EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 February 2026
EMADOC-1700519818-3036818
Human Medicines Division

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

Fycompa

Perampanel

Procedure no: EMA/PAM/0000307849

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	**Description**	**Planned date**	**Actual Date**
☐	Submission date	21 October 2025	21 October 2025
☐	Start date	1 December 2025	1 December 2025
☐	CHMP Rapporteur AR	5 January 2026	6 January 2026
☐	CHMP comments	19 January 2026	19 January 2026
☐	Updated CHMP Rapporteur AR	22 January 2026	22 January 2026
☐	RSI	29 January 2026	29 January 2026
☐	MAH's responses to RSI	3 February 2026	3 February 2026
☐	Start date	4 February 2026	4 February 2026
☐	CHMP Rapporteur AR	11 February 2026	10 February 2026
☐	CHMP comments	16 February 2026	16 February 2026
☐	Updated CHMP Rapporteur AR	19 February 2026	19 February 2026
☒	CHMP outcome	26 February 2026	26 February 2026

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1. Introduction

On 21 October 2025, the MAH submitted a completed paediatric study for Fycompa, 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 the final Clinical Study Report for Study E2007-M081-515 (Study 515) that was completed on 25 June 2025. Study 515 is an open-label, observational, prospective, multicenter study to evaluate the long-term efficacy and safety of perampanel as monotherapy in subjects age 4 years and older with focal onset seizures, carried out in Japan.

This study enrolled 61 patients, of whom 15 were less than 18 years of age. In the context of this PAM P46, we will focus only on pediatric population.

The primary objective of this study was to evaluate 24-month seizure freedom in response to perampanel monotherapy in patients 4 years of age and older with FOS.

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.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study E2007-M081-515 (Study 515) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The investigational medicinal product tested in Study 515 in patients aged 4 years and older was Fycompa and was administered at the physician’s discretion based on the dosage and administration in the package insert.

CHMP comment:

The report does not specify which pharmaceutical formulation was used in the study. ***RSI****: The Applicant is requested to indicate which pharmaceutical formulation of Fycompa was used during the study.*

The Applicant clarified in the RSI that both tablet or fine granule formulation was allowed.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study E2007-M081-515 (Study 515)

2.3.2. Clinical study 515

Description

Study 515 was an Eisai-sponsored, open-label, single-arm, multicentre, exploratory and observational study. The purpose of this study was to contribute to the establishment of clinical evidence on the effect of perampanel (PER) by accumulating data on long-term seizure suppression effects and safety, as well as changes in quality of life (QOL) related to emotional, social, and employment/school attendance. Participants included patients aged 4 years or older with a diagnosis of epilepsy with focal onset seizure (FOS) who started monotherapy with perampanel.

The study period was April 2021 to June 2025 (from the date of approval by the ethical review board to the fixation of the clinical study report) and was conducted in Japan. Enrolment period was from May 2021 to June 2022 (1 year and 2 months), and observation period from May 2021 to December 2024 (treatment period for each participant: up to 30 months).

Each participant received a research tablet for off-site assessments including seizure records and QOL questionnaires. On-site assessments included concomitant medications and adverse events at visits for routine medical care.

The drug should be administered at the physician's discretion based on the dosage and administration in the package insert.

Methods

Study participants

Participants included patients aged 4 years or older with a diagnosis of epilepsy with focal onset seizure (FOS) who started monotherapy with perampanel.

- *Inclusion criteria:*

1) Patients aged 4 years or older who can provide informed consent (or their legal representative if the patient is a minor)
2) Patients who have received a diagnosis of epilepsy with focal onset seizure as defined in the International League Against Epilepsy Classification (2017)

3) Newly diagnosed treatment-naive or recurrent patients. For patients with recurrence, those who have recurrence at least 2 years after the end of the last ASM treatment
4) Patients who start a monotherapy with PER

- *Exclusion criteria:*

1) Patients who have used an ASM (including a rescue drug) for longer than 2 weeks in total within 2 years
2) Patients previously treated with PER
3) Patients with a history of hypersensitivity to any component of PER (tablet, fine granules) (including excipients)
4) Patients with severe hepatic impairment (Child-Pugh Class C)
5) Patients who have participated in other studies and used an investigational drug or investigational device within 4 weeks of the first dose of PER
6) Patients who are judged by the investigator/sub-investigator to be ineligible

CHMP comment:

Only patients starting monotherapy with perampanel have been included in this Study. Of note, Fycompa is approved in the EU only as adjunctive treatment.

Treatments

The drug should be administered at the physician's discretion based on the dosage and administration in the package insert.

Upon electronic or written informed consent, the participant will receive the research tablet. Each participant will complete the seizure record, QOL questionnaires, and adherence using the research tablet. The investigator/sub-investigator will check concomitant medications and adverse events with participants at their visit for routine medical care.

Objective

To evaluate the efficacy and safety of PER used in anti-seizure medications (ASM) - treatment naïve patients with epilepsy. The purpose of Study 515 was to contribute to the establishment of clinical evidence on the effect of perampanel by accumulating data on long-term seizure suppression effects and safety, as well as changes in quality of life (QOL) related to emotional, social, and employment/school attendance.

Outcomes/endpoints

- *Primary endpoint:*

Seizure freedom rate at Month 24 (Months 18-24)

- *Secondary endpoints:*

1. Seizure freedom rates at Month 6 (Months 3-6), Month 12 (Months 6-12), Month 18 (Months 12-18), and Month 30 (Months 24-30)
2. Seizure freedom rate at Month 12 (Months 0-12) and Month 24 (Months 0-24)
3. PER-retention rate (at Month 6, Month 12, Month 18, Month 24, and Month 30)
4. Changes in EQ-5D-5L and PedsQL-Generic Core Scale from baseline to each evaluation time point

5. Adverse events

- *Exploratory objectives:*

1. Changes in sleep-related parameters from baseline based on data obtained in sleep assessment tests
2. PER compliance rate during the observation period
3. Factors related to efficacy (seizure freedom at Month 3, Month 12, and Month 24, etc.)

Sample size

60 patients.

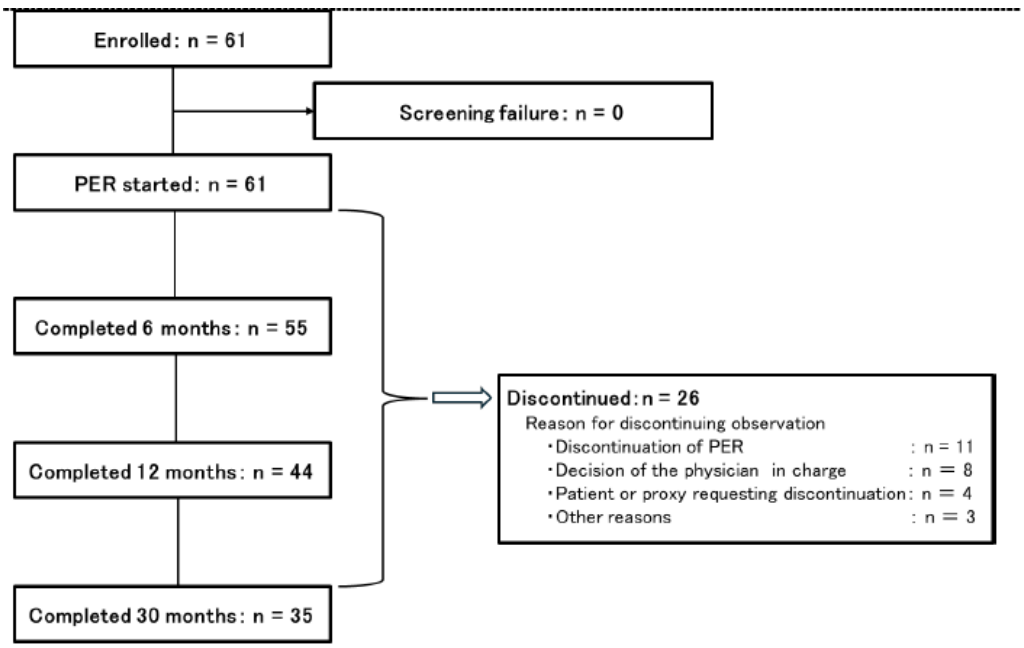
Statistical Methods

CHMP comment:

No description of statistical methods has been provided in the CSR.

Results

Figure 1: Participant flow / Recruitment / Number analysed



Between June 2021 and June 2022, 61 patients were enrolled, of whom 15 were less than 18 years of age. Of 55 patients who completed 6 months, 44 patients who completed 12 months, and 35 patients who completed 30 months, 26 patients discontinued observation. The reasons for discontinuing observation were discontinuation of PER in 11 patients, decision of the physician in charge in 8 patients (3 patients continued PER), patient or proxy requesting discontinuation in 4 patients (2 patients continued PER), and other reasons in 3 patients (1 patient continued PER).

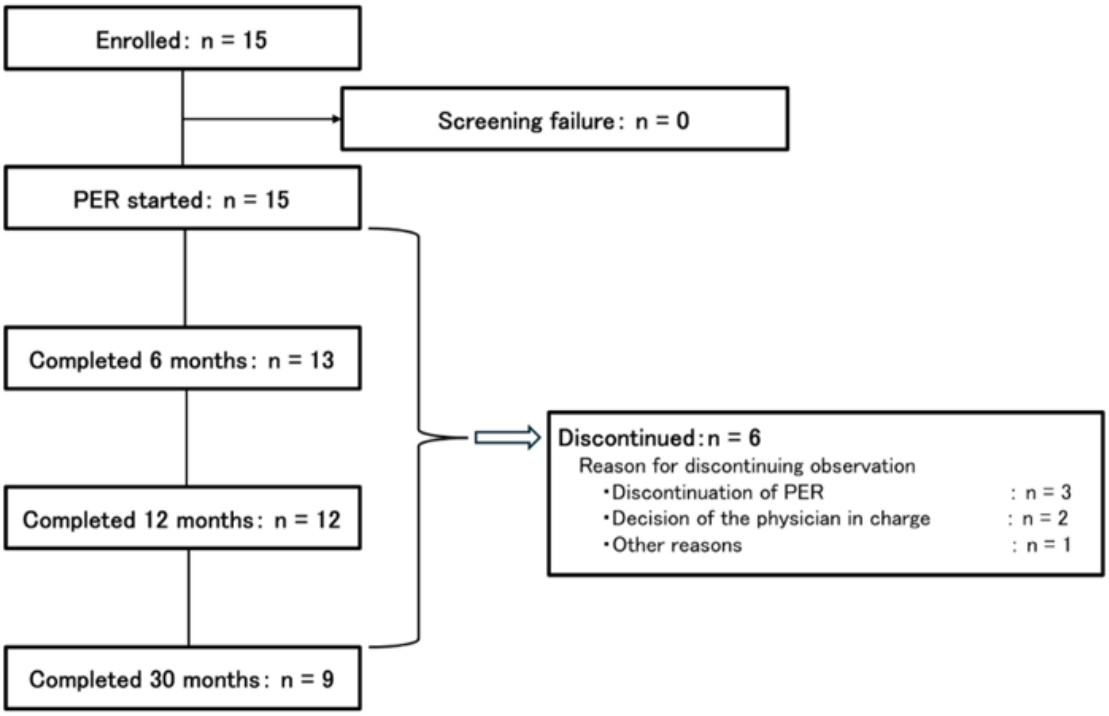
CHMP comment:

Sixty-one patients were enrolled in this study, with 15 patients less than 18 years old. Twenty-six patients were discontinued during the study.

However, no information is provided regarding discontinuation and duration of follow-up specifically in the paediatric population. ***RSI****: The Applicant is asked to provide a participant flow with only paediatric population in order to present duration of follow-up and reason of discontinuation in this specific population.*

The Applicant has provided a paediatric participant flow:

Figure 2: Study E2007-M081-515 Pediatric (<18 years) Participant Flow



During the study, 6 patients have discontinued the treatment. Thirteen patients completed 6 months, 12 the 12 months and 9 the 30 months study.

Baseline data

Of the 61 patients background, 36 (59.0%) were male; the mean age was 38.0 years (4 to 89 years); the disease duration was less than 10 years in 53 (86.9%); developmental disorders were present in 8 (13.1%); the mean seizure frequency was 0.7 (2.9) times/month; the temporal lobe was 26 (42.6%); and the frontal lobe was 16 (26.2%); seizure type were focal impaired awareness seizures (FIAS) 27 (44.3%) , focal to bilateral tonic-clonic seizures (FBTCS) 22(36.1%), and focal motor seizures (FMS) 21(34.4%) in that order; lack of sleep 13 (21.3%) was the most common seizure trigger.

Among patients less than 18 years of age, the median (min, max) age was 14.0 (4, 17) years and the mean age was 13.7 years.

The disease duration tended to be longer in the group aged 18 to < 65 years (mean 5.9 years, median 1.5 years (0 to 40 years)) than in the group aged < 18 years (mean 1.4 years, median 0.5 years (0 to 5 years)); and in the group aged ≥ 65 years (mean 2.4 years, median 0.7 years (0 to 10 years)). In the group aged < 18 years, the incidence of complicated developmental disorder was 40.0%, which was higher than in the group aged 18 to < 65 years (5.6%) and in the group aged ≥ 65 years (0.0%). In the group aged < 18 years, the average seizure frequency was 0.6 times/month, which was lower than in the group aged 18 to < 65 years (3.6 times/month) and in the group aged ≥ 65 years (3.8 times/month). The frontal lobe was the most common (46.7%) in the group aged <18 years, but the temporal lobe was the most common in the group aged 18 to < 65 years and the group aged ≥ 65 years (44.4% and 80.0%, respectively). In the seizure type, FIAS were the most common (50.0%) in the group aged 18 to < 65 years and the group aged ≥ 65 years, respectively. In the group aged < 18 years, FBTCS (46.7%), and FMS (40.0%) were the most common. In the seizure trigger, lack of sleep was the most common (40.0%) in the group aged <18 years, compared with the group aged 18 to < 65 years (16.7%) and the group aged ≥ 65 years (10.0%).

In the group aged < 18 years, the initial dose was < 2 mg in 6 patients (40.0%) and 2 mg in 9 patients (60.0%), the modal dose was 4.0 mg in the median and 3.5 mg in the mean, and less than 4mg was in 7 of 15 patients (46.6%). ASM was added in 4 patients (26.7%). All patients received 1 additional drug, lacosamide in 2 patients (13.3%), and levetiracetam in 1 patient (6.7%).

CHMP comment:

In pediatric patients, the median (min, max) age was 14.0 (4, 17) years and the mean age was 13.7 years. The incidence of complicated developmental disorder was 40.0% and the average seizure frequency was 0.6 times a month, with the most common seizure types were focal to bilateral tonic–clonic seizures (FBTCS) (46.7%) and focal motor seizures (FMS) (40.0%).

The initial dose was less than 2 mg in 40% of pediatric patients (6/15), and 2 mg in the other patients. The median modal dose was 4 mg, and 46.6% (7/15) patients received less than 4 mg.

As in the EU, Fycompa is approved only as adjunctive treatment, dosage cannot be compared.

Efficacy results

- *Primary endpoint*

The primary endpoint of Study 515 was to evaluate 24-month seizure freedom in response to perampanel monotherapy in patients 4 years of age and older with FOS (with or without FBTCS), and the primary endpoint was seizure freedom rate at 24 months (18 - 24 months).

The sustained seizure freedom rate was defined as: 1-1: Proportion using the total number of patients who started treatment as the denominator and the number of patients who were able to continue treatment without seizures during the evaluation period as the numerator; 1-2: Proportion using the number of patients evaluated during each period as the denominator and the number of patients who were able to continue treatment without seizures during the evaluation period as the numerator.

In the group aged < 18 years, both seizure freedom rate 1-1 (73.3% to 46.7%) and seizure freedom rate 1-2 (84.6% to 87.5%) tended to be higher than in other age groups (1-1: 52.8% to 44.4% in the group aged 18 to < 65 years, 60.0% to 40.0% in the group aged ≥ 65 years, 1-2: 65.5% to 84.2% in the group aged 18 to < 65 years, 66.7% to 57.1% in the group aged ≥ 65 years, respectively).

- *Secondary endpoints*

- Seizure freedom rate at 6 months (3-6 months), 12 months (6-12 months), 18 months (12-18 months), and 30 months (24-30 months)

The total number of patients for whom treatment was initiated as the denominator, and the number of patients who were able to continue treatment without seizures in the duration from the start of treatment to each assessment time point as the numerator.
The seizure freedom rate at 12 months was 53.3% in the group aged < 18 years, 40.0% in the group aged ≥ 65 years, and 27.8% in the group aged 18 to < 65 years. The seizure freedom rate was highest in the group receiving the seizure site of < 18 years. At 24 months, the seizure freedom rate in the group aged ≥ 65 years (40.0%) was higher than in the group aged < 18 years (33.3%) and the group aged 18 to < 65 years (19.4%).

- Kaplan-Meier analysis was used using the first seizure as an event.

The seizure freedom rate in the group aged < 18 years was 66.7% at 6 months, 60.0% at 12 months, 52.5% at 18 months, 52.5% at 24 months, and 52.5% at 30 months, which was the highest compared to the group aged 18 to < 65 years (54.0%, 40.5%, 36.5%, 36.5% and 36.5%, respectively) and the group aged ≥ 65 years (40.0%, 40.0%, 40.0%, 40.0% and 20.0%, respectively).

- EQ-5D-5L

The utility value of EQ-5D-5L was 0.8978 in the median at baseline in the group aged ≥ 18 years, lower than 1.0000 at baseline in the group aged < 18 years but maintained at 1.0000 from 1 month to 30 months in all groups.

- PedsQL

The total PedsQL score was 86.41 at baseline in the group aged < 18 years, lower than 92.39 at baseline in the group aged ≥ 18 years but remained similar from 1 month to 30 months.

The total PedsQL score from baseline to 30 months in the Children group was 70.65 to 76.63, which was lower throughout the evaluation period than in the Teens (91.30 to 100.00), Young Adults (94.57 to 97.83), and Adults (88.04 to 98.34) groups. There were no cases in the Young Children group.

The total PedsQL score from baseline to the 30 months in the Parents of Teens group (88.04 to 98.37) was higher than that in the Parents of Children group (75.00 to 88.04) throughout the study period.

- Treatment retention rate

The treatment retention rate in the group aged < 18 years was 86.7% at 6 months, 80.0% at 12 months, 66.7% at 18 months, 66.7% at 24 months, and 59.3% at 30 months, which was similar to that in the group aged 18 to < 65 years (83.0%, 73.9%, 64.2%, 64.2% and 61.0% respectively). The treatment retention rate in the group aged ≥ 65 years was the highest at 90.0%, 80.0%, 80.0%, 80.0%, and 80.0%, respectively.

CHMP comment:

The primary endpoint was the sustained seizure freedom rate at 24 months (18-24 months).
Regarding the pediatric population, the seizure freedom rate during the 18/24 months period is not clearly given in the CSR, however in the expert overview it is indicated that the rate was 53.3% for the 18- to 24-month time period with a range of 73.3% to 46.7% for all reported time periods.
***RSI**: The Applicant is requested to provide a clear description of the results obtained in the pediatric population. Indeed, in the CSR, evaluation periods are not clearly specified in the results of primary and secondary endpoint for the subpopulation analyses. Results from the primary endpoint (seizure freedom rate at 24 months [18-24 months]) and secondary endpoints (seizure freedom rate at 6 months [3-6 months], 12 months [6-12 months], 18 months [12-18 months], and 30 months [24-30 months]) in the pediatric population need to be clearly provided. The use of tables and/or graphical representations is encouraged to improve clarity.*
The Applicant clarified in the RSI that among all pediatric patients who started treatment, 53,3% (8/15) patients were able to continue treatment during the evaluation period (at 24 months). In addition, among the 9 patients who were evaluated during the period 18-24 months, 8 (88,9%) were able to continue treatment without seizures.

Furthermore, the Applicant clarified that the seizure freedom rate among patients evaluated during each period in the pediatric population at 6 months was 84.6%, at 12 months 83.3%, at 18 months 88.9%, and at 30 months 87.5%. ~~at 12 months was 53.3% and at 24 months 33.3%.~~
In addition, using a Kaplan-Meier analysis with the first seizure as an event, the seizure freedom rate was 66.7% at 6 months, 60.0% at 12 months, 52.5% at 18 months, 52.5% at 24 months, and 52.5% at 30 months.
Overall, in all analyses, the sustained seizure freedom rate tended to be higher in the pediatric population compared to adults and elderly, confirming the efficacy of Fycompa as first-line therapy in untreated patients. These results seem to be partially explained by the Applicant by the low seizure frequency of 0.6 times/month at the start of treatment and the high rate of FBTCS.

Concerning other secondary endpoint, Fycompa trend to increased quality of life assessed with PedsQL (from 70.65 to 76.63 from baseline to 30 months in children from 8 to 12 years, and from 91.30 to 100.0 in patients from 13 to 17 years).

As Fycompa is approved in the EU only as adjunctive treatment and not as a monotherapy, comparison with data included in the approved EU SmPC is not possible.
However, some publication assessing efficacy of perampanel as a monotherapy in the pediatric population has been published:

- In Zhou R, et al. (Perampanel and lacosamide monotherapy in pediatric patients with newly diagnosed focal epilepsy: A prospective study evaluating efficacy, tolerability, and behavior. Epilepsy Behav. 2023;146:109353. doi:10.1016/j.yebeh.2023.109353), at the 12-month follow-up, the responder rates were 65.4%, while seizure-free rates were 57.7%.

- In Zhao F, et al. (Effectiveness and tolerability of perampanel monotherapy in children with newly diagnosed focal epilepsy. Front Neurol. 2023;14:1144759. Published 2023 May 24. doi:10.3389/fneur.2023.1144759), seizure freedom varied over time, with 61.3%, 71.0%, and 71.7% of patients at the 3-, 6-, and 12-month follow-ups.

- In Gu Y, et al. (Clinical efficacy and safety of perampanel monotherapy as primary anti-seizure medication in the treatment of paediatric epilepsy: A single-centre, prospective, observational study. Epilepsia Open. 2024;9(6):2209-2218. doi:10.1002/epi4.13043), seizure freedom rates at 3, 6, 9, and 12 months were 85.45%, 79.09%, 76.24%, and 75.31%, respectively.

Overall, the results found in the literature seems comparable to the results of Study 515~~, but this will be confirmed once the Applicant presented clearly results from the primary endpoint and the first secondary endpoint~~.

Safety results

Extent of Exposure

The initial dose was less than 2 mg for 6 (40.0%) patients and 2 mg for 9 (60.0%) patients, whereas the modal dose median was 4.0 mg, mean was 3.5 mg, and less than 4 mg for 7 (46.6%) patients.

Adverse Events

The total number of patients with adverse drug reactions (ADRs), irrespective of age, was 32.8%. In the group aged less than 18 years of age, 7 events of ADR occurred in 5 (33.3%) patients, including somnolence in 2 (13.3%) patients, dizziness in 2 (13.3%) patients, affect lability in 2 (13.3%) patients, and fall in 1 (6.7%) patient. Table 1 present the summary of the AEs reported in pediatric population.

The incidence of psychiatric ADRs in the pediatric group was 13.3%. ADRs were all mild and non-serious, except for the event of fall which resulted in death (described below).

Other adverse events in the group aged less than 18 years of age had no causality to perampanel, and these events were mild and non-serious except for 1 event of mild serious epilepsy in a 13-year-old male.

Deaths, Other Serious Adverse Events (SAEs), and Other Significant Adverse Events (AEs)

A teenaged patient died from a fall approximately 8 months after perampanel monotherapy. There were no other ADRs, including aura symptoms, and the cause of the fall was unknown.

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Table 1. Summary of the AEs reported in pediatric population

Case_ID	Age	Sex	Onset_Date	Seriousness	Reported_Term	Preferred_Term	Report_Date	Severity	Seriousness	Causality	Outcome	Outcome_D	Action_Taken
804	11	Male	30/05/2022	2	Affect lability	Affect lability	11/07/2022	Mild	Non-serious	Causally related	Remission	20/10/2022	Discontinuation
603	13	Male	12/05/2022	1	SARS-CoV-2 test positive	SARS-CoV-2 test positive	21/07/2022	Mild	Non-serious	No causality	Recovery	04/08/2022	No dose change
603	13	Male	12/05/2022	1	Peeling	Skin exfoliation	28/06/2022	Mild	Non-serious	No causality	Recovery	02/07/2022	No dose change
603	13	Male	12/05/2022	1	Epilepsy aggravated	Epilepsy aggravated	28/06/2022	Mild	Serious	No causality	Recovery	09/07/2022	No dose change
303	14	Male	04/10/2021	2	Fall	Fall	19/05/2022	High	Serious	Causally related	Death	19/05/2022	Not Applicable
801	14	Male	22/03/2022	1	Pruritus cutaneous	Pruritus	25/03/2022	Mild	Non-serious	No causality	Recovery	29/03/2022	No dose change
801	14	Male	22/03/2022	1	Hepatic function disorder	Hepatic function abnormal	11/04/2022	Mild	Non-serious	No causality	Recovery	15/04/2022	No dose change
801	14	Male	22/03/2022	1	Vomiting	Vomiting	12/04/2022	Mild	Non-serious	No causality	Recovery	12/04/2022	No dose change
801	14	Male	22/03/2022	1	Inappetence	Decreased appetite	12/04/2022	Mild	Non-serious	No causality	Recovery	15/04/2022	No dose change
801	14	Male	22/03/2022	1	Diarrhoea	Diarrhoea	18/04/2022	Mild	Non-serious	No causality	Recovery	19/04/2022	No dose change
801	14	Male	22/03/2022	1	Neutropenia	Neutropenia	26/04/2022	Mild	Non-serious	No causality	Recovery	30/04/2022	No dose change
801	14	Male	22/03/2022	1	Vomiting	Vomiting	06/05/2022	Mild	Non-serious	No causality	Recovery	06/05/2022	No dose change
801	14	Male	22/03/2022	1	Queasy	Nausea	06/05/2022	Mild	Non-serious	No causality	Recovery	09/05/2022	No dose change
801	14	Male	22/03/2022	1	Inappetence	Decreased appetite	06/05/2022	Mild	Non-serious	No causality	Recovery	09/05/2022	No dose change
801	14	Male	22/03/2022	1	Queasy	Nausea	24/05/2022	Mild	Non-serious	No causality	Recovery	25/05/2022	No dose change
801	14	Male	22/03/2022	1	Stomatitis	Stomatitis	09/06/2022	Mild	Non-serious	No causality	Recovery	22/06/2022	No dose change
801	14	Male	22/03/2022	1	Febrile neutropenia	Febrile neutropenia	10/06/2022	Mild	Non-serious	No causality	Recovery	17/06/2022	No dose change
801	14	Male	22/03/2022	1	Pyrexia	Pyrexia	10/06/2022	Mild	Non-serious	No causality	Recovery	10/06/2022	No dose change
801	14	Male	22/03/2022	1	Vomiting	Vomiting	11/06/2022	Mild	Non-serious	No causality	Recovery	13/06/2022	No dose change
1501	14	Male	15/09/2021	2	Emotional instability	Affect lability	10/11/2021	Mild	Non-serious	Causally related	Unrecovered	22/10/2022	Discontinuation
1102	16	Female	28/03/2022	2	Sleepiness	Somnolence	29/03/2022	Mild	Non-serious	Causally related	Recovery	07/04/2023	No dose change
1102	16	Female	28/03/2022	2	Dizziness	Dizziness	22/07/2022	Mild	Non-serious	Causally related	Recovery	07/04/2023	Dose reduction
1102	16	Female	28/03/2022	2	COVID-19 antigen test positive	SARS-CoV-2 test positive	18/10/2022	Mild	Non-serious	No causality	Recovery	20/10/2022	No dose change
203	17	Male	30/06/2022	2	Sleepiness	Somnolence	20/07/2022	Mild	Non-serious	Causally related	Unrecovered	29/10/2024	Dose reduction
203	17	Male	30/06/2022	2	Light-headed feeling	Dizziness	20/07/2022		Non-serious	Causally related	Recovery	23/08/2022	Dose reduction

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Overall Conclusions in the Context of the Article 46/Regulation 78(14) Submission

Results showed that perampanel was used at a low dose: the median modal dose of perampanel in the pediatric population was 4.0 mg, with a mean of 3.5 mg.

In the pediatric population, seizure freedom and retention rates tended to be higher than those in other age groups.

The total number of participants with ADRs was 32.8% in all patients and 33.3% in the pediatric group, showing no change in trend. In the group aged less than 18 years of age, there was a tendency to have coexisting developmental disorders as a background (40%). The incidence of psychiatric ADRs in the pediatric group was 13.3%, and the incidence of psychiatric ADRs for the whole group was 8.2%. This difference was not significantly different.

The efficacy and safety of perampanel monotherapy in untreated patients with epilepsy, including children, at 30 months of treatment was confirmed, supporting that perampanel may be considered as a first-choice therapy. The efficacy and safety of perampanel monotherapy were similar to those reported in clinical trials and other studies in other countries. On the basis of evaluation of results from Study 515, no changes to the SmPC or regional product labelling safety information are considered necessary at this time.

CHMP comment:

During study, 15 paediatric patients were enrolled. AEs occurred in 7 patients which reported 25 events.

The PT reported were Somnolence (2), Dizziness (2), Vomiting (2), SARS-CoV-2 test positive (2), Affect lability (2), Skin exfoliation, Epilepsy aggravated, Fall, Pruritus, Hepatic function abnormal, Vomiting, Decreased appetite, Diarrhoea, Neutropenia, Nausea, Decreased appetite, Nausea, Stomatitis, Febrile neutropenia, Pyrexia.

Two cases reported serious adverse events: one case of fall (reported as high in severity), which resulted in patient's death and one case of dizziness (reported as mild in severity).

All events reported causality related to perempanel are listed in section 4.8 of the SmPC: somnolence and dizziness (very common frequency) and fall (common frequency). Affect lability is reported twice and should be related to psychotic disorders. This AE is listed with frequency uncommon in section 4.8 and is reflected in section 4.4 with a paragraph about "Aggression, psychotic disorder".

AE of skin exfoliation is reported in the context of SARS-CoV-2 infection and aggravation of epilepsy. However, SARS-CoV-2 could be responsible of dermatological manifestations. Moreover section 4.8 of the SmPC of perampanel listed AEs of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens – Johnson Syndrome (SJS) and section 4.4 contains a paragraph warning about Severe cutaneous adverse reactions (SCARs).

Vomiting is reported twice in the same patient who also reported nausea which is listed with the frequency common. However, this patient presented several other AEs including hepatic function

abnormal and skin. As hepatic disorders are considered as important potential risk in EU the sponsor is requested to provide all information concerning this case in RSI.

Regarding frequency, proportion of AEs was similar in the paediatric population compared with the overall study population (33,3% vs 32,8%) and the incidence of psychiatric side effects in paediatrics patients was not significantly different from that in the whole group (13.3% and 8.2%, respectively).

2.3.3. Discussion on clinical aspects

The aim of the study was to assessed efficacy and safety of Fycompa in treatment-naïve patients with epilepsy aged 4 years and older in the Japanese population during 30 months. Fifteen patients less than 18 years were included. The Applicant clarified in the RSI that during the 30 months of the study, 6 pediatric patients were discontinued.

Fycompa was administered at the physician's discretion based on the dosage and administration in the package insert. The Applicant clarified in the RSI that subjects were allowed to take either the tablet or fine granule formulation.

The rate of seizure freedom was assessed at different time points, from 6 to 30 months, with the primary endpoint being seizure freedom rate at 24 months (18-24 months). In addition, quality of life data was assessed.
The Applicant clarified in the RSI that among all pediatric patients who started treatment, 53,3% (8/15) patients were able to continue treatment during the evaluation period of 24 months. In addition, among the 9 patients who were evaluated during the period 18-24 months, 8 (88,9%) were able to continue treatment without seizures. In addition, the seizure freedom rate among patients evaluated during each period in the pediatric population at 6 months was 84.6%, at 12 months 83.3%, at 18 months 88.9%, and at 30 months 87.5%. Overall, these results seem comparable to literature data.
Treatment retention rate was the same in all age groups. In addition, treatment with Fycompa trend to increased quality of life assessment, from 70.65 to 76.63 from baseline to 30 months in children from 8 to 12 years, and from 91.30 to 100.0 in patients from 13 to 17 years.
In the pediatric population, seizure freedom and retention rates tended to be higher than those in other age groups. These results seem to be partially explained by the low seizure frequency of 0.6 times/month at the start of treatment and the high rate of FBTCS in the pediatric population.

Regarding safety side, the frequency of adverse events was similar in the pediatric population and in the total study population. Indeed, the total number of participants with ADRs was 32.8% in all patients and 33.3% in the pediatric group. In the group aged less than 18 years of age, there was a tendency to have coexisting developmental disorders as a background (40%). The incidence of psychiatric ADRs in the pediatric group was 13.3%, and the incidence of psychiatric ADRs for the whole group was 8.2%.
Among the 15 pediatric patients included, 7 reported a total of 25 adverse events (2 serious events). All adverse events considered related were listed in the SmPC of perampanel. The incidence of psychiatric adverse events in pediatric patients was not significantly different from that in the whole group.

One case of death following a fall was reported; this event is appropriately listed in section 4.8 of the SmPC. One case reporting abnormal hepatic function has been further detailed in the RSI as this risk is monitored as an important potential risk in the EU RMP. CIOMS were not available, as the events were non-serious and not considered related to the treatment drug. The details of the case provided by the MAH do not allow the identification of any new safety information due to limited information.

At this stage, the data submitted by the sponsor are considered to be consistent with the information currently presented in the SmPC, the RMP for perampanel and the known safety profile of the product.

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

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

1. The Applicant is requested to indicate which pharmaceutical formulation of Fycompa was used during the study.
2. The Applicant is asked to provide a participant flow with only pediatric population in order to present duration of follow-up and reason of discontinuation in this specific population.
3. The Applicant is requested to provide a clear description of the results obtained in the pediatric population. Indeed, in the CSR, evaluation periods are not clearly specified in the results of primary and secondary endpoint for the subpopulation analyses. Results from the primary endpoint (seizure freedom rate at 24 months [18-24 months]) and secondary endpoints (seizure freedom rate at 6 months [3-6 months], 12 months [6-12 months], 18 months [12-18 months], and 30 months [24-30 months]) in the pediatric population need to be clearly provided. The use of tables and/or graphical representations is encouraged to improve clarity.
4. The risk of "Hepatic Disorders (excluding hepatic disorders induced by SCARs)" is monitored as an important potential risk in the EU RMP. With regard to case 0801 reporting hepatic disorders in pediatric patient under the PT "hepatic function abnormal", the sponsor is requested to provide all available information (including the CIOMS report, if available).

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

MAH responses to Request for supplementary information

Question 1: The Applicant is requested to indicate which pharmaceutical formulation of Fycompa was used during the study.

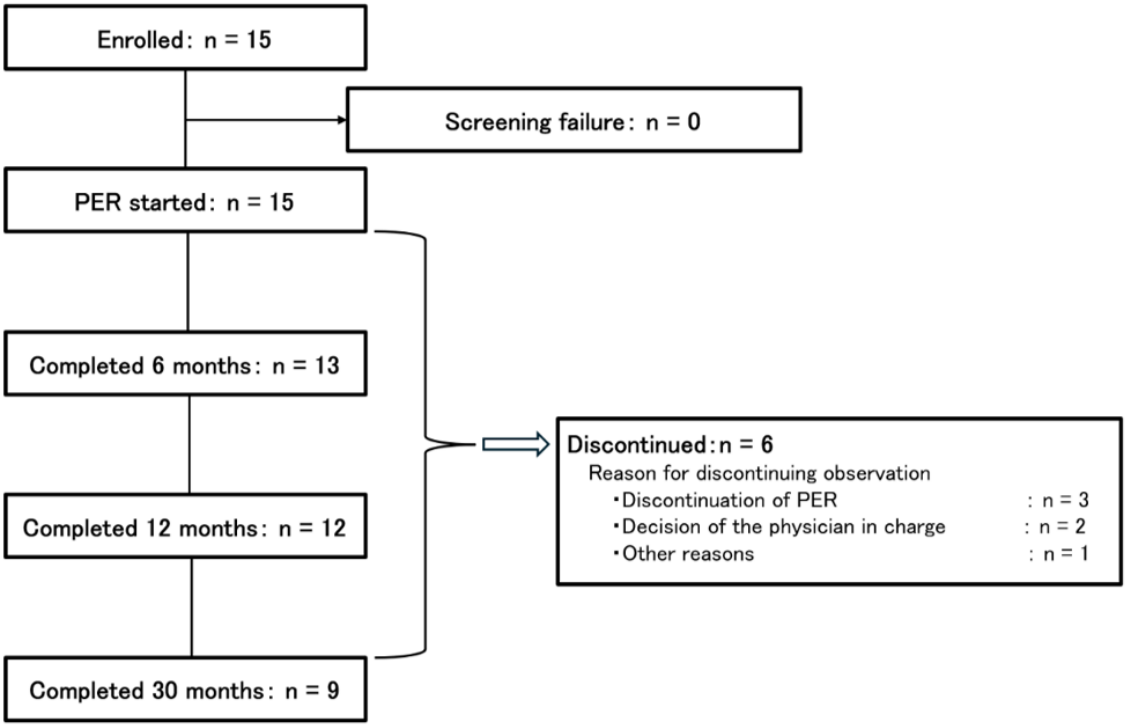
Applicant Response: Subjects were allowed to take either the tablet or fine granule formulation. Given that the formulations are equivalent in the amount of perampanel delivered, specific information on which formulation each subject took was not collected as part of the study.

CHMPs comment: *Response acceptable, the discussion and conclusion have been updated.*

Question 2: The Applicant is asked to provide a participant flow with only pediatric population in order to present duration of follow-up and reason of discontinuation in this specific population.

Applicant Response: Figure 3 provides the participant flow for pediatric subjects in study E2007-M081-515.

Figure 3: Study E2007-M081-515 Pediatric (<18 years) Participant Flow



CHMP comment: *The Applicant has provided a pediatric participant flow, indicating that 6 patients were discontinued during the study, therefore the issue is solved. The discussion and conclusion have been updated accordingly.*

Question 3: The Applicant is requested to provide a clear description of the results obtained in the pediatric population. Indeed, in the CSR, evaluation periods are not clearly specified in the results of primary and secondary endpoint for the subpopulation analyses. Results from the primary endpoint (seizure freedom rate at 24 months [18-24 months]) and secondary endpoints (seizure freedom rate at 6 months [3-6 months], 12 months [6-12 months], 18 months [12-18 months], and 30 months [24-30 months]) in the pediatric population need to be clearly provided. The use of tables and/or graphical representations is encouraged to improve clarity.

Applicant Response: A summary of results for the primary and secondary endpoints in pediatric subjects are provided in Figure 4 and Figure 5. Overall, the results show that the seizure freedom rates across pediatric, adult and elderly subjects are consistent.

Primary Endpoint in the Pediatric Population: Seizure freedom rate at 24 months (18-24 months)

The denominator was the total number of patients who started treatment, and the numerator was the number of patients who were able to continue treatment without seizures during the evaluation period was 53.3% (8/15). Conversely, the denominator was the number of patients evaluated during the period, and the numerator was the number of patients who were able to continue treatment without seizures during the evaluation period was 88.9% (8/9).

Secondary Endpoints in the Pediatric Population: Seizure freedom rate at 6 months (3-6 months), 12 months (6-12 months), 18 months (12-18 months), and 30 months (24-30 months)

The denominator was the total number of patients who started treatment, and the numerator was the number of patients who were able to continue treatment without seizures during the evaluation period was 73.3%, 66.7%, 53.3%, and 46.7%, respectively. Conversely, the denominator was the number of patients evaluated during each period, and the numerator was the number of patients who were able to continue treatment without seizures during the evaluation period was 84.6%, 83.3%, 88.9%, and 87.5%, respectively.

Figure 4: Results for Primary and Secondary Endpoint (Pediatric Population) for Study E2007-M081-515

Seizure freedom rate (1): age

Seizure freedom rate (1-1): The total number of patients who started treatment as the denominator and the number of patients who were able to continue treatment without seizures during the period as the numerator

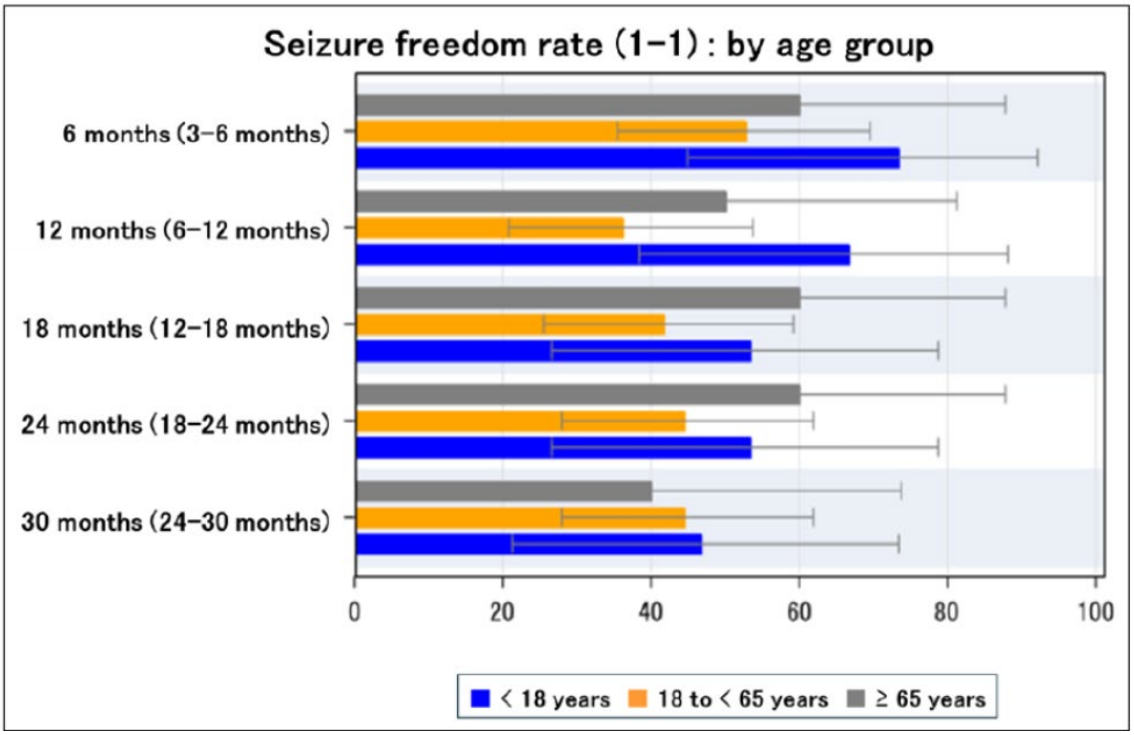
	< 18 years			18 to <65 years			≥ 65 years		
	N =15			N =36			N =10		
Period	Applicable number /tartget number	Seizure freedom rate	95% confidence interval	Applicable number /tartget number	Seizure freedom rate	95% confidence interval	Applicable number /tartget number	Seizure freedom rate	95% confidence interval
6 months (3-6 months)	11/15	73.3%	44.9 - 92.2%	19/36	52.8%	35.5 - 69.6%	6/10	60.0%	26.2 - 87.8%
12 months (6-12 months)	10/15	66.7%	38.4 - 88.2%	13/36	36.1%	20.8 - 53.8%	5/10	50.0%	18.7 - 81.3%
18 months (12-18 months)	8/15	53.3%	26.6 - 78.7%	15/36	41.7%	25.5 - 59.2%	6/10	60.0%	26.2 - 87.8%
24 months (18-24 months)	8/15	53.3%	26.6 - 78.7%	16/36	44.4%	27.9 - 61.9%	6/10	60.0%	26.2 - 87.8%
30 months (24-30 months)	7/15	46.7%	21.3 - 73.4%	16/36	44.4%	27.9 - 61.9%	4/10	40.0%	12.2 - 73.8%

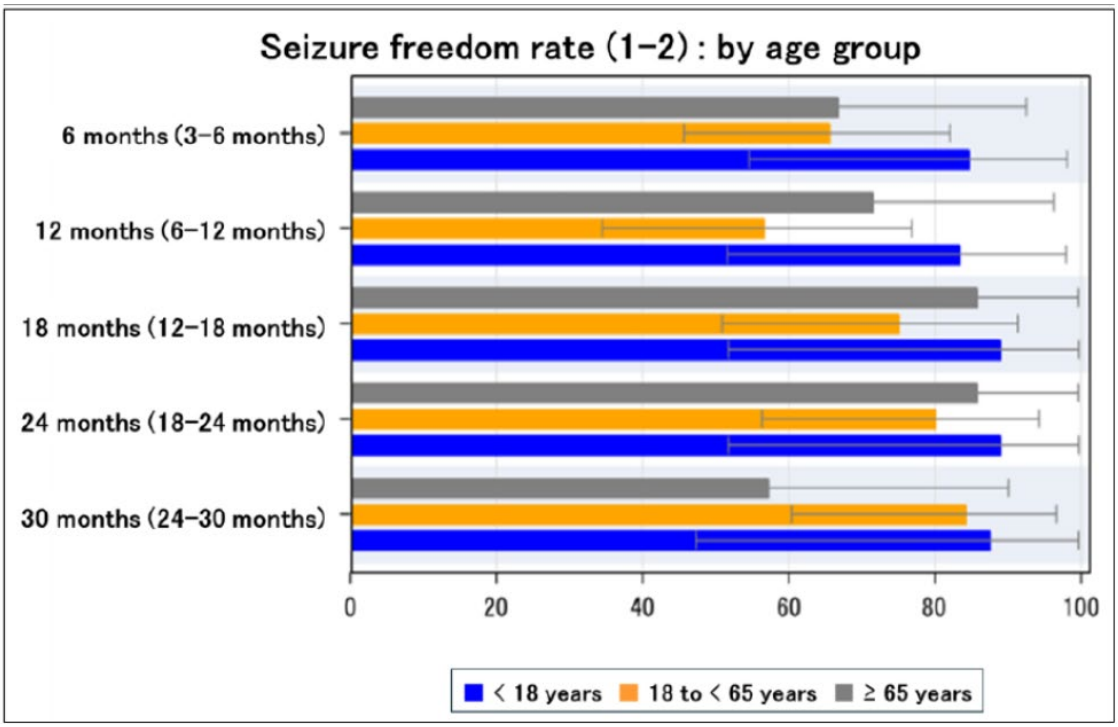
Seizure freedom rate (1-2): The number of patients evaluated during each period as the denominator and the number of patients who were able to continue treatment without seizures during the period as the numerator.

	< 18 years			18 to <65 years			≥ 65 years		
	N =13			N =29			N =9		
Period	Applicable number /tartget number	Seizure freedom rate	95% confidence interval	Applicable number /tartget number	Seizure freedom rate	95% confidence interval	Applicable number /tartget number	Seizure freedom rate	95% confidence interval
6 months (3-6 months)	11/13	84.6%	54.6 - 98.1%	19/29	65.5%	45.7 - 82.1%	6/9	66.7%	29.9 - 92.5%
12 months (6-12 months)	10/12	83.3%	51.6 - 97.9%	13/23	56.5%	34.5 - 76.8%	5/7	71.4%	29.0 - 96.3%
18 months (12-18 months)	8/9	88.9%	51.8 - 99.7%	15/20	75.0%	50.9 - 91.3%	6/7	85.7%	42.1 - 99.6%
24 months (18-24 months)	8/9	88.9%	51.8 - 99.7%	16/20	80.0%	56.3 - 94.3%	6/7	85.7%	42.1 - 99.6%
30 months (24-30 months)	7/8	87.5%	47.3 - 99.7%	16/19	84.2%	60.4 - 96.6%	4/7	57.1%	18.4 - 90.1%

Figure 5: Results for Primary and Secondary Endpoint (Pediatric, Adult and Elderly Populations) for Study E2007-M081-515

Seizure freedom rate (1): age





CHMP comment: *Clarification regarding results from primary and secondary endpoint have been provided, therefore the issue is solved. The discussion and conclusion have been updated accordingly.*

Question 4: The risk of "Hepatic Disorders (excluding hepatic disorders induced by SCARs)" is monitored as an important potential risk in the EU RMP. With regard to case 0801 reporting hepatic disorders in pediatric patient under the PT "hepatic function abnormal", the sponsor is requested to provide all available information (including the CIOMS report, if available).

Applicant Response: Because this is a non-serious, non-related case, the information a CIOMS form for this subject is not available. A summary for this subject is provided below. All adverse events for the subject are provided in the attached appendix.

The subject was a 14-year-old male with a past medical history of brain tumor, constipation, gastroesophageal reflux disease, anorexia, alopecia, and fatigue. Concomitant medications included esomeprazole, elobixibat, aprepitant, filgrastim, cefepime, carboplatin, and etoposide. From 25 March 2022 to 29 March 2022, the subject had an event of pruritis, during which study drug was continued, and which was treated with a heparinoid. The subject received his first dose of perampanel 1 mg daily on 22 March 2022. On 11 April 2022, a nonserious event of hepatic function abnormal (preferred term) was reported, which was mild in severity. Laboratory values were not reported. At the time of the abnormal hepatic function event, the subject was taking perampanel 2mg daily. No action was taken with study drug, which was continued. Recovery from the event was reported on 15 April 2022. The investigator classified the event of hepatic function abnormal as not related to study drug.

Patient Information

Subject Id	0801
Age (years)	14
Sex	Male

Perampanel Hydrate

Therapy date	2022/3/22 ~ continue
Daily dose	Start: 1 mg/day, AE onset: 2 mg/day

Adverse Event: Hepatic function disorder (LLT: Hepatic function disorder; PT: Hepatic function abnormal)

Reaction onset	2022/4/11
Severity	Mild
Seriousness (reporter/Mfr)	Non serious/ Non serious
Causality (reporter/Mfr)	Nor related/Not related
Outcome, date	Recovered, 2022/4/15
Action taken with drug, Treatment	Continue, None

CHMP comment:

The CIOMS regarding case of *hepatic function abnormal was not available. However, the MAH reported that the subject was a 14-year-old male with a past medical history of brain tumor, constipation, gastroesophageal reflux disease, anorexia, alopecia, and fatigue. Concomitant medications included esomeprazole, elobixibat, aprepitant, filgrastim, cefepime, carboplatin, and etoposide. The subject received his first dose of perampanel 1 mg daily on 22 March 2022 and experienced pruritus from 25 March 2022 to 29 March 2022. Study drug was continued, and the event of pruritus was treated with a heparinoid. On 11 April 2022, a nonserious event of hepatic function abnormal (preferred term) was reported, which was mild in severity. Laboratory values were not reported. At the time of the abnormal hepatic function event, the subject was taking perampanel 2mg daily. No action was taken with study drug, which was continued. Recovery from the event was reported on 15 April 2022. The investigator classified the event of hepatic function abnormal as not related to study drug.*

Response provided by the MAH does not allow to identified any new safety information. Response is acceptable, the discussion and conclusion have been updated.