
Safety Analysis Set: Extension

	Age Group (Years)			
Category	2-<12 (N=30)	12-<18 (N=10)	18-<65 (N=18)	Total (N=58)
Age (year)*				
n	30	10	18	58
Mean (SD)	6.8 (2.85)	14.7 (1.77)	23.3 (5.04)	13.3 (8.17)
Median	7.0	14.5	21.5	11.0
Min, Max	2, 11	13, 17	18, 35	2, 35
Age group , n (%)				
2-<12 years	30 (100)	0	0	30 (51.7)
12-<18 years	0	10 (100)	0	10 (17.2)
>=18 to <65 years	0	0	18 (100)	18 (31.0)
>=65 years	0	0	0	0
Sex, n (%)				
Male	15 (50.0)	9 (90.0)	10 (55.6)	34 (58.6)
Female	15 (50.0)	1 (10.0)	8 (44.4)	24 (41.4)
Race, n (%)				
White	10 (33.3)	4 (40.0)	10 (55.6)	24 (41.4)
Black or African American	5 (16.7)	0	0	5 (8.6)
Japanese	6 (20.0)	4 (40.0)	6 (33.3)	16 (27.6)
Other Asian	5 (16.7)	1 (10.0)	1 (5.6)	7 (12.1)
Native Hawaiian or Other	1 (3.3)	0	0	1 (1.7)
Other	3 (10.0)	1 (10.0)	1 (5.6)	5 (8.6)
Ethnicity, n (%)				
Hispanic or Latino	1 (3.3)	2 (20.0)	3 (16.7)	6 (10.3)
Not Hispanic or Latino	29 (96.7)	8 (80.0)	15 (83.3)	52 (89.7)

Table 14.1.4.1.2
Epilepsy-Specific Medical History by Age Group
Safety Analysis Set: Extension

Category	Age Group (Years) 2-<12 (N=30)	12-<18 (N=10)	18-<65 (N=18)	Total (N=58)
Time since diagnosis (years)[a]				
n	30	10	18	58
Mean (SD)	4.35 (3.211)	11.22 (5.008)	16.16 (8.510)	9.20 (7.694)
Median	4.19	13.12	16.70	7.38
Min, Max	0.0, 11.4	2.7, 17.0	0.3, 33.1	0.0, 33.1
Etiology				
Unknown	16 (53.3)	5 (50.0)	10 (55.6)	31 (53.4)
Head injury/cranial trauma	2 (6.7)	0	0	2 (3.4)
CNS infection	3 (10.0)	0	0	3 (5.2)
Structural brain anomalies or malformations	3 (10.0)	0	2 (11.1)	5 (8.6)
Vascular brain anomalies	0	1 (10.0)	0	1 (1.7)
Perinatal events	1 (3.3)	2 (20.0)	0	3 (5.2)
Genetic	3 (10.0)	0	3 (16.7)	6 (10.3)
Family history of epilepsy	1 (3.3)	0	0	1 (1.7)
Other	1 (3.3)	2 (20.0)	3 (16.7)	6 (10.3)
Suspected Localization of Epileptogenic Region				
Idiopathic	5 (16.7)	1 (10.0)	7 (38.9)	13 (22.4)
Symptomatic	17 (56.7)	7 (70.0)	7 (38.9)	31 (53.4)
Temporal lobe	9 (30.0)	3 (30.0)	4 (22.2)	16 (27.6)
Frontal lobe	8 (26.7)	4 (40.0)	5 (27.8)	17 (29.3)
Parietal lobe	6 (20.0)	2 (20.0)	2 (11.1)	10 (17.2)
Occipital lobe	5 (16.7)	2 (20.0)	2 (11.1)	9 (15.5)
Other	9 (30.0)	4 (40.0)	3 (16.7)	16 (27.6)
Missing	8	2	4	14
Seizure type (history)				
Tonic-Atonic	29 (96.7)	10 (100)	18 (100)	57 (98.3)
Myoclonic with fall	9 (30.0)	4 (40.0)	2 (11.1)	15 (25.9)
Myoclonic without fall	15 (50.0)	6 (60.0)	4 (22.2)	25 (43.1)
Partial	9 (30.0)	4 (40.0)	7 (38.9)	20 (34.5)
Absence	6 (20.0)	1 (10.0)	2 (11.1)	9 (15.5)
Atypical Absence	12 (40.0)	4 (40.0)	8 (44.4)	24 (41.4)
Clonic	2 (6.7)	3 (30.0)	0	5 (8.6)
PGTC	8 (26.7)	7 (70.0)	14 (77.8)	29 (50.0)
Other	10 (33.3)	1 (10.0)	2 (11.1)	13 (22.4)

CHMP's comment:

The baseline and disease characteristics were similar between subjects of the core study and those entering in Extension A once the core study completed. The accurate proportion slightly varied for each parameter, since only a proportion of subjects (83%, 58/70 subjects) entered in Extension A.

Number analysed / Extent of exposure

- Core Study

The overall mean (SD) cumulative duration of exposure in the Core Study was comparable between the perampanel group (17.0 [3.49] weeks) and the placebo group (17.3 [2.60] weeks).

The mean (SD) daily dose received was 6.2 (1.34) mg. The mean (SD) modal (the most frequent) daily dose was 6.8 (1.77) mg, with a majority of subjects (61.8%) receiving a modal daily dose of 8 mg.

By age subgroup, the mean (SD) cumulative duration of exposure to perampanel was 18.2 (0.70) weeks for children, 14.3 (5.85) weeks for adolescents, and 16.7 (3.73) weeks for the adults.

The mean (SD) daily dose was 5.8 (1.55) mg for children, 6.2 (1.53) mg for adolescents, and 6.6 (0.85) mg for adults. The modal dose was 8 mg for 50.0% of children, 66.7% of adolescents, and 75.0% of adults.

- Extension Phase

For those subjects who entered the Extension Phase of the study, the overall mean (SD) cumulative duration of exposure to perampanel was 56.4 (38.20) weeks. The mean (SD) daily dose received during the Entire Treatment Period was 6.7 (1.96) mg, and the mean (SD) modal dose was 7.0 (2.41) mg.

By age subgroup, the mean (SD) cumulative duration of exposure to perampanel was 53.4 (28.83) weeks for children, 65.3 (59.65) weeks for adolescents, and 56.4 (39.09) weeks for adults. The mean (SD) daily dose by age subgroups was 6.4 (2.33) mg for children, 6.5 (1.45) mg for adolescents, and 7.1 (1.50) mg for adults. In all age subgroups, the modal dose was 8 to <12 mg for the majority of subjects.

Efficacy results

Due to the termination of the study by the sponsor and the resulting reduction in sample size, the study had lower power to detect a statistically significant difference between treatment groups.

The primary efficacy results (median percent change in drop seizure frequency) and key secondary efficacy results (median percent change in total seizure frequency and 50% responder rate in drop and total seizures) are summarized below.

The primary and key secondary efficacy results are also presented by age subgroups, but the small sample sizes for children (N=16 perampanel and 19 placebo), adolescents (N=6 perampanel and 7 placebo), and adults (N=12 perampanel and 10 placebo) limits the interpretability of these results by age.

Of the 58 subjects in the Extension Phase, 30 were children, 10 were adolescents, and 18 were adults.

- **Primary efficacy endpoint**: Percent Change in Drop Seizure Frequency (per 28 days)
  - Core Study

Subjects treated with perampanel in the Core Study showed a numerically greater decrease from baseline in median drop seizure frequency compared with the placebo group, which did not reach statistical significance. In the perampanel group, the median frequency per 28 days in drop seizures decreased from 46.56 to 32.14, compared with a decrease from 77.65 to 62.31 in the placebo group.

The median percent change from baseline was -23.07% for perampanel group compared with -4.51% for placebo group, with a median difference (95% CI) for perampanel versus placebo of -19.3% (-49.2%, 4.8%), P=0.107 as shown in the following table:

Table 14.2.1.1
Drop Seizure Frequency per 28 Days and Percent Change During Treatment Summary
Full Analysis Set

	Placebo (N=36)		Perampanel (N=34)	
Analysis Window Statistic	Actual	Percent Change	Actual	Percent Change
Prerandomization Phase				
n	36		34	
Mean (SD)	111.31 (112.585)		108.62 (157.559)	
Median	77.65		46.56	
Min, Max	7.5, 481.1		6.2, 645.0	
Treatment Phase				
n	36	36	34	34
Mean (SD)	107.57 (128.957)	2.49 (65.196)	74.09 (114.640)	-12.86 (85.724)
Median	62.31	-4.51	32.14	-23.07
Min, Max	2.6, 549.3	-86.2, 201.8	2.2, 508.0	-96.4, 371.4
Median Difference to Placebo[a]				-19.3
(95% Confidence Interval)[a]				(-49.2, 4.8)
P-value compared to Placebo[b]				0.107

CHMP's comment:

Due to the lack of statistical significance on this primary endpoint (median difference (95% CI) for perampanel versus placebo of -19.3% (-49.2%, 4.8%), P=0.107), all subsequent efficacy results are descriptive.

Further analysis were conducted by age subgroup where the median percent change from baseline in drop seizure frequency per 28 days was as follows:

- Children: -54.25% for the perampanel group, -8.04% for the placebo group

- Adolescents: -3.51% for the perampanel group, +10.67% for the placebo group

- Adults: -17.48% for the perampanel group, -1.79% for the placebo group

Even if the results seem better numerically in children than in adolescents, no relevant conclusion can be drawn from these results which are only descriptive.

- Extension Phase

For those subjects who entered the Extension Phase of the study, the overall median percent change from baseline in drop seizure frequency during perampanel treatment was -29.49%. And the overall median percent change from baseline in drop seizure frequency during perampanel treatment was -35.67% in children, -12.00% in adolescents and -35.42% in adults.

- **Secondary efficacy endpoint**: Percent Change in Total Seizure Frequency (per 28 days)
  - Core Study

Subjects in the perampanel group showed a numerically greater decrease from baseline in median total seizure frequency per 28 days compared with the placebo group, with the median total seizure frequency decreasing from 142.55 to 99.33 in the perampanel group, compared with an increase from 110.76 to 124.56 in the placebo group.

The median percent change from baseline was -18.23% for perampanel group compared with -6.53% for placebo group, with a median difference (95% CI) for perampanel versus placebo of -17.6% (-41.7%, 6.1%) as shown in the following table:

Table 14.2.2.1
Total Seizure Frequency per 28 Days and Percent Change During Treatment Summary
Full Analysis Set

	Placebo (N=36) n (%)		Perampanel (N=34) n (%)	
Analysis Window Statistic	Actual	Percent Change	Actual	Percent Change
Prerandomization Phase				
n	36		34	
Mean (SD)	264.34 (387.152)		460.19 (1270.353)	
Median	110.76		142.55	
Min, Max	17.6, 1754.3		15.3, 6858.0	
Treatment Phase				
n	36	36	34	34
Mean (SD)	280.22 (519.498)	7.13 (63.706)	235.00 (438.895)	-16.20 (48.769)
Median	124.56	-6.53	99.33	-18.23
Min, Max	10.5, 2827.1	-63.6, 266.8	2.4, 2041.5	-96.9, 103.5
Median Difference to Placebo[a]				-17.6
(95% Confidence Interval)[a]				(-41.7, 6.1)

CHMP's comment:

Further analysis were conducted by age subgroup where the median percent change in total seizures was as follows:

By age subgroup, the median percent change in total seizures was as follows:

- *Children: -27.14% for the perampanel group, -5.15% for the placebo group*
- *Adolescents: +10.64% for the perampanel group, -9.96% for the placebo group*
- *Adults: -15.79% for the perampanel group, -0.63% for the placebo group*

Same observation as for the primary endpoint: Even if the results seem better numerically in children than in adolescents, no relevant conclusion can be drawn from these results which are only descriptive.

- Extension Phase

For those subjects who entered the Extension Phase of the study, the overall median percent change from baseline in total seizure frequency during perampanel treatment was -26.09%. And the overall median percent change from baseline in total seizure frequency during perampanel treatment was -33.91% in children, -12.52% in adolescents and -36.84% in adults.

- **Secondary efficacy endpoint**: 50% Responder Rate in Drop Seizure Frequency
  - Core Study

Overall, the percentage of subjects with a 50% or greater reduction in drop seizure frequency relative to baseline during the Core Study Maintenance Period was numerically greater in the perampanel group (44.1%) compared with the placebo group (25.0%), with an odds ratio (95% CI) of 2.6 (0.92%, 7.50%) as shown in the following table:

Table 14.2.2.5
50% Responder Rate in Drop Seizure Frequency during Maintenance-LOCF
Full Analysis Set

	Placebo (N=36)	Perampanel (N=34)
Responder		
Yes, n(%)	9 (25.0)	15 (44.1)
No, n(%)	27 (75.0)	19 (55.9)
Total	36 (100)	34 (100)
Odds ratio (95% CI)[a]		2.6 (0.92, 7.50)

CHMP's comment:

Further analysis were conducted by age subgroup where the 50% responder rate in drop seizures was as follows:

By age subgroup, the 50% responder rate in drop seizures was as follows:

- *Children: 56.3% responders in perampanel group, 31.6% responders in placebo group*
- *Adolescents: 33.3% responders in perampanel group, 0% responders in placebo group*
- *Adults: 33.3% responders in perampanel group, 30.0% responders in placebo group*

Same observation as for the primary endpoint: Even if the results seem better numerically in children than in adolescents, no relevant conclusion can be drawn from these results which are only descriptive.

- Extension Phase

For those subjects who entered the Extension Phase, 37.9% showed a 50% or greater decrease in drop seizure frequency during perampanel treatment. The 50% responder rate was 43.3% for children, 10.0% for adolescents, and 44.4% for adults.

- **Secondary efficacy endpoint**: 50% Responder Rate in Total Seizure Frequency
  - Core Study

Overall, the percentage of subjects with a 50% or greater reduction in total seizure frequency relative to baseline during the Core Study Maintenance Period was numerically greater in the perampanel group (32.4%) compared with the placebo group (16.7%), with an odds ratio (95% CI) of 2.9 (0.88%, 9.84%) (Table 14.2.2.9) as shown in the following table:

Table 14.2.2.9
50% Responder Rate in Total Seizure Frequency during Maintenance-LOCF
Full Analysis Set

	Placebo (N=36)	Perampanel (N=34)
Responder		
Yes, n(%)	6 (16.7)	11 (32.4)
No, n(%)	30 (83.3)	23 (67.6)
Total	36 (100)	34 (100)
Odds ratio (95% CI)[a]		2.9 (0.88, 9.84)

CHMP's comment:

Further analysis were conducted by age subgroup where the 50% responder rate in total seizures was as follows:

By age subgroup, the 50% responder rate in total seizures was as follows:

- *Children: 37.5% responders in perampanel group, 26.3% responders in placebo group*
- *Adolescents: 33.3% responders in perampanel group, 0% responders in placebo group*
- *Adults: 25.0% responders in perampanel group, 10.0% responders in placebo group*

Same observation as for the primary endpoint: Even if the results seem better numerically in children than in adolescents, no relevant conclusion can be drawn from these results which are only descriptive.

- Extension Phase

For those subjects who entered the Extension Phase of the study, 34.5% showed a 50% or greater decrease in total seizure frequency during perampanel treatment. The 50% responder rate was 43.3% for children, 0% for adolescents, and 38.9% for adults.

- **Other Secondary Efficacy Results**

The results of other secondary efficacy endpoints are not displayed in this report.

Safety results

- **Overview of Adverse Events**

  - Core Study

The AEs are presented Table 4 below for subjects in the core study Safety Analysis Set:

Table 4 Overview of Treatment-Emergent Adverse Events in the Core Study – Safety Analysis Set

Category	Placebo (N=36) n(%)	Perampanel (N=34) n(%)
TEAEs	26 (72.2)	29 (85.3)
Treatment-related TEAEs[a]	8 (22.2)	22 (64.7)
Severe TEAEs	0	3 (8.8)
Serious TEAEs[b]	1 (2.8)	6 (17.6)
Deaths	0	0
Other SAEs[c]	1 (2.8)	6 (17.6)
Life Threatening	0	1 (2.9)
Requires inpatient hospitalization or prolongation of existing hospitalization	1 (2.8)	6 (17.6)
Persistent or significant disability or incapacity	0	0
Congenital anomaly / birth defect	0	0
Important medical events	0	0
TEAEs leading to study drug dose adjustment	3 (8.3)	17 (50.0)
TEAEs leading to study drug withdrawal	0	3 (8.8)
TEAEs leading to study drug dose increase	0	1 (2.9)
TEAEs leading to study drug dose reduction	3 (8.3)	15 (44.1)
TEAEs leading to study drug dose interruption	0	1 (2.9)

The incidence of TEAEs in the Core Study was higher in the perampanel group (85.3%) than the placebo group (72.2%). The incidence of treatment-related TEAEs was also higher in the perampanel group (64.7%) than the placebo group (22.2%). No deaths occurred during the Core Study. SAEs occurred in 6 (17.6%) subjects in perampanel group and 1 (2.8%) subject in placebo group (See Section on Serious Adverse Events), and 3 (8.8%) subjects in the perampanel group experienced a TEAE leading to study drug withdrawal compared to no subjects in the placebo group.

  - Extension Phase

For those subjects who entered the Extension Phase of the study, the overall incidence of TEAEs during perampanel treatment was 86.2%. Treatment-related TEAEs were reported by 62.1% of subjects. SAEs were reported by 11 (19.0%) subjects, 2 of which resulted in death (See Section on Deaths and Serious Adverse Events). A total of 8 (13.8%) subjects experienced a TEAE leading to study drug withdrawal.

- **Common Treatment-Emergent Adverse Events**

  - Core Study

TEAEs that occurred in 5% or more subjects in either treatment group reported during the Core Study are summarized by MedDRA (Version 21.0) SOC and PT in Table 5 below.

Table 5 Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects in Either Treatment Group by Decreasing Frequency in the Core Study - Safety Analysis Set

MedDRA Preferred Term	Placebo (N=36) n (%)	Perampanel (N=34) n (%)
Subjects with any TEAE	26 (72.2)	29 (85.3)
Somnolence	2 (5.6)	8 (23.5)
Irritability	1 (2.8)	5 (14.7)
Upper respiratory tract infection	1 (2.8)	4 (11.8)
Decreased appetite	0	4 (11.8)
Diarrhoea	1 (2.8)	3 (8.8)
Drooling	1 (2.8)	3 (8.8)
Fatigue	1 (2.8)	3 (8.8)
Balance disorder	0	3 (8.8)
Gait disturbance	0	3 (8.8)
Rash	0	3 (8.8)
Vomiting	5 (13.9)	2 (5.9)
Cough	2 (5.6)	2 (5.9)
Nasopharyngitis	2 (5.6)	2 (5.9)
Pneumonia	2 (5.6)	2 (5.9)
Dehydration	1 (2.8)	2 (5.9)
Skin laceration	1 (2.8)	2 (5.9)
Constipation	0	2 (5.9)
Hordeolum	0	2 (5.9)
Influenza	0	2 (5.9)
Lethargy	0	2 (5.9)
Nausea	0	2 (5.9)
Peripheral swelling	0	2 (5.9)
Sedation	0	2 (5.9)
Weight increased	0	2 (5.9)
Pyrexia	5 (13.9)	1 (2.9)
Agitation	2 (5.6)	1 (2.9)
Bronchitis	3 (8.3)	0

The following TEAEs were the most common in the perampanel group, occurring with an incidence of at least 10% in the perampanel group and with a greater incidence than in the placebo group:

- Somnolence: perampanel: 8 (23.5%) subjects vs placebo: 2 (5.6%) subjects
- Irritability: perampanel: 5 (14.7%) subjects vs placebo: 1 (2.8%) subject
- Upper respiratory infection: perampanel: 4 (11.8%) subjects vs placebo: 1 (2.8%) subject
- Decreased appetite: perampanel: 4 (11.8%) subjects vs placebo: no subjects

CHMP's comment:

The most common TEAE with an incidence of at least 10% in the perampanel group and with a greater incidence than in the placebo group are either well-known AE and stated in the SmPC of perampanel (somnolence, irritability, decreased appetite) or unspecific (upper respiratory infection).

By age subgroup, the most common TEAEs (occurring in >2 subjects in the perampanel group and with a greater incidence than in the placebo group) were as follows as shown in Table 1:

Table 1 Treatment-Emergent Adverse Events Occurring in 2 or More Subjects in Either Treatment Group by Decreasing Frequency in Children and Adolescents in the Core Study - Safety Analysis Set

MedDRA Preferred Term	Placebo n (%)	Perampanel n (%)
Children (2 to <12 years)	**(N=19)**	**(N=16)**
Subjects with any TEAE	16 (84.2)	13 (81.3)
Upper respiratory tract infection	0	4 (25.0)
Gait disturbance	0	3 (18.8)
Vomiting	3 (15.8)	2 (12.5)
Nasopharyngitis	2 (10.5)	2 (12.5)
Somnolence	2 (10.5)	2 (12.5)
Drooling	1 (5.3)	2 (12.5)
Decreased appetite	0	2 (12.5)
Fatigue	0	2 (12.5)
Hordeolum	0	2 (12.5)
Lethargy	0	2 (12.5)
Pyrexia	3 (15.8)	1 (6.3)
Pneumonia	2 (10.5)	1 (6.3)
Bronchitis	2 (10.5)	0
Cough	2 (10.5)	0
Adolescents (12 to <18 years)	**(N=7)**	**(N=6)**
Subjects with any TEAE	5 (71.4)	5 (83.3)
Somnolence	0	2 (33.3)

- Children (N=16 perampanel and 19 placebo): upper respiratory tract infection (25.0% vs 0%), and gait disturbance (18.8% vs 0%)
- Adolescents (N=6 perampanel and 7 placebo): none occurred in >2 subjects
- Adults (N=12 perampanel and 10 placebo): irritability (33.3% vs 10.0%) and somnolence (33.3% vs 0%)

CHMP's comment:

The most common TEAEs (occurring in >2 subjects in the perampanel group and with a greater incidence than in the placebo group) are either well-known AE and stated in the SmPC of perampanel (gait disturbance, irritability) or unspecific (upper respiratory infection).

- Extension Phase

For those subjects who entered the Extension Phase of the study, the most common (≥10%) TEAEs during perampanel treatment were somnolence (11 [19.0%] subjects), pyrexia (8 [13.8%] subjects), decreased appetite, irritability, nasopharyngitis, upper respiratory tract infection (7 [12.1%] subjects each), and constipation (6 [10.3%] subjects).

By age subgroup, the most common TEAEs (occurring in >2 subjects) for those subjects who entered the Extension Phase were as follows:

- Children (N=30): pyrexia (6 [20.0%] subjects), nasopharyngitis and upper respiratory tract infection (5 [16.7%] subjects each), somnolence, decreased appetite, drooling, and seizure (4 [13.3%] subjects each), and constipation, aggression, gait disturbance, influenza, vomiting, bronchitis, and pneumonia (3 [10.0%] subjects)

- Adolescents (N=10): somnolence (3 [30.0%] subjects)
- Adults (N=18): irritability (5 [27.8%] subjects), somnolence (4 [22.2%] subjects), decreased appetite, constipation, and agitation (3 [16.7%] subjects each)

CHMP's comment:

The most common TEAEs (occurring in >2 subjects) for those subjects who entered the Extension Phase are mainly well-known AE and stated in the SmPC of perampanel (somnolence, decreased appetite, gait disturbance, irritability, aggression) or unspecific (constipation, nasopharyngitis, upper respiratory infection, influenza, vomiting, bronchitis, and pneumonia). Drooling and seizure may either be study drug related or symptoms of the uncontrolled disease and/or lack of therapeutic effect (treatment ineffective).

- **Analysis of Adverse Events**

Adverse Events by Maximum Severity

Overall, most TEAEs were mild or moderate. A total of 3 (8.8%) subjects in the perampanel group and no subjects in the placebo group had severe TEAEs. Severe TEAEs in perampanel-treated subjects included cardiac arrest, vertigo, respiratory syncytial virus infection, somnolence, atrophic pharyngitis, and respiratory distress (1 [2.9%] subject each).

CHMP's comment:

One of the severe TEAE related to the cardiac arrest in the perampanel group was thoroughly assessed: The narrative of the cardiac arrest is referred to for more details regarding the cardiac arrest in a 12-year-old that occurred on 2017 (Study Day 41). The following statement extracted from the narrative means that the cardiac arrest is not related to perampanel: "events of respiratory distress, hypernatraemia, cardiac arrest, sinus tachycardia and pneumonia resolved on 2017 (Study Day 48) and the subject was discharged from the hospital on the same day (Study Day 48). The cause of respiratory distress could have been due to a mucous plug. As per the investigator, the respiratory arrest might have led to all other complications including hypoinflated lungs, cardiac arrest, and pneumonia. The subject had no adverse events ongoing at the time of respiratory distress".

Treatment-Related Adverse Events

- Core Study

Overall, the incidence of TEAEs considered by the investigator to be related to study drug was higher in the perampanel group (64.7%) compared with the placebo group (22.2%). Treatment-related events occurring in ≥10% of subjects in the perampanel group and greater than placebo group included somnolence (14.7% vs 5.6%), irritability (14.7% vs 2.8%), and decreased appetite (11.8% vs 0%).

By age subgroup, the incidence of treatment-related TEAEs in the Core Study was higher in the perampanel group compared with the placebo group in all age subgroups (children: 50.0% vs 21.1%, adolescents: 50.0% vs 14.3%, and adults: 91.7% vs 30.0%). The most common treatment-related TEAEs (occurring in >2 subjects in the perampanel group and with a greater incidence than the placebo group) by age subgroup were as follows

- Children (N=16 perampanel and 19 placebo): gait disturbance (18.8% vs 0%)
- Adolescents (N=6 perampanel and 7 placebo): none occurred in >2 subjects
- Adults (N=12 perampanel and 10 placebo): irritability (33.3% vs 10.0%) and somnolence (25.0% vs 0%)

CHMP's comment:

The treatment related AE are well-known AE and stated in the SmPC (somnolence, irritability, decreased appetite, gait disturbance, somnolence).

- Extension Phase

Treatment-related TEAEs for those subjects who entered the Extension Phase are summarized by MedDRA SOC and PT in Table 14.3.1.5.1.Ext. Overall, 36 (62.1%) subjects had TEAEs considered by the investigator to be related to study drug. For those subjects who entered the Extension Phase of the study, the most common ($\geq$10%) treatment-related TEAEs during perampanel treatment were somnolence (7 [12.1%] subjects) and irritability (6 [10.3%] subjects.

By age subgroup, the most common treatment-related TEAEs (occurring in >2 subjects) for those subjects who entered the Extension Phase were as follows:

- Children (N=30): gait disturbance and drooling (3 [10.0%] subjects each)
- Adolescents (N=10): none occurred in >2 subjects
- Adults (N=18): irritability (5 [27.8%] subjects), somnolence, decreased appetite, and agitation (3 [16.7%] subjects each)

CHMP's comment:

*The treatment related AE are well-known AE and stated in the SmPC (somnolence, irritability, decreased appetite, gait disturbance, somnolence). The Applicant should discuss the relevance to include in the PI agitation considered by the investigator to be related to study drug. (**RSI**).*

Deaths:

No subjects died during the Core Study.

In the Extension Phase, 1 adult subject (23 years old) died due to cytogenetic abnormality (complications due to chromosomal abnormality [trisomy 4p plus monosomy 18p]), and 1 adolescent subject (17 years old) died due to sudden unexplained death in epilepsy (SUDEP). Neither event was considered related to the study drug.

CHMP's comment:

Both narratives of the deaths during the Extension were checked and neither of these fatal events were drug-related.

The narrative of the death is referred to for more details regarding the death in a 23-year-old that occurred on 2020 (Study Day 610, Extension Day 491). The following statement extracted from the narrative means that the death is not related to perampanel: "On 2019 (Study Day 516; Extension Day 390), it was reported that the subject had fever and found unresponsive and lying face down in bed. On the same day (Study Day 516, Extension Day 390), the subject died due to complications due to chromosomal abnormality [trisomy 4P plus monosomy 18P]). The event was classified as severe in severity and serious (fatal). No autopsy was performed. Ongoing events at the time of cytogenetic abnormality included: gait disturbance (since 2018), constipation (since 2019), and pyrexia (2019-2019). The investigator classified the events of pneumatosis intestinalis, cough, and cytogenetic abnormality to be not related to study drug. The investigator classified the event of irritability to be related to study drug".

The narrative of the death is referred to for more details regarding the death in a 17-year-old that occurred on 2019 (Study Day 516, Extension Day 390). The following statement extracted from the

narrative means that the death is not related to perampanel: "On 2020 (Study Day 609, Extension Day 490), during Extension B Phase 2 mg, the subject went out for a walk and later slept. No seizure was noted. On the next day (Study Day 610; Extension Day 491), in the morning, the woke up and found that the subject was not breathing. The subject was transported to an emergency hospital, but was in a state of cardiorespiratory arrest. The subject's death was confirmed, and a systemic computerized tomogram scan revealed no abnormalities, based on which a diagnosis of sudden death was made. The event of sudden unexplained death in epilepsy was classified as severe in severity and serious. It was unknown if an autopsy was performed. Other ongoing event at the time of death included: dizziness (2019 –2020). The subject discontinued from the Extension study early due to sudden unexplained death in epilepsy and had the last dose of study drug on 2020 (Study Day 609; Extension Day 490). The investigator classified the events of fall, dental caries, and sudden unexplained death in epilepsy to be not related to study drug".

Serious Adverse Events:

- Core Study

The incidence of SAEs was higher in the perampanel group (6 [17.6%] subjects) compared with the placebo group (1 [2.8%] subject).

In the perampanel group, 3 of the subjects with SAEs were in children (decreased appetite, respiratory syncytial virus infection, seizure, mental status changes, and vomiting), 1 subject was an adolescent (respiratory distress), and 2 subjects were adults (dehydration and epilepsy).

In the placebo group, SAEs occurred in 1 child (gastrointestinal hemorrhage, pneumonia aspiration, and pneumonia). Each treatment-emergent SAE was experienced by no more than 1 subject in each treatment group as shown in Table 6:

Table 6 Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term in the Core Study – Safety Analysis Set

MedDRA System Organ Class Preferred Term	Placebo (N=36) n (%)	Perampanel (N=34) n (%)
Subjects with any TEAE	1 (2.8)	6 (17.6)
Gastrointestinal disorders	1 (2.8)	1 (2.9)
Gastrointestinal haemorrhage	1 (2.8)	0
Vomiting	0	1 (2.9)
Infections and infestations	1 (2.8)	1 (2.9)
Pneumonia	1 (2.8)	0
Respiratory syncytial virus infection	0	1 (2.9)
Metabolism and nutrition disorders	0	2 (5.9)
Decreased appetite	0	1 (2.9)
Dehydration	0	1 (2.9)
Nervous system disorders	0	2 (5.9)
Epilepsy	0	1 (2.9)
Seizure	0	1 (2.9)
Psychiatric disorders	0	1 (2.9)
Mental status changes	0	1 (2.9)
Respiratory, thoracic and mediastinal disorders	1 (2.8)	1 (2.9)
Pneumonia aspiration	1 (2.8)	0
Respiratory distress	0	1 (2.9)

- Extension Phase

For those subjects who entered the Extension Phase of the study, a total of 11 (19.0%) subjects experienced a SAE during perampanel treatment. Four of these subjects had SAEs in both the Extension Phase as well as the Core Study (3 randomized to perampanel and 1 randomized to placebo in the Core Study). The remaining 7 subjects experienced SAEs in the Extension Phase only.

Of the 11 subjects who had an SAE, 8 subjects were children, 1 was an adolescent, and 2 were adults. SAEs that occurred in 2 or more subjects included pneumonia (in 3 children), and influenza and seizure in 2 children each. SAEs by age subgroup were as follows:

- Children (N=30): pneumonia (3 [10.0%] subjects), influenza and seizure 2 [6.7%] subjects each), and asthma, bronchitis, decreased appetite, hematemesis, lethargy, lower respiratory tract infection viral, mental status change, microcytic anemia, quadriplegia, respiratory syncytial virus infection, seizure cluster, sepsis, sleep apnea syndrome, and vomiting (1 [3.3%] subject each)
- Adolescents (N=10): dental caries and SUDEP (1 [10.0%] subject)
- Adults (N=18): cough, crytogenetic abnormality, infected skin ulcer, and pneumatosis intestinalis (1 [5.6%] subjects each)

CHMP's comment

*The Applicant is requested to comment the outcome of each of the 6 SAE during the core study and 11 SAE during the Extension Phase (**RSI**).*

TEAEs Leading to Discontinuation of Study Drug:

- Core Study

In the Core Study, few subjects discontinued from study drug due to TEAEs, including 3 (8.8%) subjects (1 adolescent and 2 adults) in perampanel group and no subjects in placebo group. The TEAEs leading to study drug discontinuation were angioedema and drooling in 1 adolescent subject, dehydration and abnormal loss of weight in 1 adult subject, and epilepsy in another adult subject.

- Extension Phase

For those subjects who entered the Extension Phase of the study, a total of 8 (13.8%) subjects had a TEAE leading to study drug discontinuation. Of the 8 subjects who discontinued study drug due to a TEAE, 3 subjects were children (aggression [2 subjects] and seizure), 2 were adolescents (fatigue and SUDEP), and 3 were adults (agitation [2 subjects], insomnia, and sedation).

TEAEs Related to Abuse Potential

No subjects had a TEAE suggestive of abuse potential in the Core Study or in the Extension Phase.

TEAEs Related to Suicidality

No subjects had a positive score (≥1) in suicidal behavior or suicidal ideation based on C-SSRS assessment at baseline (lifetime or within 6 months before screening) or on-treatment in either the Core Study or the Extension Phase and no TEAEs related to suicidality occurred in the Core Study or Extension Phase.

TEAEs Related to Alertness or Cognition

TEAEs related to alertness or cognition were reported in 13 (38.2%) subjects in the perampanel group and 4 (11.1%) subjects in the placebo group in the Core Study. The most common TEAE (reported in ≥

10% of subjects) in this category was somnolence (perampanel: 8 [23.5%] subjects, placebo: 2 [5.6%] subjects)

For those subjects who entered the Extension Phase, 19 (32.8%) subjects had TEAEs related to Alertness or Cognition. The most common TEAE (reported in ≥10% of subjects) in this category was somnolence (11 [19.0%] subjects).

TEAEs Related to Hostility/Aggression

TEAEs related to hostility/aggression were reported in 1 (2.9%) subject in the perampanel group and no subjects in the placebo group. TEAEs related to hostility/aggression occurred with a higher incidence in the perampanel group (8 [23.5%] subjects) compared with the placebo group (4 [11.1%] subjects). None of these events were considered serious and none led to discontinuation of study drug. The most common TEAE (reported in ≥10% of subjects) in this category was irritability (perampanel: 5 [14.7%] subjects, placebo: 1 [2.8%] subject).

For those subjects who entered the Extension Phase, 4 (6.9%) subjects had TEAEs of hostility/aggression.

TEAEs Related to Psychosis and Psychotic Disorders

TEAEs related to psychosis and psychotic disorders were reported in 1 (2.9%) subject in the perampanel group and no subjects in the placebo group. None of these events (affective disorder and hallucinations) were considered serious and none led to discontinuation of study drug.

For those subjects who entered the Extension Phase, no subjects had a TEAE related to psychosis and psychotic disorders.

TEAEs Related to Status Epilepticus/Convulsions

TEAEs related to status epilepticus/convulsions were reported with a similar incidence in the perampanel group (4 [11.8%] subjects) and the placebo group (3 [8.3%] subjects).

For those subjects who entered the Extension Phase, 11 (19.0%) subjects had TEAEs in the SMQ of convulsions.

CHMP's comment:

These TEAE related to status epilepticus/convulsions are followed in the PSUR and the PI may be updated if relevant.

TEAEs of Drug-Related Hepatic Disorder Abnormalities

TEAEs of hepatic related laboratory abnormalities were reported in no subjects in the perampanel group and 1 (2.8%) subject in the placebo group.

For those subjects who entered the Extension Phase, 3 (5.2%) subjects had TEAEs of drug-related hepatic disorders.

CHMP's comment:

As stated in the PI, cases of hepatotoxicity (mainly hepatic enzyme increased) with perampanel in combination with other antiepileptic drugs have been reported. If hepatic enzymes elevation is observed, monitoring of liver function should be considered.

TEAEs Related to Cardiac and ECG Abnormalities

TEAEs related to cardiac and ECG abnormalities were reported in 3 (8.8%) subjects in the perampanel group and no subjects in the placebo group.

For those subjects who entered the Extension Phase, 4 (6.9%) subjects had TEAEs related to cardiac and ECG abnormalities.

CHMP's comment:

*The Applicant is requested to provide an assessment of the TEAEs related to cardiac and ECG abnormalities that occurred in the core study and in the Extension phase (**RSI**).*

TEAEs Related to Rash

TEAEs related to rash were reported in 6 (17.6%) subjects in the perampanel group and 3 (8.3%) subjects in the placebo group.

For those subjects who entered the Extension Phase, 11 (19.0%) subjects had TEAEs related to rash.

TEAEs Related to Falls

TEAEs of fall occurred in 1 subject in the perampanel group and no subjects in the placebo group. Events identified using SMQ of accident/injury occurred in 6 subjects in the perampanel group and 4 subjects in the placebo group during the Randomization Phase. The rate of accident/injury events per subject-month was similar in the perampanel group (0.045) and placebo group (0.041).

- **Other safety findings**

Laboratory results

Overall, and by age subgroup, there were no changes of clinical importance in mean laboratory values over time in either the perampanel group or the placebo group in the Core Study. A shift analysis revealed no shifts of clinical concern for hematology, clinical chemistry, or urinalysis parameters, overall and by age subgroup. The patterns of shifts were similar in the placebo and perampanel groups. Treatment-emergent markedly abnormal laboratory results occurred infrequently, overall and by age subgroup.

Vital signs

Overall, no changes of clinical importance were observed in mean vital signs over time (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate and temperature).

The incidence of clinically notably weight increase (increase of >7%) was greater in the perampanel group (16 [47.1%] subjects) compared with the placebo group (5 [13.9%] subjects), and fewer subjects in the perampanel group had clinically notable weight decreases (1 [2.9%] subject) compared with the placebo group (3 [8.3%] subjects).

By age subgroup, a greater mean increase in weight in the perampanel group compared with the placebo group was most apparent in the adolescents. The mean change from baseline to end of treatment by age subgroups were as follows:

- Children: similar weight increase in perampanel (1.34 kg) and placebo (1.06 kg)
- Adolescent: greater weight increase in perampanel (2.78 kg) versus placebo (0.37 kg)
- Adult: similar weight increase in perampanel (1.27 kg) and placebo (1.56 kg)

CHMP's overall Conclusion on study 338

From an efficacy aspect, subjects treated with perampanel showed a numerically greater decrease in median drop seizure frequency (primary endpoint) compared with the placebo group, which did not reach statistical significance. The same trend of some improvement in the perampanel groups compared to placebo is overall observed for the key secondary endpoints during the core study. These data are however only descriptive and no robust / relevant conclusion can be drawn from these results. The Applicant considers that the treatment difference for the primary endpoint did not reach statistical significance given the reduced sample size due to early study termination and lower power to detect treatment effects. Although not requested, conducting a similar study in more favourable conditions would allow to confirm this assumption.

From a safety aspect, the overall TEAEs reported during treatment with perampanel were consistent with the known safety profile for perampanel. The most common (≥10% in the perampanel group and greater incidence than in the placebo group) TEAEs during the core Study were somnolence, irritability, upper respiratory tract infection, and decreased appetite. Few subjects discontinued due to TEAEs (3 [8.8%] subjects in the perampanel group versus 0 subjects in the placebo group). There were no deaths during the core study, but 2 deaths both unrelated occurred during the Extension Phase. No TEAEs of suicidal ideation/behavior were reported, and no subjects had a positive score based on C-SSRS assessment. No clinically notable effects were observed on laboratory assessments or vital signs. Some clarifications are requested regarding the outcome of the SAE, the TEAEs related to cardiac and ECG abnormalities and the relevance to include in the PI the AE agitation considered by the investigator to be related to study drug. The TEAE related to status epilepticus/convulsions are followed in the PSUR and the PI may be updated if relevant.

1.3.3. Discussion on clinical aspects

EISAI submitted final study results and report related to paediatric population for Study E2007-G000-338 (referred to as Study 338). This study 338 was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study (Core Study) followed by an Extension Phase (Extension A and Extension B) of perampanel as adjunctive therapy in subjects 2 years of age and older with inadequately controlled seizures associated with Lennox-Gastaut Syndrome (LGS). The study enrolled 70 subjects (planned 142 subjects, (71 placebo, 71 perampanel)) of which 34 were treated with perampanel in the study, 22 of whom were less than 18 years of age. A total of 61 subjects completed the Core Study (29 perampanel, of whom 20 were less than 18 years of age), and 58 of them entered Extension A (40 were less than 18 years of age). A total of 32 subjects completed Extension A, (23 were less than 18 years of age); and 13 of them entered Extension B (9 were less than 18 years of age).

The primary objective of the study was to demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in reducing the incidence of drop seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS.

The results of Study 338 showed that perampanel as adjunctive treatment was generally well tolerated and safe in subjects with inadequately controlled seizures associated with LGS. Perampanel treatment resulted in a numerically greater decrease from baseline in median drop seizure frequency and total seizure frequency compared with placebo, and resulted in a numerically greater percentage of subjects with a 50% reduction in drop and total seizures.

Due to the termination of the study by the sponsor and the resulting reduction in sample size, the study had lower power to detect a statistically significant difference between treatment groups. To

confirm this assumption, the Applicant is invited to conduct the same trial in more favourable conditions.

The adverse events (AEs) described in Study 338 are consistent with the known safety profile for perampanel in the population studied (children, adolescent, and adult subjects). A review of these AEs does not suggest new or unexpected information. The most common (≥10% in the perampanel group and greater incidence than in the placebo group) TEAEs during the core Study were somnolence, irritability, upper respiratory tract infection, and decreased appetite. There were no deaths during the core study, but 2 deaths both unrelated occurred during the Extension Phase. No TEAEs of suicidal ideation/behavior were reported, and no subjects had a positive score based on C-SSRS assessment. No clinically notable effects were observed on laboratory assessments or vital signs. Some clarifications are requested regarding the outcome of the SAE, the TEAEs related to cardiac and ECG abnormalities and the relevance to include in the PI the AE agitation considered by the investigator to be related to study drug. The TEAE related to status epilepticus/convulsions are followed in the PSUR and the PI may be updated if relevant.

On the basis of a review of the AEs and TEAEs in Study 338, no additional changes to the Summary of Product Characteristics (SmPC) or regional product labelling safety information are requested by the Applicant. The data submitted do not influence the benefit risk balance for perampanel. Perampanel continues to possess a favorable benefit-risk profile for the treatment of indicated seizure types.

2. Rapporteur's CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required. Following assessment of the MAH responses to RSI, the PAM can be considered as fulfilled.

3. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The Applicant should discuss the relevance to include in the PI agitation considered by the investigator to be related to study drug.
2. The Applicant is requested to comment the outcome of each of the 6 SAE during the core study and 11 SAE during the Extension Phase.
3. The Applicant is requested to provide an assessment of the TEAEs related to cardiac and ECG abnormalities that occurred in the core study and in the Extension phase.

The timetable is a 30 day response timetable without clock stop.

MAH responses to Request for supplementary information

1/The Applicant should discuss the relevance to include in the PI agitation considered by the investigator to be related to study drug.

Applicant's Response

Eisai does not believe that agitation needs to be included in the product label considering the following:

1. Lennox-Gastaut syndrome (LGS) is a severe epileptic encephalopathy where intellectual development is often delayed and behavioral problems (including agitation and aggression) are common.
   Given the disease background and comorbidities, there may be a natural tendency of a higher reporting rate of agitation as an adverse event (AE) in this patient population, regardless of whether the patient was receiving perampanel or not.
   During the blinded randomization phase in Study 338, the incidence of agitation was higher in placebo group relative to perampanel treatment group. Specifically, there were 2 subjects (2/36 [5.6%]) who experienced agitation while receiving placebo, but only 1 subject (1/34 [2.9%]) who experienced agitation while receiving perampanel. In the overall study (Core Study and Extension Phase), the overall incidence of agitation remained low with agitation reported by 3 subjects (3/58 [5.2%]) while receiving perampanel treatment.

2. Due to the small sample size, the occurrence of an event even in a single subject will result in an incidence rate of approximately 2.9% that falls within the definition of "common (≥ 1/100 to < 1/10)" category even though the true incidence may be low.

3. In a Phase 3 clinical study (Study E2007-G000-332) of similar sample size in patients with primary generalized tonic-clonic seizures of idiopathic generalized epilepsy, agitation was reported in 2 subjects (2/82 [2.4%]) in the placebo group, but 1 subject (1/81 [1.2%]) in the perampanel treatment group during the blinded randomization phase.
   The incidence of agitation remained low with agitation reported by 3 subjects (3/114 [2.6%]) during Extension Phase where all subjects received perampanel treatment.
   The safety evaluation in Study 332, which is similar to that observed in the LGS Study 338, was found acceptable to the EMA without agitation being listed in the SmPC.

The SmPC has warnings for aggression and notes that significant changes in mood or patterns of behavior have been observed with perampanel therapy (Section 4.4). Considering the language is already included in the product label, this review based on cases of agitation does not support an update to the product information at this time.

CHMP's comment:

The provided Applicant's arguments (epileptic encephalopathy showing per se behavioral problems including agitation and aggression; during the blinded randomization phase in Study 338, incidence of agitation higher in placebo group relative to perampanel treatment group; safety evaluation in this study 338 similar to that of study 332 in PGTCS of IGE, without the addition of the AE agitation in the SmPC; incidence of this AE remaining low in the extension phase of study) are considered acceptable and therefore the addition of the AE agitation in the PI is not considered relevant.

Issue solved.

2/The Applicant is requested to comment the outcome of each of the 6 SAE during the core study and 11 SAE during the Extension Phase.

Applicant's Response

During the core study, there were 6 subjects (3 children, 1 adolescent, and 2 adults) who experienced 8 serious adverse events (SAEs) while receiving or following perampanel treatment. The events are summarized below in Table 1 and case narratives are attached in Appendix 1.

The outcomes of the 8 SAEs were as follow: 7 resolved and 1 not resolved at the time of the study report. Of the 7 events which resolved, there were 5 events which resolved without changes to perampanel dose or treatment interruption, indicative of a negative dechallenge.

One event resolved after perampanel was discontinued, and the other resolved after perampanel dose was reduced (positive dechallenge).

Table 1 Listing of Treatment-Emergent Serious Adverse Events During the Core Study

Subject ID Age(yr), Sex, Race	Study Phase/ Period of AE Onset	Dose at or prior to AE Onset/Days Since Last Dose to AE Onset	Duration of treatment[a] (Days)	System Organ Class/ Preferred Term/ Investigator Term	AE Start Date /Study Day – AE Stop Date /Study Day	AE Dura-tion (Days)	Seri-ous/ crit-eria	Associated with special situations ?	Severity/ Relation-ship to Study drug	Study drug action taken/ other action taken	Outcome/ TEAE?
48311001 2, M, W	Core Study/ Maintena nce	8 mg / 37	131	Infections and infestations/ Respiratory syncytial virus infection/ RSV Infection	2018-01-01 / 117 – 2018-01-04 / 120	4	Yes: 3	No	Severe/ No	Dose Not Changed/ Treatment Given	Recovered/ Resolved/Y
42011003 3, M, OA	Core Study/ Titratio n	6 mg / 1	137	Metabolism and nutrition disorders/ Decreased appetite/ Anorexia (Poor oral intake)	2020-01-22 / 41 – 2020-01-23 / 42	2	Yes: 3	No	Mild/ Yes	Dose Reduced/ Treatment Given	Recovered/ Resolved/Y
48351003 8, M, W	Core Study/ Maintena nce	3 mg / 1	131	Nervous system disorders/ Seizure/ Breakthrough Seizures	2017-09-12 / 96 – 2017-09-14 / 98	3	Yes: 3	No	Moderate/ No	Dose Not Changed/ None	Recovered/ Resolved/Y
	Core Study/ Maintena nce	3 mg / 1	131	Psychiatric disorders/ Mental status changes/ Mental status change with unknown cause	2017-09-12 / 96 – 2017-09-14 / 98	3	Yes: 3	No	Moderate/ No	Dose Not Changed/ None	Recovered/ Resolved/Y
	Core Study/ Maintena nce	3 mg / 1	131	Gastrointestinal disorders/ Vomiting/ worsening emesis	2017-09-29 / 113 – 2017-10-06 / 120	8	Yes: 3	No	Moderate/ No	Dose Not Changed/ None	Recovered/ Resolved/Y
48091004 12, F, W	Core Study/ Titratio n	4 mg / 1	63	Respiratory, thoracic and mediastinal disorders/ Respiratory distress/ Respiratory Distress	2017-09-25 / 41 – 2017-10-02 / 48	8	Yes: 2, 3	No	Severe/ No	Dose Not Changed/ Treatment Given	Recovered/ Resolved/Y
49061003 34, F, J	Core Study/ Titratio n	6 mg / 1	73	Nervous system disorders/ Epilepsy/ Worsening epileptic seizure	2020-03-09 / 22 – --		Yes: 3	No	Moderate/ Yes	Drug Withdrawn/ Multiple	Not Recovered/ Not Resolved/Y

Subject ID Age(yr), Sex, Race	Study Phase/ Period of AE Onset	Dose at or prior to AE Onset/Days Since Last Dose to AE Onset	Duration of treatment[a] (Days)	System Organ Class/ Preferred Term/ Investigator Term	AE Start Date /Study Day – AE Stop Date /Study Day	AE Dura-tion (Days)	Seri-ous/ crit-eria	Associated with special situations ?	Severity/ Relation-ship to Study drug	Study drug action taken/ other action taken	Outcome/ TEAE?
49041003 39, F, J	Core Study/ Maintena nce	6 mg / 1	52	Metabolism and nutrition disorders/ Dehydration/ dehydration	2019-09-13 / 47 – 2019-09-19 / 53	7	Yes: 3	No	Moderate/ Yes	Drug Withdrawn/ Multiple	Recovered/ Resolved/Y

Source: Listing 16.2.7
TEAE = Treatment-Emergent Adverse Event
A TEAE is defined as an adverse event with an onset date, or a worsening in severity from baseline (pre-treatment), on or after the first dose of study drug up to 28 days following study drug discontinuation.
a: Duration of treatment = date of last dose of study drug - date of first dose of study drug + 1. NA means that subject never took study drug.
MedDRA Version 24.0

During the Extension Phase, there were a total of 11 subjects (8 children, 1 adolescent, and 2 adults) who developed a total of 22 SAEs (18 events during the extension treatment period and 4 during the no-treatment follow-up period). The events are summarized below in Table 2 and case narratives are attached in Appendix 2.

During the extension treatment period, the outcomes of the 18 SAEs were as follow: 17 resolved without changes to perampanel dose or treatment interruption and 1 not resolved at the time of the study report.

During the extension follow-up period, the outcomes of the 4 SAEs were as follows: 2 events resolved with medical treatment and 2 with a fatal outcome (sudden unexplained death in epilepsy [SUDEP] in one subject and complications due to chromosomal abnormality [trisomy 4p plus monosomy 18p] in another subject; both events were deemed unrelated to perampanel).

Table 2 Listing of Treatment-Emergent Serious Adverse Events During Extension Phase

Subject ID Age(yr), Sex, Race	Study Phase/ Period of AE Onset	Dose at or prior to AE Onset/Days Since Last Dose to AE Onset	Duration of treatment[a] (Days)	System Organ Class/ Preferred Term/ Investigator Term	AE Start Date /Study Day - AE Stop Date /Study Day	AE Dura-tion (Days)	Seri-ous/ crit-eria	Associated with special situations ?	Severity/Re lation-ship to Study drug	Study drug action taken/ other action taken	Outcome/ TEAE?
48311001 2, M, W	Extensi on Phase/ Ext Mainten ance	8 mg / 1	131	Infections and infestations/ Pneumonia/ pneumonia	2018-09-10 / 369 - 2018-09-12 / 371	3	Yes: 3	No	Severe/ No	Dose Not Changed/ Treatment Given	Recovered/R esolved/Y
	Extensi on Phase/ Ext Mainten ance	5.5 mg / 1	131	Nervous system disorders/ Seizure/ seizure exacerbation	2018-10-16 / 405 - 2018-10-20 / 409	5	Yes: 3	No	Severe/ No	Dose Not Changed/ None	Recovered/R esolved/Y
49081001 2, M, J	Extensi on Phase/ Ext Conversi on	2 mg / 1	125	Respiratory, thoracic and mediastinal disorders/ Sleep apnoea syndrome/ sleep apnea	2021-01-25 / 130 - --		Yes: 3	No	Mild/ Yes	Dose Reduced/ None	Not Recovered/N ot Resolved/Y
	Extensi on Phase/ Ext Conversi on	6 mg / 1	125	Infections and infestations/ Pneumonia/ pneumonia	2021-02-07 / 143 - 2021-02-20 / 156	14	Yes: 3	No	Moderate/ No	Dose Not Changed/ Treatment Given	Recovered/R esolved/Y
	Extensi on Phase/ Ext Mainten ance	6 mg / 1	125	Nervous system disorders/ Quadriplegia/ SUSPECTED AGGRAVATION OF SPASTIC QUADRIPLEGIA	2021-03-15 / 179 - 2021-03-30 / 194	16	Yes: 3	No	Mild/ No	Dose Not Changed/ Treatment Given	Recovered/R esolved/Y

Subject ID Age(yr), Sex, Race	Study Phase/ Period of AE Onset	Dose at or prior to AE Onset/Days Since Last Dose to AE Onset	Duration of treatment[a] (Days)	System Organ Class/ Preferred Term/ Investigator Term	AE Start Date /Study Day - AE Stop Date /Study Day	AE Dura-tion (Days)	Seri-ous/ crit-eria	Associated with special situations ?	Severity/Re lation-ship to Study drug	Study drug action taken/ other action taken	Outcome/ TEAE?
42011003 3, M, OA	Extensi on Phase/ Ext Mainten ance	6 mg / 1	137	Infections and infestations/ Lower respiratory tract infection viral/ Suspicious of acute viral lower respiratory infection	2020-06-22 / 193 - 2020-06-30 / 201	9	Yes: 3	No	Moderate/ No	Dose Not Changed/ Treatment Given	Recovered/R esolved/Y
48071007 5, F, B	Extensi on Phase/ Ext Mainten ance	8 mg / 1	119	Respiratory, thoracic and mediastinal disorders/ Asthma/ Acute asthma exacerbation	2019-12-20 / 292 - 2019-12-23 / 295	4	Yes: 3	No	Severe/ No	Dose Not Changed/ Treatment Given	Recovered/R esolved/Y
	Extensi on Phase/ Ext Mainten ance	8 mg / 1	119	Blood and lymphatic system disorders/ Microcytic anaemia/ Microcytic Anemia	2019-12-20 / 292 - 2019-12-23 / 295	4	Yes: 3	No	Severe/ No	Dose Not Changed/ Treatment Given	Recovered/R esolved/Y
	Extensi on Phase/ Ext Mainten ance	8 mg / 1	119	Gastrointestinal disorders/ Haematemesis/ hematemesis	2019-12-20 / 292 - 2019-12-23 / 295	4	Yes: 3	No	Severe/ No	Dose Not Changed/ Treatment Given	Recovered/R esolved/Y
32011001 6, M, W	Extensi on Phase/ Ext Mainten ance	2 mg / 1	133	Infections and infestations/ Bronchitis/ acute bronchitis	2020-10-25 / 263 - 2020-10-29 / 267	5	Yes: 3	No	Severe/ No	Dose Not Changed/ Treatment Given	Recovered/R esolved/Y

Subject ID Age(yr), Sex, Race	Study Phase/ Period of AE Onset	Dose at or prior to AE Onset/Days Since Last Dose to AE Onset	Duration of treatment[a] (Days)	System Organ Class/ Preferred Term/ Investigator Term	AE Start Date /Study Day - AE Stop Date /Study Day	AE Dura-tion (Days)	Seri-ous/ crit-eria	Associated with special situations ?	Severity/Re lation-ship to Study drug	Study drug action taken/ other action taken	Outcome/ TEAE?
48351003 8, M, W	Extensi on Phase/ Ext Mainten ance	2 mg / 1	131	Nervous system disorders/ Lethargy/ Lethargy	2018-01-30 / 236 - 2018-02-18 / 255	20	Yes: 3	No	Moderate/ No	Dose Not Changed/ None	Recovered/Re solved/Y
	Extensi on Phase/ Ext Mainten ance	2 mg / 1	131	Infections and infestations/ Influenza/ Influenza A	2018-02-14 / 251 - 2018-02-18 / 255	5	Yes: 3	No	Moderate/ No	Dose Not Changed/ None	Recovered/Re solved/Y
49011001 9, M, J	Extensi on Phase/ Ext Conversion	4 mg / 1	130	Infections and infestations/ Influenza/ Influenza B virus infection	2018-01-14 / 160 - 2018-01-20 / 166	7	Yes: 3	No	Moderate/ No	Dose Not Changed/ Treatment Given	Recovered/Re solved/Y
49071002 9, F, J	Extensi on Phase/ Extensi on B	4 mg / 1	126	Nervous system disorders/ Seizure cluster/ Seizure cluster	2020-08-20 / 688 - 2020-11-11 / 771	84	Yes: 3	No	Moderate/ No	Dose Not Changed/ Treatment Given	Recovered/Re solved/Y
	Extensi on Phase/ Extensi on B	4 mg / 1	126	Infections and infestations/ Pneumonia/ Pneumonia	2020-08-25 / 693 - 2020-09-04 / 703	11	Yes: 3	No	Moderate/ No	Dose Not Changed/ Treatment Given	Recovered/Re solved/Y
	Extensi on Phase/ Extensi on B	4 mg / 1	126	Infections and infestations/ Sepsis/ Sepsis	2020-08-25 / 693 - 2020-09-07 / 706	14	Yes: 3	No	Moderate/ No	Dose Not Changed/ Treatment Given	Recovered/Re solved/Y

Subject ID Age(yr), Sex, Race	Study Phase/ Period of AE Onset	Dose at or prior to AE Onset/Days Since Last Dose to AE Onset	Duration of treatment[a] (Days)	System Organ Class/ Preferred Term/ Investigator Term	AE Start Date /Study Day - AE Stop Date /Study Day	AE Dura-tion (Days)	Seri-ous/ crit-eria	Associated with special situations ?	Severity/Re lation-ship to Study drug	Study drug action taken/ other action taken	Outcome/ TEAE?
49021002 17, M, J	Extensi on Phase/ Ext Conversion	8 mg / 1	119	Gastrointestinal disorders/ Dental caries/ tooth decay	2019-05-28 / 133 - 2019-05-30 / 135	3	Yes: 3	No	Moderate/ No	Dose Not Changed/ None	Recovered/Re solved/Y
	Follow-Up	2 mg / 2	119	General disorders and administration site conditions/ Sudden unexplained death in epilepsy/ SUDEP(sudden death)	2020-09-16 / 610 - 2020-09-16 / 610	1	Yes: 1	No	Severe/ No	Not Applicable / Withdrawn From Study	Fatal/Y
48481002 21, F, O	Extensi on Phase/ Ext Conversion	8 mg / 1	133	Infections and infestations/ Infected skin ulcer/ Sacral ulcer with Abscess	2021-03-25 / 163 - 2021-04-02 / 171	9	Yes: 3	No	Moderate/ No	Dose Not Changed/ Treatment Given	Recovered/Re solved/Y
48251003 23, F, W	Follow-Up	8 mg / 2	126	Gastrointestinal disorders/ Pneumatosis intestinalis/ Pneumatosis of intestines	2019-09-11 / 496 - 2019-09-11 / 496	1	Yes: 3	No	Severe/ No	Not Applicable / Treatment Given	Recovered/Re solved/Y
	Follow-Up	8 mg / 2	126	Respiratory, thoracic and mediastinal disorders/ Cough/ chronic cough	2019-09-11 / 496 - 2019-09-11 / 496	1	Yes: 3	No	Moderate/ No	Not Applicable / Treatment Given	Recovered/Re solved/Y
	Follow-Up	8 mg / 22	126	Congenital, familial and genetic disorders/ Cytogenetic abnormality/ Complications due to chromosomal abnormality (trisomy 4p plus monosomy 18p)	2019-10-01 / 516 - 2019-10-01 / 516	1	Yes: 1	Yes	Severe/ No	Not Applicable / None	Fatal/Y

Source: Listing 16.2.7
TEAE = Treatment-Emergent Adverse Event
A TEAE is defined as an adverse event with an onset date, or a worsening in severity from baseline (pre-treatment), on or after the first dose of study drug up to 28 days following study drug discontinuation.
a: Duration of treatment = date of last dose of study drug - date of first dose of study drug + 1. NA means that subject never took study drug.
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CHMP's comment:

During the core study, 6 subjects experienced 8 SAE while receiving or following perampanel treatment. 7 SAE resolved and 1 SAE was not resolved. This last SAE was a worsening of epileptic seizure in an, 34 years of age considered related to the study drug by the investigator and of moderate severity. The subject discontinued the study due to this SAE.

During the extension study, 11 subjects (mostly children) developed a total of 22 SAEs (of whom 4 during the no-treatment follow-up period). 17 SAE resolved without changes to perampanel dose or treatment interruption and 1 SAE was not resolved (sleep apnea syndrome related to study drug in patient an, 2 years of age, who discontinued the treatment and the study which was terminated). During the extension follow-up, among the 4 SAE, 2 events resolved and 2 SAE showed a fatal outcome (1 SUDEP, 1 complications due to chromosomal abnormality [trisomy 4p plus monosomy 18p]. Both deaths were considered unrelated to perampanel, which is acceptable since these patients did not more receive the study treatment. Moreover, SUDEP events may occur even under treatment and details of the death due to chromosomal abnormality complications were not available since no autopsy was performed.

The Applicant commented the outcome of each of the SAE during the core study and SAE during the Extension Phase without any specific signal or the need of an additional statement in the PI which is considered acceptable.

Issue solved.

3/The Applicant is requested to provide an assessment of the TEAEs related to cardiac and ECG abnormalities that occurred in the core study and in the Extension phase.

Applicant's Response

Throughout the study, TEAEs related to cardiac and ECG abnormalities were reported in a total of 5 subjects (1 child, 1 adolescent, and 3 adults) who experienced 7 adverse events while receiving perampanel. Of these, 3 subjects experienced 5 events (peripheral swelling [2], cardiac arrest [1], mental status changes [1], and sinus tachycardia [1]) during the Core Study. Two subjects experienced 2 events (orthostatic hypotension [1] and tachycardia [1]) during the Extension Phase. Note that the summary table for the Extension Phase was generated based on cumulative data (i.e., Core Study and Extension Phase) collected from those subjects who completed Core Study and entered Extension Phase. That is, a subject with TEAE(s) of interest occurring during Core Study (even though there was no events during Extension Phase) would appear under both the Core Study summary table and the Extension Phase summary table in the Clinical Study Report. The events are summarized below in Table 3 and Table 4 with case narratives attached in Appendix 3.

A review of the cases noted that the reports of cardiac and ECG abnormalities do not suggest a causal relationship of the event to perampanel, either due to insufficient information to provide an assessment, or due to the presence of confounders including prior history of that could be contributory. All the events were considered not related to perampanel by the investigator. Additionally, all the events resolved with no interruption nor changes to perampanel dose, suggestive of a negative dechallenge.

Table 3 Events of Cardiac and ECG abnormalities

Subject ID	Age/ Gender	Event preferred term (PT) Name	Action taken with drug	Event Outcome	Medical history	Concomitant antiepileptics meds	Comment
48351003	8 Years/ Male	Mental status changes	Dose maintained	Resolved	Achlorhydria Gastrostomy Vitamin B complex deficiency Congenital central nervous system anomaly Cerebral palsy Microcephaly	rufinamide valproate semisodium zonisamide diazepam	The subject experienced mental status changes and breakthrough seizure, requiring hospitalization. There was generalized slowing and generalized very high voltage epileptiform activity consistent with Lennox-Gastaut syndrome. It was reported that the subject was prone to altered mental status of unclear cause. The acute increase in seizure activity was assessed to be related to the viral gastroenteritis. Perampanel was continued. Event resolved.
48091004	12 Years/ Female	Cardiac arrest Sinus tachycardia Peripheral Swelling	Dose maintained	Resolved	Nausea Cerebral cyst Seasonal allergy Spinal fusion surgery Hip arthroplasty Femur fracture Scoliosis Myringotomy Microcephaly Cerebral palsy Congenital central nervous system anomaly Gastrooesophageal reflux disease	zonisamide levetiracetam clonazepam diazepam	The subject experienced respiratory distress, which required hospitalization and considered life threatening by the investigator. The subject was intubated and placed on a ventilator and developed endotracheal intubation complication of atrophic pharyngitis, cardiac arrest, and sinus tachycardia. Perampanel was continued and the events recovered. The events, cardiac arrest and sinus tachycardia were considered to be not related to perampanel and noted the respiratory arrest might have led to all other complications including cardiac arrest by the investigator.
48481002	21 Years / Female	Peripheral Swelling	Dose maintained	Resolved	Developmental delay Intellectual disability	valproic acid levetiracetam	The subject experienced peripheral swelling. Perampanel was continued. Event resolved. The event was not related to perampanel. Perampanel was continued. Event resolved. The event was not related to perampanel.
48481001	23 Years / Female	Tachycardia	Dose maintained	Resolved	Intellectual disability Mononucleosis Pneumonia Constipation		The subject experienced tachycardia. Perampanel was continued. Event resolved. The event was not related to perampanel.
48131002	35 Years / Male	Orthostatic hypotension	Dose maintained	Resolved	Gastroesophageal reflux disease Anxiety disorder Depression Type 2 diabetes mellitus Corpus callosotomy	rufinamide lamotrigine valproate	The subject experienced the event. Perampanel was continued. Event recovered. Of note, the subject had elevated cholesterol levels during the study.

Table 4 Listing of Treatment-Emergent Adverse Events by MedDRA SMQ[a] Terms Related to Cardiac and ECG Events Throughout the Core Study and Extension Phase

Subject ID Age(yr), Sex, Race	Study Phase/ Period of AE Onset	Dose at or prior to AE Onset/Days Since Last Dose to AE Onset	Duration of treatment[b] (Days)	System Organ Class/ Preferred Term/ Investigator Term	AE Start Date /Study Day - AE Stop Date /Study Day	AE Duration (Days)	Serious/ criteria	Associated with special situations?	Severity/ Relationship to Study drug	Study drug action taken/ other action taken	Outcome/ TEAE?
48351003 8, M, W	Core Study/ Maintenance	3 mg / 1	131	General disorders and administration site conditions/ Peripheral swelling/ Generalized swelling of legs	2017-08-03 / 56 / 56 - 2017-09-23 / 107 / 107	52	No	No	MILD/ No	Dose Not Changed/ None	Recovered /Resolved /Y
	Core Study/ Maintenance	3 mg / 1	131	Psychiatric disorders/ Mental status changes/ Mental status change with unknown cause	2017-09-12 / 96 / 96 - 2017-09-14 / 98 / 98	3	Yes: 3	No	MODERATE/ No	Dose Not Changed/ None	Recovered /Resolved /Y
48091004 12, F, W	Core Study/ Titration	4 mg / 1	63	Cardiac disorders/ Cardiac arrest/ Cardiac arrest	2017-09-25 / 41 - 2017-10-02 / 48	8	No	No	SEVERE/ No	Dose Not Changed/ Treatment Given	Recovered /Resolved /Y
	Core Study/ Titration	4 mg / 1	63	Cardiac disorders/ Sinus tachycardia/ Sinus tachycardia	2017-09-25 / 41 - 2017-10-02 / 48	8	No	No	MODERATE/ No	Dose Not Changed/ None	Recovered /Resolved /Y
48481002 21, F, O	Core Study/ Titration	8 mg / 1	133	General disorders and administration site conditions/ Peripheral swelling/ swollen hands	2020-11-15 / 33 / 33 - 2020-11-17 / 35 / 35	3	No	No	MODERATE/ No	Dose Not Changed/ Treatment Given	Recovered /Resolved /Y

Subject ID Age(yr), Sex, Race	Study Phase/ Period of AE Onset	Dose at or prior to AE Onset/Days Since Last Dose to AE Onset	Duration of treatment[b] (Days)	System Organ Class/ Preferred Term/ Investigator Term	AE Start Date /Study Day - AE Stop Date /Study Day	AE Duration (Days)	Serious/ criteria	Associated with special situations?	Severity/ Relationship to Study drug	Study drug action taken/ other action taken	Outcome/ TEAE?
48481001 23, F, OA	Extension Phase/ Ext Conversion	8 mg / 1	119	Cardiac disorders/ Tachycardia/ tachycardia	2021-02-12/ 155 / 155 - 2021-02-12 / 155 / 155	1	No	No	MILD/ No	Dose Not Changed/ None	Recovered /Resolved /Y
48131002 35, M, W	Extension Phase/ Ext Conversion	8 mg / 1	126	Vascular disorders/ Orthostatic hypotension/ orthostatic hypotension	2017-09-07 / 169 / 43 - 2017-09-07 / 169 / 43	1	No	No	MODERATE/ No	Dose Not Changed/ Treatment Given	Recovered /Resolved /Y

Source: ADSL, ADAE
a: SMQ of Cardiac arrhythmia terms(incl bradyarrhythmias and tachyarrhythmias), Arrhythmia related investigations, signs and symptoms, Cardiac failure, Cardiomyopathy, Ischaemic heart disease, Torsade de pointes/QT prolongation
b: Date of last dose of study drug - date of first dose of study drug + 1. NA means that subject never took study drug.
Age is age at Informed Consent; M = Male, F = Female; W = White, B = Black or African American, J = Japanese, C = Chinese, OA = Other Asian,
P = Native Hawaiian or other Pacific Islander, N = American Indian or Alaska Native, O = Other.
Seriousness Criteria: 1=Death, 2=Life threatening, 3=Requires inpatient hospitalization or prolongation of exiting hospitalization, 4=Persistent or significant disability or incapacity, 5=Congenital anomaly/birth defect, 6=Important medical event
TEAE = Treatment-emergent adverse event
MedDRA Version 24.0

CHMP's comment:

The Applicant provided a review of the TEAEs related to cardiac and ECG abnormalities that occurred in the core study and in the extension phase.

The reports of cardiac and ECG abnormalities do not suggest a causal relationship of the event to perampanel, in some cases due to insufficient information to allow a thorough assessment, in other cases due to the presence of confounders/comorbidities (prior history).The events were overall considered not related to perampanel by the investigator. Additionally, all the events resolved with no interruption nor changes to perampanel dose.

Regarding the event of cardiac arrest at Day 63 in a 12 years old female during the core study while receiving 4 mg perampanel, the subject experienced respiratory distress, which required hospitalization considered life threatening by the investigator. The subject was intubated and placed on

a ventilator and developed endotracheal intubation complication of atrophic pharyngitis, cardiac arrest, and sinus tachycardia. Perampanel was continued and the events recovered. The events, cardiac arrest and sinus tachycardia were considered to be not related to perampanel. It was considered that the respiratory arrest might have led to all other complications including cardiac arrest by the investigator.

Issue solved.

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

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report

Clinical studies

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report