30 January 2025
EMA/CHMP/56277/2025
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/P46/030

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	14 Oct 2024	14 Oct 2024	☐
☐	CHMP Rapporteur Assessment Report	18 Nov 2024	15 Nov 2024	☐
☐	CHMP members comments	02 Dec 2024	02 Dec 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Dec 2024	05 Dec 2024	☐
☐	Request for supplementary information (RSI)	12 Dec 2024	12 Dec 2024	☐
☐	CHMP Rapporteur Assessment Report	15 Jan 2025	15 Jan 2025	☐
☐	CHMP members comments	20 Jan 2025	20 Jan 2025	☐
☐	Updated CHMP Rapporteur Assessment Report	23 Jan 2025	23 Jan 2025	☐
☒	CHMP adoption of conclusions:	30 January 2025	30 January 2025	☐

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1. Introduction

On the 25th of September 2024, the MAH submitted a completed paediatric study for Fycompa 2, 4, 6, 8, 10 and 12 mg Tablets, 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-M091-508 (Study 508) that was completed on 13 March 2020. This Study 508 was a prospective, multicenter, open label, non-comparative, post-marketing surveillance study to evaluate safety & efficacy of perampanel as adjunctive therapy in patients with partial-onset seizures with or without secondary generalized seizure aged 12 years and older, that was conducted in India. Patients were enrolled to receive perampanel based on independent clinical judgment of treating physicians/Principle Investigator as per the approved Package Insert in India.

The study enrolled 200 patients (planned 200 patients), all of which were treated with perampanel, 32 of whom were less than 18 years of age. In the context of this PAM P46, we will focus only on adolescent population.

The primary objective of this Phase 4 multi-centre study was to assess the safety of perampanel in the treatment of partial-onset seizures in patients aged 12 years and older.

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

2.2. Information on the pharmaceutical formulation used in the study

The investigational medicinal product tested in Study 508 in patients aged 12 years and older was Fycompa 2, 4, 6, 8, 10 and 12 mg Tablets.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study E2007-M091-508 (Study 508).

2.3.2. Clinical study

Description

Study 508 was a prospective, multicenter, open label, non-comparative, post-marketing surveillance study to evaluate safety & efficacy of perampanel as adjunctive therapy in patients with partial-onset seizures with or with secondary generalized seizure aged 12 years and older. Patients were enrolled to receive perampanel based on independent clinical judgment of treating physicians/Principle Investigator as per the approved Package Insert in India. The study enrolled 200 patients (planned 200 patients), all of which were treated with perampanel, 32 of whom were less than 18 years of age.

The primary objective of this Phase 4 multi-centre study was to assess the safety of perampanel in the treatment of partial-onset seizures in patients aged 12 years and older.

The study was conducted at 12 study sites in India.

Since Study 508 was an observational, postmarketing study, all patients received perampanel oral tablets (2-, 4-, 6-, 8-, 10-, or 12 mg) per the approved PI in India, based on the investigator's discretion. The study consisted of a Screening and Enrolment Visit (Day 1) and a Treatment Period (6 months). For each patient, visits during the Treatment Period were conducted each month. Once enrolled, seizure diaries were issued to the patients, and they were monitored during the treatment of perampanel for 6 months and up to 30 days post-treatment in case of serious adverse events (SAEs). If a patient withdrew from the study (due to lack of efficacy or intolerance) or was lost to follow-up, the patient was monitored for the collection of adverse events (AEs). Baseline seizure count (frequency) data were collected prior to the first dose. Seizure frequencies from prospective diary entries were used to assess the baseline seizure count and the efficacy endpoints. Baseline characteristics, perampanel dose, together with dose adjustment, AEs (if any), laboratory parameters (if any), serum pregnancy test, and other safety parameters, such as physical examination findings, vital signs, were assessed in the general clinical practice.

CHMP comment:

The applicant did not provide results of this study 6 months after the end as it is regulatory mandated. However, the applicant has justified the delay (covid pandemia), therefore this is acceptable.

This observational post marketing was conducted in patients aged ≥12 y-o. In the context of this PAM P46, Rapporteur focused only on adolescent population (e.g. 32/200 patients).

This study enrolled 32 patients of less than 18 y-o, treated with Fycompa as adjunctive therapy in patients with partial-onset seizures with or with secondary generalized seizure.

This study being a post-marketing observational study, prescription and dosage were chosen by the treating physicians/investigator based on the approved Package Insert (PI) in India.

Screening and enrolment were done at Day 1 and Treatment period lasted 6 months. Visit during the treatment period has been done every month.

Methods

Study participants

- Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Male or female patients age greater than or equal to 12 years at the time of informed consent.

2. Patient prescribed perampanel for the adjunctive treatment of partial onset seizures based on independent clinical judgment of treating physicians.

3. Patients who provide informed consent to the treating physician.

- Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Participation in another study involving administration of an investigational drug or device whilst participating in this observational study.

2. Hypersensitivity [allergic] to perampanel

Treatments

Since this is an observational study, perampanel will be prescribed as an adjunctive treatment of partial onset seizures with or without secondary generalized seizures in patients with epilepsy aged 12 years or older based on independent clinical judgment of investigator as per the approved Package Insert in India. Subjects will be provided free Medication [Fycompa (perampanel)] for use in this Study by the Study Sponsor.

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent will be recorded on the Prior & Concomitant Medication CRF or Non-Pharmacological Procedures CRF.

The total duration of treatment for each patient was 6 months.

CHMP comment:

This study aimed to include subjects > 12 years treated with Fycompa for the adjunctive treatment of partial onset seizures.

According to Central Drugs Standard Control Organisation of India (CDSCO), the only indication for perampanel is "The adjunctive treatment of partial-onset seizures with or without secondary generalized seizures in patients with epilepsy aged 12 years and older", explaining that this study has been only be conducted in this population.

This study being prospective, prescription of perampanel was based on independent clinical judgment of the investigator.

Objective(s)

- *Primary Objective*

To assess the safety of perampanel in the treatment of partial onset seizures in patients of age 12 years and older with epilepsy.

- *Secondary Objective(s)*

1. To assess the change in seizure frequency with perampanel as adjunctive treatment of partial onset seizures in patients of age 12 years and older with epilepsy
2. To assess the responder rate (50% seizure frequency reduction) with perampanel as adjunctive treatment of partial onset seizures in patients of age 12 years and older with epilepsy
3. To evaluate proportion of seizure free patients at the end of 3-months, and 6-months and last 3 months during the treatment period.

Outcomes/endpoints

- *Primary Endpoint*

The number and types of adverse events reported by the Investigator or the patient

- *Secondary Endpoint(s)*

1. The percent change in seizure frequency per 28 days during the treatment period (6 months) relative to baseline
2. The 50% responder rate (percentage of patients who experienced at least 50% reduction in seizure frequency over treatment period of 6 months relative to baseline) of the patients over treatment period relative to baseline.
3. Proportion of subjects who achieved a seizure-free status for 3-months, and 6-months and last 3 months during the treatment period.

Sample size

Up to 200 Indian patients were planned to be enrolled to receive perampanel as per the approved Product Information (PI) based on independent clinical judgment of the treating physicians/Principal Investigator. The study was conducted at 12 study sites in India.

Randomisation and blinding (masking)

NA

Statistical Methods

The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 post dose safety assessment.

The Efficacy Analyses set, those who completed the treatment period of 6 months will be included. In addition, as sensitivity analysis will be conducted on analysis set with Last Observation carried forward (LOCF).

Efficacy Assessments will be done for following efficacy end points

☐ The percent change in seizure frequency per 28 days during the treatment period (6 months) relative to baseline

☐ The 50% responder rate (percentage of patients who experienced at least 50% reduction in seizure frequency over treatment period of 6 months relative to baseline) of the patients over treatment period relative to baseline.

☐ Proportion of subjects who achieved a seizure-free status for 3-months, and 6-months and last 3 months during the treatment period.

For percent change in seizure frequency, 50% responder rate and seizure-free proportion, those who completed the treatment period of 6 months will be included. In addition, as sensitivity analysis will be conducted on analysis set with Last Observation carried forward (LOCF).

☐ Summary statistics for efficacy endpoints and 95% CI will be performed.

Results

Participant flow / Recruitment / Number analysed

A total of 200 patients were screened and enrolled in the study (Overall Population). Of these, 32 patients were between the ages of 12 to 17 years (Adolescent Population). A total of 174 (87.0%) patients in the Overall Population and 26 (81.25%) patients in the Adolescent Population completed the study according to the protocol.

Six (18.75%) of the 32 patients in the Adolescent population withdrew from the study. Of the 6 patients who withdrew in the Adolescent Population, the reasons for study withdrawal were lost to follow-up (3 [50.0%] patients), withdrawal of consent (1 [16.67%] patient), significant protocol violation (1 [16.67%] patient), and other (1 [16.67%] patient).

CHMP comment:

32 adolescent patients were screened and enrolled in this study, and 26 completed the study according to the protocol. The reasons for this 6 withdrawn adolescent patient were: lost to follow-up (3 [50.0%] patients), withdrawal of consent (1 [16.67%] patient), significant protocol violation (1 [16.67%] patient), and other (1 [16.67%] patient, due to non-compliance).

Baseline data

The mean (SD) age in the Overall Population was 28.68 (±12.41) years. Median age was 24 years with a range of 12 to 67 years.

Table 1:Types of seizures in adolescent population (age 12 to 17 years)

Serial Nos.	Seizure types		Number of Patients	Percentage
A	**Partial Onset Seizures**		**29**	**90.62%**
	1	**Simple partial with Secondary Generalization**	**1**	**3.13%**
	2	**Complex Partial**	**21**	**65.63%**
		2.1 Complex Partial	17	53.13%
		2.2 Complex Partial Seizure with Secondary Generalized Tonic-clonic	4	12.50%
	3	**Partial Onset with Second Generalization[a]**	**1**	**3.13%**
	4	**Secondary Generalized Tonic-clonic[a]**	**6**	**18.75%**
B	**Generalized Onset Seizures**		**3**	**9.38%**
	1	**Generalized Tonic-clonic**	**3**	**9.38%**
Total			**32**	**100%**

a: Simple vs complex partial not specified.

The mean compliance rate per visit for all 32 patients in the Adolescent Population was 95.94%, 97.36%, 97.20%, 98.62%, 97.55%, and 98.78% at Visit 2, 3, 4, 5, 6, and 7, respectively. The mean

compliance rate per visit for the 26 adolescent patients who completed all study visits till Visit 7 was 97.13%, 97.15%, 97.10%, 98.62%, 97.55%, and 98.78% at Visit 2, 3, 4, 5, 6, and 7, respectively.

CHMP comment:

In the adolescent population, the majority of patients had complex partial onset seizures (65.63% [21/32]), including complex partial seizures with secondary generalized tonic-clonic (12.50% [4/32]). Six (6) patients (18.75%) had secondary generalized tonic clonic seizures.

3/32 (3.38%) adolescent patients had generalized Tonoc-clinic seizure. this population was not supposed to be included. The MAH is asked to justify these inclusions ***(RSI)****: Clarification regarding the inclusion of 3 adolescent patients with generalized onset seizures has been made in the RSI (see Section 4, Agency question 2). As the seizure history information recorded in the CRF is with regards to the first seizure only and not the full seizure history, patients with both partial-onset seizures and generalized onset seizures has been included.*

The compliance rate were at least 95.94% (corresponding to visit 2) in the adolescent population, which seems acceptable.

Efficacy results

Of the 26 adolescent patients that completed all study visits:

☐ The median percent change from baseline in seizure frequency was -92.50%, -90.11%, -90.21%, -92.78%, -99.26%, and -100.00% at Visit 2, 3, 4, 5, 6, and 7, respectively.

☐ 25 (96.15%) patients had a 50% reduction (responder rate) in seizure frequency.

☐ 10 (38.46%) patients were free from seizures at the end of 3 months, 13 (50.00%) patients were free from seizures at the end of 6 months, and 16 (61.54%) patients were free from seizures at the end of the last 3 months of the treatment period.

Of the 29 adolescent patients with LOCF (Last Observation Carried Forward):

☐ The median percent change from baseline in seizure frequency was -91.67%, -86.89%, -86.67%, -90.00%, -98.52%, and -100.00% at Visit 2, 3, 4, 5 ,6, and 7, respectively.

☐ 28 (96.55%) patients had a 50% reduction (responder rate) in seizure frequency.

☐ 11 (37.93%) patients were free from seizures at the end of 3 months, 14 (48.28%) patients were free from seizures at the end of 6 months, and 17 (58.62%) patients were free from seizures at the end of the last 3 months of the treatment period.

Table 2: Change in seizure frequency

Number of subject who completed all the visits between age 12 to 17 = 26

Visit	Label	Mean	Std Dev	Median	Minimum	Maximum	Lower 95% CL for Mean	Upper 95% CL for Mean
V2	Percentage Change in visit 2 from Baseline	-25.79	259.08	-92.50	-100.00	1233.33	-130.43	78.86
V3	Percentage Change in visit 3 from Baseline	-11.63	291.62	-90.11	-100.00	1400.00	-129.42	106.16
V4	percentage Change in visit 4 from Baseline	9.77	342.36	-90.21	-100.00	1666.67	-128.51	148.06
V5	Percentage Change in visit 5 from Baseline	55.53	675.99	-92.78	-100.00	3366.67	-217.51	328.57
V6	Percentage Change in visit 6 from Baseline	5.09	448.75	-99.26	-100.00	2200.00	-176.16	186.35
V7	Percentage Change in visit 7 from Baseline	-72.71	91.24	-100.00	-100.00	366.67	-109.56	-35.86

Number of Subjects with last observation carried forward between age 12 to 17 = 26

Visit	Label	Mean	Std Dev	Median	Minimum	Maximum	Lower 95% CL for Mean	Upper 95% CL for Mean
V2	Percentage Change in visit 2 from Baseline	-21.77	248.10	-91.67	-100.00	1233.33	-116.15	72.60
V3	Percentage Change in visit 3 from Baseline	-15.84	276.43	-86.89	-100.00	1400.00	-120.99	89.31
V4	percentage Change in visit 4 from Baseline	0.76	324.70	-86.67	-100.00	1666.67	-122.75	124.27
V5	Percentage Change in visit 5 from Baseline	41.79	640.11	-90.00	-100.00	3366.67	-201.70	285.27
V6	Percentage Change in visit 6 from Baseline	-3.43	424.85	-98.52	-100.00	2200.00	-165.04	158.17
V7	Percentage Change in visit 7 from Baseline	-73.19	86.49	-100.00	-100.00	366.67	-106.09	-40.29

CHMP comment:

The first secondary endpoint was to assess the change in seizure frequency with perampanel as adjunctive treatment of partial onset seizures.

In the 26 adolescent population that completed the study, the median percent change from baseline in seizure frequency was -92.50%, -90.11%, -90.21%, -92.78%, -99.26%, and -100.00% at Visit 2, 3, 4, 5, 6, and 7, respectively. These results were comparable to the overall population of this study (-90.00%, -93.00%, -96.67%, -96.11%, -98.43%, and -100.00% at Visit 2, 3, 4, 5, 6, and 7, respectively).

For the 29 patients with LOCF, the median percent change from baseline in seizure frequency was -91.67%, -86.89%, -86.67%, -90.00%, -98.52%, and -100.00% at Visit 2, 3, 4, 5, 6, and 7, respectively. These results were comparable to the overall population of this study (-90.83%, -90.83%, -95.00%, -94.17%, -97.56%, -100.00% at Visit 2, 3, 4, 5, 6, and 7, respectively).

Table 3: Responder rate

Number of subjects completed all study visits between age 12 to 17= 26

Were Subjects experienced 50 % reduction in Seizure Frequency				
Fifty percent reduction	Frequency	Percent	Cumulative Frequency	Cumulative Percent
No	1	3.85	1	3.85
Yes	25	96.15	26	100.00

Number of subjects with last observation carried forward age between 12 to 17 years= 29

Were Subjects experienced 50 % reduction in Seizure Frequency				
Fifty percent reduction	Frequency	Percent	Cumulative Frequency	Cumulative Percent
No	1	3.45	1	3.45
Yes	28	96.55	29	100.00

CHMP comment:

The second secondary endpoint was to assess the responder rate (50% seizure frequency reduction) in the adolescent population.
Among the 26 patients who completed the study, 25 (96.15%) patients had a 50% reduction (responder rate) in seizure frequency, and among the 29 patients with LOCF, 28 (96.55%) patients had a 50% reduction in seizure frequency. These results were comparable to the overall population of this study (145 [83.33%] of the 174 patients that completed the study, and 156 [82.11%] of the 190 patients with LOCF).

Table 4: Proportion of subject with seizure free status

Number of subjects who completed all the visits Between age 12 to 17= 26

Subjects with seizure free status at 3-Months				
Seizure zero at three Months	Frequency	Percent	Cumulative Frequency	Cumulative Percent
No	16	61.54	16	61.54
Yes	10	38.46	26	100.00

Subjects with seizure free status at 6-Months				
Seizure zero at six months	Frequency	Percent	Cumulative Frequency	Cumulative Percent
No	13	50.00	13	50.00
Yes	13	50.00	26	100.00

Subjects with seizure free status at last 3-Months				
Seizure zero last three Months	Frequency	Percent	Cumulative Frequency	Cumulative Percent
No	10	38.46	10	38.46
Yes	16	61.54	26	100.00

Number of subjects with last observation carried forward betweenage 12 to 17= 29

Subjects with seizure free status at 3-Months				
Seizure zero at there Months	Frequency	Percent	Cumulative Frequency	Cumulative Percent
No	18	62.07	18	62.07
Yes	11	37.93	29	100.00

Subjects with seizure free status at 6-Months				
Seizure zero at six months	Frequency	Percent	Cumulative Frequency	Cumulative Percent
No	15	51.72	15	51.72
Yes	14	48.28	29	100.00

Subjects with seizure free status at last 3-Months				
Seizure zero last three Months	Frequency	Percent	Cumulative Frequency	Cumulative Percent
No	12	41.38	12	41.38
Yes	17	58.62	29	100.00

CHMP comment:

The third secondary endpoint was to evaluate the proportion of seizure free patients at the end of 3-months, and 6-months and last 3 months during the treatment period.

Concerning the 26 patients who completed the study, 10 (38.46%) were free from seizures at the end of 3 months, 13 (50.00%) at the end of 6 months, and 16 (61.54%) at the end of the last 3 months of the treatment period. These results were comparable to the overall population of this study (respectively 76 [43.68%], 86 [49.43%] and 99 [56.90%] of the 174 patients that completed the study).

In the 29 patients with LOCF, 11 (37.93%) were free from seizures at the end of 3 months, 14 (48.28%) at the end of 6 months, and 17 (58.62%) at the end of the last 3 months of the treatment period. These results were comparable to the overall population of this study (respectively 81 [42.63%], 92 [48.42%] and 105 [55.26%] of the 190 patients with LOCF).

Even if the number of subjects in the adolescent population is low in this study, these efficacy results confirm the efficacy profile of perampanel in the Indian adolescent population.

Safety results

The Safety Analysis Set was the group of subjects who received at least 1 dose of study drug and had at least 1 post dose safety assessment.

A total of 199 subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Of the 199 subjects, 32 patients were those aged <18 years.

Extent of Exposure

The median duration of perampanel exposure was 175 days for 199 patients in the *Overall Population and* 174 of them completed all study visits till Visit 7.

For the 32 patients under 18 years old, the median duration of exposure was 173.5 days *and* 26 of them completed all study visits till Visit 7.

The main daily dose at screening was 2.14 mg in the overall population and 2.08 mg in patient under 18 years old. At visit 6 the mean daily dose was 4.78 in the overall population and 5.23 mg in the adolescent population.

Adverse Events

AEs were reported for the Overall Population. Patients were monitored during the treatment of perampanel for 6 months and up to 30 days post-treatment in case of serious adverse events. If a patient withdrew from the study or was lost to follow-up, the patient was monitored for the collection of adverse events.

Thirty-six (18.09%) of the 199 patients in the Safety Analysis Set reported a total of 60 non serious AEs during the study. There were none serious adverse events (SAEs).

Of the 36 patients who reported AEs, 30 patients (83.33%; 46 events) reported Grade 1 (mild) AEs and 6 patients (16.67%; 14 events) reported Grade 2 (moderate) AEs. No Grade 3 (severe) AEs were reported.

The most common AEs (reported by ≥5 patients) by system organ class (SOC) were Nervous system disorders (16 [8.04%] patients), General disorders and administration site conditions (8 [4.02%] patients), and Psychiatric disorders (5 [2.51%] patients).

AEs by preferred term (PT) in the SOC of Nervous system disorders were dizziness (6 [3.02%] patients), somnolence (5 [2.51%] patients), headache (3 patients), ataxia, (2 [1.01%] patients), and paraesthesia (1 [0.5%] patient). Other AEs (reported by ≥2 patients in the Safety Analysis Set) by PT in the remaining SOCs were decreased appetite (4 [2.01%] patients), irritability, pyrexia, gait disturbance (3 [1.51%] patients each), weight increased, and vertigo (2 [1.01%] patients each). The following AEs were reported by 1 (0.5%) patient each: abdominal pain, back pain, cough, diarrhoea, fatigue, gastroenteritis, hallucination, mouth ulceration, nasopharyngitis, pain in extremity, pruritis, sneezing, suicidal ideation, swelling face, and vision blurred.

Of the 36 patients who reported AEs, 15 (41.67%; 18 events) patients reported AEs that were considered related to the study drug and 21 (58.33%; 42 events) patients reported AEs that were not related. Among these cases, 11 (30.55%) patients reported AEs that required treatment. 3 patients (8.33%) recovered with sequel and the 33 remaining patient recovered without sequel (33 [91.67%] patients).

Deaths, Other SAEs, and Other Significant AEs

There were no deaths, SAEs, or other significant AEs observed in the study.

Vital Signs and Physical

Findings Most vital sign measurements were normal across all study visits. No abnormalities in vital sign measurements or other physical findings, including weight, were considered clinically significant.

CHMP comment:

During the study 36 cases were reported in overall population. These cases reported 60 adverse events (30 case reported grade 1 AEs and 6 case reported grade 2 AEs). There was no serious adverse event reported. Among the 60 events 15 were considered related to the treatment and 42 were not considered related to the perampanel.

In the overall population, the most frequently reported AEs in the Safety Analysis Set were dizziness (6 events), somnolence (5 events), and decreased appetite (4 events). These events are common in subjects treated with perampanel and are already listed in section 4.8 of the perampanel SmPC. Other listed effects were reported: weight increase and vertigo (2), irritability, gait disturbance, back pain,

fatigue, hallucination, suicidal ideation, and blurred vision (1). The AEs of headache and pyrexia were each reported by three patients and were considered unrelated to perampanel. Other cases with a single event were either considered unrelated to perampanel or were listed in section 4.8 of the SmPC.

*Paediatric population (patient aged between 12 and 17 years old) reported 6 non serious AEs (ataxia, vertigo, irritability, paraesthesia, fever and cough). Ataxia was a grade 2 AEs while other reported events were grade 1 AEs. Ataxia, vertigo and irritability are listed in the perampanel SmPC section 4.8. The other effects (paraesthesia, cough, pyrexia) were considered as not related by the MAH. As no detailed information is available in the report study on these cases, the MAH is requested to provide CRFs for the paediatric cases. The MAH should discuss these reported cases **(RSI)**.*

2.3.3. Discussion on clinical aspects

The aim of this study was to assess safety and efficacy of Fycompa (perampanel) as adjunctive therapy in patients with partial-onset seizures with or without secondary generalized seizure aged 12 years and older in Indian population during 6 months. Few patients with generalized onset seizures have also been included. The MAH has clarified this point in a RSI: as the seizure history information recorded in the CRF is with regards to the first seizure only and not the full seizure history, patients with both partial-onset seizures and generalized onset seizures has been included.

Fycompa was taken as a single oral dose once daily. The dose of 2-, 4-, 6-, 8-, 10-, or 12 mg was based on the investigator's discretion per the approved PI in India.

The primary endpoint was the number and types of adverse events reported by the Investigator or the patient. Regarding the safety, the AEs described in this study are overall consistent with the known safety profile for Fycompa described in the SmPC.

The safety results of the study reported that 36 subjects (18.6%) experienced at least one AEs. When scrutinizing more in detail with PT classification, the most common AE from MedDRA SOC Nervous System Disorders are those already stated in the SmPC: dizziness and somnolence.

Regarding paediatric cases, there were 6 cases reported. The 3 AEs considered as related (ataxia, irritability and vertigo) were listed while AEs not listed in SmPC of perampanel and reported were not considered related (pyrexia, paraesthesia and cough). The MAH is requested to provide additional information regarding these cases **(RSI).**

Three different secondary endpoint were assessed during this study. First, the percent change in seizure frequency per 28 days during the treatment period (6 months) relative to baseline was minimum -90.11% (at visit 3) and maximum -100.00% (at visit 7) for the 26 adolescent patients who completed the study. Secondly, 25/26 (96.15%) patients who completed the study had a 50% responder rate over treatment period relative to baseline. Finally, the proportion of subjects who achieved a seizure-free status for 3-months, and 6-months and last 3 months during the treatment period was respectively 10/26 (38.46%), 13/26 (50.00%) and 16/26 (61.54%) in the 26 adolescent patients that completed the study.

All of these results were comparable to the overall study population. However, these results should be considered cautiously regarding the low number of paediatric subjects.

3. Rapporteur's CHMP overall conclusion and recommendation:

☒ Fulfilled:

4. Request for supplementary information

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

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

Safety

1. The MAH is requested to provide the CRF of all paediatric patients who have experienced AEs, in particular AEs considered unrelated to treatment. The MAH is requested to discuss these cases.

Clinical aspects

2. Three adolescent patients with generalized onset seizures have been included in this study. However, it is specified in the inclusion criteria that only patient with partial onset seizures will be included. The MAH is asked to justify the inclusion of these 3 patients that do not meet the inclusion criteria.

MAH responses to Request for supplementary information

Agency Question 1
The MAH is requested to provide the CRF of all paediatric patients who have experienced AEs, in particular AEs considered unrelated to treatment. The MAH is requested to discuss these cases.

Company Response
Among the 32 patients aged 12 to ≤17 years, 6 subjects (mean age: 15 years, 5 males and 1 female) experienced 14 adverse events (AEs). The AEs included needle prick like sensation (6 AEs in 1 patient), fever (1 AE each in 2 patients) and ataxia, cough, increase in weight, irritability, somnolence, and vertigo (1 patient each).
Severity was mild for 11 of 14 AEs, with the 3 remaining AEs moderate. No grade 3 (severe) AEs or serious adverse event (SAEs) were reported. All AEs were transient, except for 1 patient who experienced ataxia and somnolence, which was reported as recovered with sequelae. Study drug was continued in 5 patients and was interrupt in 1 patient before being reintroduced. Three patients reporting AEs had treatment administered for the AE. Four of the 6 subjects were receiving concomitant antiepileptic drugs. There were no trends related to dose of study drug or days elapsed after first dose of study drug. The safety findings from paediatric patients remains comparable to that of the overall study population, and the incidence and profile of AEs was consistent with the known safety profile of perampanel.

CHMP discussion:
The six paediatric cases reported 14 AEs, none of which were serious or severe (grade 3). AEs reported include needle-prick-like sensation, fever, ataxia, cough, weight gain, irritability, somnolence, and vertigo. Ataxia, irritability, weight gain, somnolence, and vertigo are listed in the SmPC of perampanel. The AEs not listed were pyrexia, cough, and paraesthesia.

The MAH discussed paediatric cases, and corresponding CRFs for each patient were provided.

Fever was reported in two cases. The TTOs were 130 days and 138 days, respectively. In the first case, the AE reached grade 2 severity (moderate) and resolved within 4 days after treatment discontinuation

and subsequent reintroduction. There was no positive rechallenge. In the second case, the AE was grade 1 in severity and resolved within a day with specific treatment. Concomitant treatments included phenytoin, levetiracetam, and clobazam.

Cough was reported in one patient 118 days after the initiation of perampanel. The AE, graded as severity 1, resolved within a day. Perampanel treatment was continued. Concomitant treatments included phenytoin and clobazam, which have several respiratory AEs listed in their SmPCs. Therefore, causality was deemed unrelated to perampanel.

Paraesthesia, described as a needle-prick-like sensation, was reported by one patient. This AE first occurred 7 days after the initiation of treatment and was observed on days 18, 69, 74, 75, and 122. The AEs were of grade 1 severity and resolved on the same day without specific treatment or discontinuation of perampanel. However, due to the lack of information and the use of co-treatments (clobazam, levetiracetam, and zonisamide), all of which list paraesthesia in their prescribing information, it is not possible to draw any conclusions regarding the role of perampanel in this case.

Clarification has been provided regarding three cases of unrelated effects. The information presented does not allow for the identification of new safety findings concerning the pediatric use of perampanel.
Issue solved.

Agency Question 2
Three adolescent patients with generalized onset seizures have been included in this study. However, it is specified in the inclusion criteria that only patient with partial onset seizures will be included. The MAH is asked to justify the inclusion of these 3 patients that do not meet the inclusion criteria.

Company Response
In Study E2007-M091-508, inclusion criterion for determination of POS was "Patients prescribed Perampanel for the adjunctive treatment of partial-onset seizures based on independent clinical judgment". This description therefore does not exclude the presence of generalized onset seizures, as the two conditions can co-exist (Jeha et al, 2006; Wantanabe, 1989). The seizure history information recorded in the CRF is with regards to the first seizure only. Full seizure history data for each subject was not collected.

CHMP discussion:
Clarification regarding the inclusion of 3 adolescent patients with generalized onset seizures has been made. As the seizure history information recorded in the CRF is with regards to the first seizure only and not the full seizure history, patients with both partial-onset seizures and generalized onset seizures has been included.
Issue solved.