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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/P46/027

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	17 Jul 2023	17 Jul 2023	☐
☐	CHMP Rapporteur Assessment Report	21 Aug 2023	18 Aug 2023	☐
☐	CHMP members comments	04 Sep 2023	N/A	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Sep 2023	N/A	☐
☐	Request for supplementary information	14 Sep 2023	14 Sep 2023	☐
☐	Re-start	20 Sep 2023	20 Sep 2023	☐
☐	CHMP Rapporteur Assessment Report	27 Sep 2023	25 Sep 2023	☐
☐	CHMP members comments	02 Oct 2023	N/A	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Oct 2023	N/A	☐
☒	CHMP adoption of conclusions:	12 Oct 2023	12 Oct 2023	☐

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1. Introduction

On 19 June 2023, the MAH submitted a completed paediatric study for Fycompa 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 final study results and report related to paediatric population for Study E2007-M081-503 (referred to as Study 503). This study 503 was a specified Japanese prospective post-marketing observational study following approval of Fycompa Tablets 2 mg and 4 mg by the Japan Pharmaceuticals and Medical Devices Agency (PMDA). The purpose of Study 503 was to evaluate the long-term safety and efficacy of perampanel oral tablets in real-world adolescent epileptic patients, aged 12 to 17 years, with partial seizures (including secondary generalized seizures) or tonic-clonic seizures. No adult patients participated in this study.

The study enrolled 507 subjects (planned 500 subjects, 50 of which would have tonic-clonic seizures) all of whom were less than 18 years of age and treated with perampanel in the study.

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.

The Japanese regulatory procedure for this type of study requires that the CSR be reviewed by the PMDA before it can be considered as the final CSR. However, it will be several years until the PMDA review and approve the CSR for Study 503, which is likely to be 2025 – 2026. Therefore, Eisai has decided to submit Study 503 for Art. 46 review now, and if PMDA revise the CSR a further Art. 46 submission will be made within 6 months of the PMDA's decision.

This study was conducted to meet local (Japanese) regulations and was not part of the PIP obligations.

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 503 was Fycompa as 2 mg and 4 mg oral tablets. Perampanel was orally administered once daily before bedtime.

2.3. Clinical aspects

2.3.1. Introduction

This is a prospective post-marketing observational study conducted following approval the 28th March 2016 of Fycompa Tablets 2 mg and 4 mg in Japan. The study was conducted in accordance with the Risk Management Plan (RMP) and the protocol submitted to the PMDA the 15th April 2016.

2.3.2. Clinical study

Description/Methods

This is a prospective post-marketing observational study assessing the long-term safety and efficacy of Fycompa tablets in adolescent epileptic patients with partial seizure (including secondary generalized seizure) or tonic-clonic seizure in Japan.

Table 1: Observation schedule

Study items	CRF (1)					CRF (2)		CRF (1) (2) (only for patients who discontinued treatment)	
	4 weeks before administration	At the start of administration	At Week 12 of administration	At Week 24 of administration	At Week 52 of administration	At Week 76 of administration	At Week 104 of administration	At discontinuation Note 1)	At 4 weeks after discontinuation
Patient backgrounds	-	○	-	-	-	-	-	-	-
Use status of Fycompa	-	←	―	―	―	―	→	-	-
Concomitant medications	←	―	―	―	―	―	―	―	→
Concomitant therapy for epilepsy	←	―	―	―	―	―	―	―	→
Blood levels of oral antiepileptic drugs	←	―	―	―	―	―	―	―	→
Effects on the growth of children	-	○	○	○	○	○	○	○	○
Presence of influence (worsening) of Fycompa on developmental disorder or cognitive dysfunction	-	○	○	○	○	○	○	○	○
Seizure type and seizure frequency	○Note 2)	○	○	○	○	○	○	○	○
Overall improvement	-	-	○	○	○	○	○	○	-
Laboratory tests	←	―	―	―	―	―	―	―	→
Abuse	-	←	―	―	―	―	―	―	→
Dependency	-	-	-	-	-	-	-	-	○Note 3)
Adverse events	-	←	―	―	―	―	―	―	→

○: Performed, -: Not applicable

The observation period for a patient was 52 weeks after the start of administration of Fycompa and 104 weeks at maximum. If the administration of Fycompa was discontinued before Week 104 of treatment, a follow-up period of 4 weeks after discontinuation was anticipated.

Study participants

Inclusion criteria:

Patients with epilepsy aged 12 to 17 years and with partial seizures (including secondary generalized seizures) or tonic-clonic seizures

Exclusion criteria:

Patients with a history of treatment with Fycompa

Treatments

Fycompa® (perampanel) 2- and 4-mg Tablets

The usual oral dosage for adults and children 12 years of age or older is initially 2 mg once daily as perampanel at bedtime, and the daily dose may then be increased by 2 mg at intervals of 1 week or longer.

The maintenance dose is 8 mg once daily in the absence of concomitant antiepileptic drugs that accelerate the metabolism of this product, or 8 - 12 mg once daily in the presence of such concomitant drugs.

Dosage may be increased or decreased as necessary by 2 mg at intervals of 1 week or longer depending on the symptoms, but the maximum daily dose should not be over 12 mg.

Objective/outcomes/endpoints

This study was conducted to assess the safety and efficacy of Fycompa administered for a long period to adolescent epileptic patients with partial seizure (including secondary generalized seizure) or tonic-clonic seizure.

Safety endpoints:

- Unexpected adverse drug reactions (ADRs were defined as adverse events [AEs] for which a causal relationship with the study drug could not be ruled out; unexpected ADRs were defined as ADRs which is not listed in the Japanese perampanel PI)

- Occurrence of adverse reactions

- Factors that may affect the safety or efficacy

- Occurrence of adverse events related to dizziness, balance disorder, ataxia, and muscle relaxation and occurrence of falls

- Occurrence of adverse events related to psychiatric symptoms (aggression...)

Areas of safety of interest included: dizziness, balance disorder, ataxia and fall, hostility and aggression, muscle relaxation, dependence, suicidal ideation and suicidal behaviour, effects on the cardiovascular system, effects on the growth of children, and safety in epileptic patients with tonic-clonic seizure.

Efficacy endpoints:

- Presence of seizures by seizure type from 1 year to 4 weeks before the start of administration of perampanel. In addition, seizure frequency for each seizure type from the 4 weeks before to the evaluation point was investigated at the start of administration of perampanel, at Week 12, Week 24, Week 52, Week 76, and Week 104 (or at discontinuation and Week 4 after discontinuation).

- 50% responder rate (defined as the proportion of subjects with 50% or greater reduction in seizure frequency from baseline) at Weeks 12, 24, 52, 76, and 104 and by seizure type

- Overall improvement of a patient's conditions by the use of a 7-rank scale for "markedly improved", "considerably improved", "slightly improved", "unchanged", "slightly worsened", "considerably worsened", "markedly worsened", or "not assessable" at baseline and each evaluation time point. Efficacy evaluation criteria were defined as efficacy rates calculated based on the number of patients assessed as "markedly improved", "considerably improved", or "slightly improved".

Sample size

500 patients, with an aim to include 50 patients with tonic-clonic seizure among the total patients.

Rationale: 300 patients are required to detect at least 1 adverse event that occurs at a frequency of 1% with 95% confidence. On the assumption that the dropout rate until Week 52 after the start of administration of Fycompa is 40%, the planned number of patients to be registered was set at 500 to secure about 300 patients who completed the study during the 52-week observation period. The planned number of patients with tonic-clonic seizure in this study was set at 50, which is 10% of the total number of patients.

Randomisation and blinding (masking) / Statistical Methods

NA

Results

Participant flow

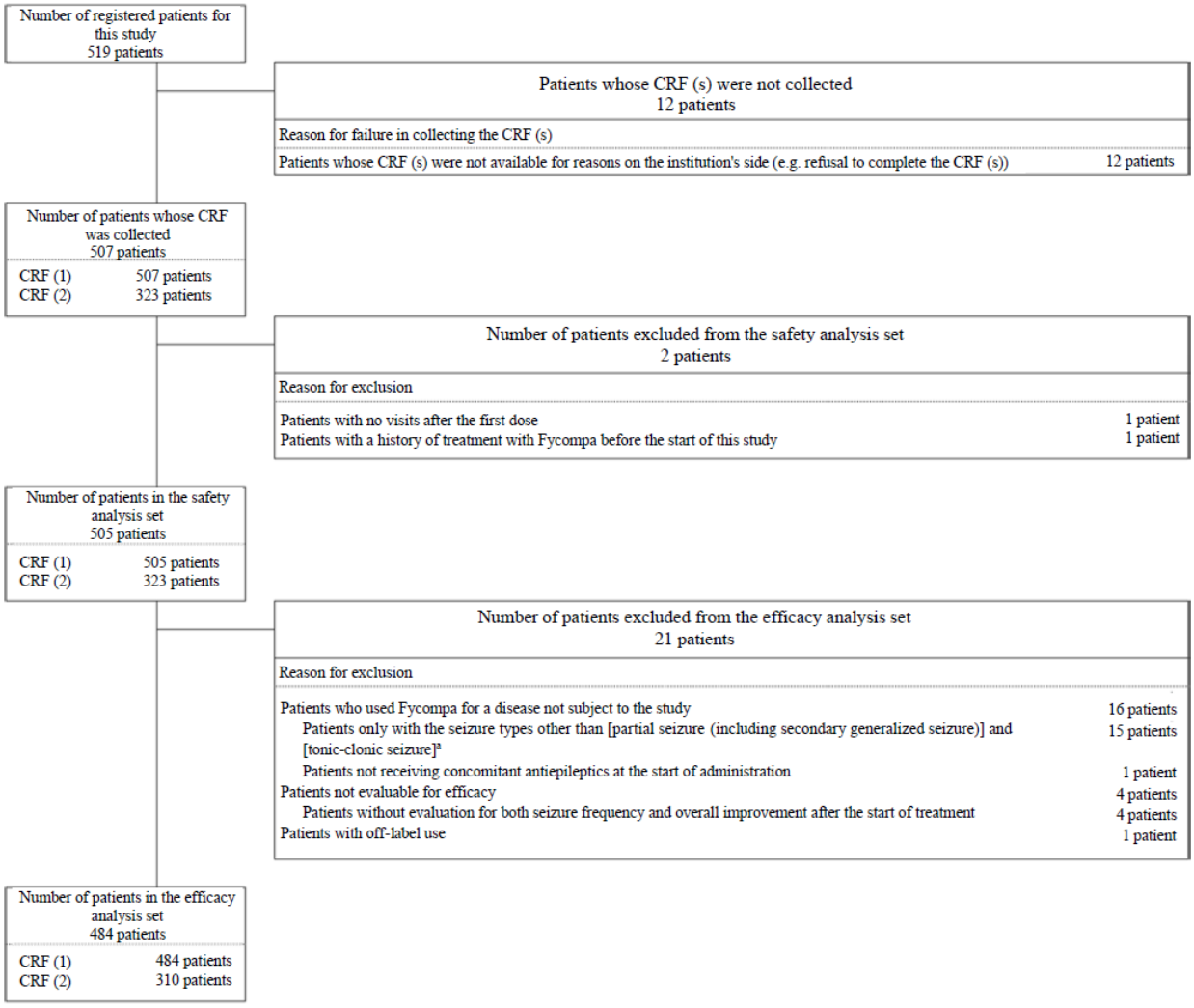
A total of 519 patients registered for this study, of which case report forms (CRFs) were retrieved from a total of 507 patients from 136 sites throughout Japan.

Of the 507 patients whose CRFs were obtained, 505 patients were included in the Safety Analysis Set and 484 patients were included in the Efficacy Analysis Set (see Figure below).

Two patients were excluded from the number of patients whose CRF was collected: 1 patient with no visits after the 1st dose and 1 patient with a history of treatment with perampanel before the start of this study.

Additional 21 patients were excluded from the Safety Analysis Set: 15 patients had a seizure type other than POS (including Secondary Generalized Seizures = SGS) or PGTCS for a year before the start of administration of perampanel, 1 patient did not receive concomitant antiepileptics at the start of administration, 4 patients were without evaluation for both seizure frequency and overall improvement after the start of administration, and 1 patient was reported with off-label use.

Figure 1:



a: Data were tallied by type of seizures observed within 1 year before the start of treatment.

<u>CHMP comment</u>:

The planned sample size of about 300 patients who completed the study during the 52-week observation period taking into account a dropout rate of 40% is achieved with 484 patients (and 310 patients at week 104) for the efficacy analysis set. The safety analysis set includes 505 patients at week 52 and 323 at week 104.

The patients' exclusion of the safety analysis do not raise any concern.

Recruitment/Baseline data/Number analysed

In the overall safety analysis set, the mean (SD) age of patients was 14.4 (±1.7) years, with a minimum age of 12 and maximum age of 17 years.

Males accounted for 59.41% (300/505) of patients in the overall safety analysis set:

Table 2: List of patient backgrounds

Item	Category	Patients in the safety analysis set		Patients in the efficacy analysis set	
		Number of patients	%	Number of patients	%
Number of patients analyzed		505		484	
Gender	Male	300	(59.41)	287	(59.30)
	Female	205	(40.59)	197	(40.70)
	No pregnancy/lactation[a]	205	(100.00)	197	(100.00)
Age (years)	12	106	(20.99)	101	(20.87)
	13	78	(15.45)	76	(15.70)
	14	81	(16.04)	79	(16.32)
	15	86	(17.03)	84	(17.36)
	16	77	(15.25)	71	(14.67)
	17	77	(15.25)	73	(15.08)
	Unknown	0	(0.00)	0	(0.00)
Age (years) Summary statistics	Number of patients	505		484	
	Mean ± standard deviation	14.4 ± 1.7		14.3 ± 1.7	
	Median	14.0		14.0	
	(Min, Max)	(12,17)		(12,17)	

The majority of patients had epilepsy for 10 or more years (319/505 [63.17%] patients).

Symptomatic epilepsy was reported for 405/505 (80.20%) patients and idiopathic epilepsy for 66/505 (13.07%) patients, while the epilepsy classification for 34/505 (6.73%) patients was "others/unknown".

The majority of patients (76.04% [384/505]) had partial epilepsy, 21.19% (107/505) of patients had generalized epilepsy and 2.77% (14/505) had undetermined epilepsy.

The most common seizure type was POS including SGS (71.49% [361/505] patients).

PGTCS were reported for 15.64% (79/505) patients.

Table 3:

Duration of disease (years)	< 1	25	(4.95)	23	(4.75)
	1≤ < 3	35	(6.93)	34	(7.02)
	3≤ < 5	28	(5.54)	28	(5.79)
	5≤ < 10	96	(19.01)	93	(19.21)
	10≤	319	(63.17)	304	(62.81)
	< 10	184	(36.44)	178	(36.78)
	10≤	319	(63.17)	304	(62.81)
	< 5	88	(17.43)	85	(17.56)
	5≤	415	(82.18)	397	(82.02)
	Unknown	2	(0.40)	2	(0.41)
Seizure type (Type of seizures that was observed at the start of administration of Fycompa)[h]	Partial seizures (including secondary generalized seizures)[b]	361	(71.49)	356	(73.55)
	Tonic-clonic seizure[b]	79	(15.64)	79	(16.32)
	Other seizure types than those mentioned above only (including patients without seizure/unknown)	78	(15.45)	62	(12.81)
Classification of epilepsy (Idiopathic/symptomatic)	Idiopathic	66	(13.07)	63	(13.02)
	Symptomatic	405	(80.20)	388	(80.17)
	Others/Unknown	34	(6.73)	33	(6.82)
Classification of epilepsy (partial/generalized)	Partial epilepsy[b]	384	(76.04)	374	(77.27)
	Generalized epilepsy[b]	107	(21.19)	97	(20.04)
	Undetermined epilepsy[b]	14	(2.77)	13	(2.69)
	Others/Unknown[b]	5	(0.99)	5	(1.03)

The majority of patients (45.15% [228/505]) had unknown aetiology; amongst patients with known aetiology, abnormal development of brain structure (15.64% [79/505]), and hereditary disease 13.86% [70/505]) were the most common.

Table 4:

Etiology of epilepsy	Hereditary disease[b]	70	(13.86)	64	(13.22)
	Abnormal development of brain structure[b]	79	(15.64)	74	(15.29)
	Perinatal event[b]	42	(8.32)	42	(8.68)
	Head trauma[b]	7	(1.39)	7	(1.45)
	Brain tumor[b]	12	(2.38)	10	(2.07)
	Cerebrovascular disorder[b]	15	(2.97)	15	(3.10)
	Degenerative disease[b]	3	(0.59)	3	(0.62)
	Brain infection[b]	35	(6.93)	34	(7.02)
	Immune diseases[b]	7	(1.39)	5	(1.03)
	Other[b]	30	(5.94)	28	(5.79)
	Unknown[b]	228	(45.15)	224	(46.28)

Developmental disorder or cognitive impairment was reported for 379/505 (75.05%) of patients.

Psychiatric symptoms (aggression…) or suicide-related actions within 2 years before the start of administration of perampanel were present in 13.86% (70/505) patients.

The most common symptom was aggression in 61.43% (43/70) patients.

There were no suicide-related behaviours.

Table 5:

Presence of developmental disorder or cognitive impairment	No	121	(23.96)	118	(24.38)
	Yes	379	(75.05)	361	(74.59)
	Unknown	5	(0.99)	5	(1.03)
Psychiatric symptoms (aggression, etc.) or suicide-related actions within 2 years before the start of administration of Fycompa Or suicide-related behavior	No	426	(84.36)	411	(84.92)
	Yes	70	(13.86)	67	(13.84)
	Aggression[d]	43	(61.43)	41	(61.19)
	Depression[d]	6	(8.57)	6	(8.96)
	Suicide-related behavior[d]	0	(0.00)	0	(0.00)
	Other[d]	26	(37.14)	25	(37.31)
	Unknown	9	(1.78)	6	(1.24)

The majority of patients in the overall safety analysis set used concomitant oral antiepileptics at the start of administration of perampanel (504/505 [99.80%]), of which 425/504 (84.33%) patients used 2 or more AEDs and 79/504 (15.67%) patients used 1 AED.

Concomitant use of EIAEDs was reported for 142/505 (28.12%) patients (at the start of administration of perampanel).

Table 6:

Presence of concomitant drugs (at the start of administration of Fycompa)	No	1	(0.20)	0	(0.00)
	Yes	504	(99.80)	484	(100.00)
Presence of concomitant drugs (during the observation period)	No	0	(0.00)	0	(0.00)
	Yes	505	(100.00)	484	(100.00)
Presence of concomitant therapies for epilepsy (at the start of administration of Fycompa)	No	487	(96.44)	467	(96.49)
	Yes	18	(3.56)	17	(3.51)
Concomitant use of antiepileptics that enhance metabolism of perampanel (at the start of administration of Fycompa)	No	363	(71.88)	345	(71.28)
	Yes	142	(28.12)	139	(28.72)
Concomitant use of major oral antiepileptics (at the start of administration of Fycompa)	No	1	(0.20)	0	(0.00)
	Yes	504	(99.80)	484	(100.00)

Table 7: Concomitant use of major oral antiepileptics (1 agent of concomitant oral antiepileptics)

		Patients in the safety analysis set		Patients in the efficacy analysis set	
		Number of patients (%)		Number of patients (%	
Number of patients analyzed		505		484	
Concomitant use of major oral antiepileptics at the start of administration of Fycompa	No	1	(0.20)	0	(0.00)
	Yes	504	(99.80)	484	(100.00)
Number of drugs[ac]	Concomitant use of ≥ 2 agents	425	(84.33)	408	(84.30)
	Concomitant use of 1 agent only	79	(15.67)	76	(15.70)
Names of concomitant drugs in patients receiving 1 concomitant drug only[b]	Levetiracetam	27	(34.18)	26	(34.21)
	Sodium valproate	18	(22.78)	17	(22.37)
	Lamotrigine	14	(17.72)	13	(17.11)
	Carbamazepine	8	(10.13)	8	(10.53)
	Clonazepam	3	(3.80)	3	(3.95)
	Clobazam	3	(3.80)	3	(3.95)
	Zonisamide	2	(2.53)	2	(2.63)
	Gabapentin	1	(1.27)	1	(1.32)
	Phenytoin	1	(1.27)	1	(1.32)
	Phenobarbital	1	(1.27)	1	(1.32)
	Lacosamide	1	(1.27)	1	(1.32)

Drugs concomitantly used at the start of administration of Fycompa are tallied.

a: The denominator is the number of patients with concomitant use.

b: The number of patients who concomitantly used only one drug is used as the denominator.

c: When drugs with the same generic name are used in a patient, they are counted as one drug.

CHMP comment:

In the safety analysis set, a panel of 505 patients were included in this study. All patients were aged between 12 and 17 years old. Males accounted for 59.41% (300/505) of patients. 319/505 [63.17%] patients had epilepsy for 10 or more years.

The most common seizure type was POS including SGS (71.49% [361/505] patients). PGTCS were reported for 15.64% (79/505) patients.

The majority of patients (45.15% [228/505]) had unknown aetiology; abnormal development of brain structure (15.64% [79/505]), and hereditary disease 13.86% [70/505]) were the most common known aetiology.

Developmental disorder or cognitive impairment was reported for 379/505 (75.05%) of patients. Psychiatric symptoms (aggression…) or suicide-related actions within 2 years before the start of administration of perampanel were present in 13.86% (70/505) patients. The most common symptom was aggression in 61.43% (43/70) patients. There were no suicide-related behaviours. The symptom "aggression" is commonly described in the epileptic population regardless of the antiepileptic perampanel treatment.

The majority of patients used concomitant oral antiepileptics at the start of administration of perampanel (504/505 [99.80%]), of which 425/504 (84.33%) patients used 2 or more AEDs and 79/504 (15.67%) patients used 1 AED. The most commonly drugs used in addition to perampanel were levetiracetam (34.18%), valproate (22.78%), lamotrigine (17.72%) and carbamazepine (10.13%).

Efficacy results

- Percent change in seizure frequency (by seizure type)

For the main seizure types, the median percent changes in seizure frequency at the time of the final evaluation were:

–50.00 for simple partial seizures (with motor signs),

–73.33 for simple partial seizures (without motor signs),

–28.57 for complex partial seizures,

–62.58 for secondary generalized seizures,

–20.00 for tonic-clonic seizures.

Table 8: Seizure frequency and percent change (by seizure type)

Seizure type	Summary statistics	At the start of administration		At Week 12 of administration		At Week 24 of administration		At the time of final evaluation	
		Observed value	% Change	Observed value	% Change*	Observed value	% Change*	Observed value	% Change*
Simple partial seizures (with motor signs)	Number of patients	56		44	38	45	40	58	50
	Mean ± standard deviation	37.6 ± 50.5	-	33.3±59.2	-22.08 ± 51.81	31.2±47.0	-33.19±56.87	26.3±43.0	-41.19± 53.13
	Median	20.0		8.0	-34.59	11.0	-32.29	9.0	-50.00
	(Min, Max)	(0,226)		(0,342)	(-100.0,150.0)	(0,240)	(-100.0,200.0)	(0,233)	(-100.0,200.0)
Simple partial seizures (without motor signs)	Number of patients	21		18	13	18	12	23	17
	Mean ± standard deviation	25.0 ± 40.7	-	7.6±9.5	-36.97 ± 42.06	9.0±16.0	-53.30±40.87	19.4±35.5	-56.21±45.24
	Median	6.0		3.0	-6.25	2.0	-50.00	4.0	-73.33
	(Min, Max)	(0,150)		(0,30)	(-100.0,0.0)	(0,62)	(-100.0,0.0)	(0,150)	(-100.0,0.0)
Complex partial seizures	Number of patients	256		217	204	191	178	261	239
	Mean ± standard deviation	55.3 ± 153.0	-	48.8±153.2	-17.68 ± 82.58	49.6±166.2	-28.69±63.08	44.9±151.3	-6.26± 246.87
	Median	10.0		8.0	-20.71	8.0	-28.57	6.0	-28.57
	(Min, Max)	(0,2000)		(0,2000)	(-100.0,600.0)	(0,2000)	(-100.0,400.0)	(0,2000)	(-100.0,2900.0)
Secondary generalized seizure	Number of patients	166		142	117	127	105	170	138
	Mean ± standard deviation	18.1 ± 56.0	-	9.6±26.2	-39.83 ± 81.81	8.4±28.8	-43.23±66.04	8.3±21.0	26.32±849.40
	Median	3.0		1.0	-50.00	1.0	-50.00	1.0	-62.58
	(Min, Max)	(0,588)		(0,200)	(-100.0,600.0)	(0,280)	(-100.0,300.0)	(0,112)	(-100.0,9900.0)
Partial seizures total	Number of patients	343		291	276	262	245	353	325
	Mean ± standard deviation	53.1 ± 140.3	-	44.7±142.1	-21.75 ± 81.86	44.1±149.2	-30.65±64.89	41.3±137.2	-20.62±159.48
	Median	12.0		8.0	-27.62	6.5	-39.68	6.0	-38.46
	(Min, Max)	(0,2080)		(0,2080)	(-100.0,600.0)	(0,2080)	(-100.0,400.0)	(0,2080)	(-100.0,1900.0)
Absence seizure	Number of patients	10		9	6	7	4	11	7
	Mean ± standard deviation	76.5 ± 152.2	-	62.8±115.0	-15.24 ± 43.10	48.2±126.5	-70.68±37.99	62.5±130.4	-21.43±36.91
	Median	4.0		4.0	-10.00	0.0	-81.25	4.0	0.00
	(Min, Max)	(0,420)		(0,300)	(-75.0,50.0)	(0,335)	(-100.0,-20.2)	(0,350)	(-100.0,0.0)
Myoclonic seizures	Number of patients	21		18	12	17	11	22	13
	Mean ± standard deviation	577.2±2167.7	-	57.3±91.9	-29.63 ± 34.94	59.5±109.5	-29.85±37.05	45.0±93.8	-22.04± 90.54
	Median	20.0		15.0	-19.44	8.0	-20.00	3.0	-50.00
	(Min, Max)	(0,9999)		(0,280)	(-100.0,0.0)	(0,300)	(-100.0,0.0)	(0,350)	(-100.0,242.9)
Tonic-clonic seizure	Number of patients	91		70	61	65	57	95	77
	Mean ± standard deviation	31.7 ± 81.0	-	19.0±45.9	-33.71 ± 50.31	35.0±144.3	-41.91±55.89	31.0±122.7	-12.45±164.76
	Median	4.0		2.0	-20.00	2.0	-50.00	2.0	-20.00
	(Min, Max)	(0,560)		(0,300)	(-100.0,150.0)	(0,1120)	(-100.0,150.0)	(0,1120)	(-100.0,1300.0)

- 50% responder rate

In the 484 patients included in the Efficacy Analysis Set, the 50% responder rate in seizure frequency at the time of the final evaluation was:

- 56.00% (28/50 patients) for simple POS (with motor signs),
- 58.82% (10/17 patients) for simple POS (without motor signs),
- 46.86% (112/239 patients) for complex POS,
- 57.97% (80/138 patients) for secondary generalized seizures,
- 41.56% (32/77 patients) for PGTCS.

Table 9: 50% responder rate in seizure frequency (by seizure type)

Seizure type	Item	At Week 12 of administration	At Week 24 of administration	At Week 52 of administration	At Week 76 of administration	At Week 104 of administration	At discontinuation	At the time of final evaluation
Simple partial seizures (with motor signs)	Number of patients[a]	38	40	36	28	25	17	50
	Number of patients who achieved 50% reduction (%)	16 (42.11)	18 (45.00)	24 (66.67)	18 (64.29)	19 (76.00)	4 (23.53)	28 (56.00)
	95% confidence interval	(26.31,59.18)	(29.26,61.51)	(49.03,81.44)	(44.07,81.36)	(54.87,90.64)	(6.81,49.90)	(41.25,70.01)
Simple partial seizures (without motor signs)	Number of patients[a]	13	12	10	7	6	9	17
	Number of patients who achieved 50% reduction (%)	6 (46.15)	8 (66.67)	8 (80.00)	6 (85.71)	5 (83.33)	3 (33.33)	10 (58.82)
	95% confidence interval	(19.22,74.87)	(34.89,90.08)	(44.39,97.48)	(42.13,99.64)	(35.88,99.58)	(7.49,70.07)	(32.92,81.56)
Complex partial seizures	Number of patients[a]	204	178	141	118	98	102	239
	Number of patients who achieved 50% reduction (%)	73 (35.78)	71 (39.89)	78 (55.32)	68 (57.63)	64 (65.31)	30 (29.41)	112 (46.86)
	95% confidence interval	(29.21,42.78)	(32.64,47.48)	(46.72,63.69)	(48.19,66.67)	(55.02,74.64)	(20.80,39.25)	(40.40,53.40)
Secondary generalized seizure	Number of patients[a]	117	105	87	73	69	45	138
	Number of patients who achieved 50% reduction (%)	68 (58.12)	59 (56.19)	67 (77.01)	50 (68.49)	50 (72.46)	16 (35.56)	80 (57.97)
	95% confidence interval	(48.64,67.18)	(46.17,65.86)	(66.75,85.36)	(56.56,78.87)	(60.38,82.54)	(21.87,51.22)	(49.28,66.32)
Partial seizures total	Number of patients[a]	276	245	198	158	137	131	325
	Number of patients who achieved 50% reduction (%)	106 (38.41)	106 (43.27)	120 (60.61)	91 (57.59)	89 (64.96)	38 (29.01)	156 (48.00)
	95% confidence interval	(32.64,44.42)	(36.97,49.72)	(53.43,67.46)	(49.49,65.41)	(56.35,72.91)	(21.41,37.58)	(42.45,53.58)
Absence seizure	Number of patients[a]	6	4	3	3	3	4	7
	Number of patients who achieved 50% reduction (%)	1 (16.67)	3 (75.00)	3 (100.00)	2 (66.67)	1 (33.33)	0 (0.00)	1 (14.29)
	95% confidence interval	(0.42,64.12)	(19.41,99.37)	(29.24,100.00)	(9.43,99.16)	(0.84,90.57)	(0.00,60.24)	(0.36,57.87)
Myoclonic seizures	Number of patients[a]	12	11	9	8	8	3	13
	Number of patients who achieved 50% reduction (%)	4 (33.33)	3 (27.27)	5 (55.56)	4 (50.00)	5 (62.50)	0 (0.00)	7 (53.85)
	95% confidence interval	(9.92,65.11)	(6.02,60.97)	(21.20,86.30)	(15.70,84.30)	(24.49,91.48)	(0.00,70.76)	(25.13,80.78)
Tonic-clonic seizure	Number of patients[a]	61	57	40	38	33	32	77
	Number of patients who achieved 50% reduction (%)	24 (39.34)	30 (52.63)	23 (57.50)	23 (60.53)	22 (66.67)	6 (18.75)	32 (41.56)
	95% confidence interval	(27.07,52.69)	(38.97,66.02)	(40.89,72.96)	(43.39,75.96)	(48.17,82.04)	(7.21,36.44)	(30.43,53.36)

CHMP comment:

Considering the efficacy data for both endpoints (50% responder rate and percent change of *seizure frequency), Fycompa is less effective in the treatment of complex partial seizures and tonic-clonic seizures than for simple partial seizures with or without motor signs or SGS, which is likely due to the more refractory condition of complex partial seizures and tonic-clonic seizures than POS.*

Through a multivariate analysis, 2 factors were found to have a statistically significant impact of the 50% responder rate.

Indeed, the 50% responder rate was lower in patients with developmental disorder or cognitive impairment, even whether the specific contributing factors were unknown and in the patients for which the baseline number of major concomitant oral AEDs was recorded as 2 or more AEDs which could be in case of a more refractory condition of the underlying disease in patients using more AEDs.

- Comparison to other results of phase 3 studies

For comparison, in Study 335, a Phase 3 study in subjects with POS, the 50% responder rate in seizure frequency was 19.4% (34/175 subjects) in the placebo group, 23.0% (40/174 subjects) in the 4 mg/day group, 36.0% (63/175 subjects) in the 8 mg/day group, and 43.3% (78/180 subjects) in the 12 mg/day group.

Table 10: 50% responder rate in seizure frequency in Phase 3 clinical study on partial seizure in epileptic patients (Study 335)

	Placebo group	4 mg/day group	8 mg/day group	12 mg/day group
50% responder rate in seizure frequency	19.4%	23.0%	36.0%	43.3%

CHMP comment:

Study 335 was assessed within the framework of a P46 procedure in February 2021 and was a phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel group study with an open-label extension phase in adults and adolescents aged 12 years and older who had a diagnosis of inadequately controlled partial-onset seizures. The study was conducted in Australia, China, Korea, Japan, Malaysia, Taiwan, and Thailand. Subjects were randomized to 1 of 4 treatment groups (4, 8, 12 mg/day of perampanel, or placebo) in a 1:1:1:1 ratio. The study randomised 710 subjects (planned 680 subjects, 170 subjects per treatment group) into the Core phase, 73 of whom were less than 18 years of age. The primary objective of Study 335 was to confirm the efficacy of perampanel (4, 8, and 12 mg) compared to placebo given as an adjunctive therapy in subjects with refractory partial-onset seizures. The secondary objectives were a) to evaluate the safety and tolerability of perampanel compared to placebo given as an adjunctive therapy in subjects with refractory partial-onset seizures, b) to evaluate the long-term maintenance effect of perampanel (4, 8, and 12 mg) given as an adjunctive therapy in subjects with refractory partial-onset seizures. Of the 679 subjects of the Safety Analysis Set, 73 (around 10%) subjects were aged 12 to <18 years.

Even whether the provided study 335 data are interesting, their relevance for comparison with those of study 503 is not considered adequate in particular since the study methodology, the included population and the dosing groups are different.

The results of study 503 indicate that the responder rate in the adolescent population is distributed between around 40 and 60% as follows, with the smallest rate of responders in case of PGTCS:

- *56.00% (28/50 patients) for simple POS (with motor signs),*
- *58.82% (10/17 patients) for simple POS (without motor signs),*
- *57.97% (80/138 patients) for SGS,*
- *46.86% (112/239 patients) for complex POS,*
- *41.56% (32/77 patients) for PGTCS.*

These efficacy results confirm the known efficacy profile of perampanel in the adolescent population.

According to the Applicant, in Study 332, a Phase 3 study in PGTCS, the incidence was 39.5% (32/81 subjects) in the placebo group and 64.2% (52/81 subjects) in the 8 mg/day group, were considered similar to those in this study.

Table 11: 50% responder rate in seizure frequency in Phase 3 clinical study on tonic-clonic seizure in epileptic patients (Study 332)

	Placebo group	8 mg/day group
50% responder rate in seizure frequency	39.5%	64.2%

CHMP comment:

The CSR of the Core Study 332 is dated 19 Aug 2014 and the Final CSR of the Extension Study is dated 24 Feb 2016. Study 332 was a double-blind, randomized, placebo-controlled, multicenter, parallel-group study with an open-label extension phase to assess the efficacy and safety of adjunctive perampanel in primary generalized tonic-clonic seizures in subjects with epilepsy aged 12 years and older. The primary objective was to demonstrate the efficacy of adjunctive perampanel therapy, compared to placebo on PGTC seizures. The secondary objective was to evaluate the safety and tolerability of perampanel in subjects with inadequately controlled PGTC seizures.

In spite of knowledge that such an indirect comparison has no robust value, the MAH is asked to clarify to what extent the 50% responder rate on PGTCS in study 332 in the 8 mg perampanel group (64.2%) could be considered "similar" (according to the Applicant) to the 50% responder rate on PGTCS in study 503 in the overall perampanel group (41.56%). Moreover, according to the provided results, the 50% responder rate on PGTCS in study 503 (41.56%) is even rather similar to the 50% responder rate on PGTCS in study 503 in the placebo group (39.50%).

- Overall improvement

The efficacy rate of overall improvement (number of patients assessed as "markedly improved", "considerably improved", or "slightly improved"/total number of the patients excluding those assessed as "not assessable") at the time of the final evaluation was as follows for the following parameters:

- Intensity of seizure, 50.43% (232/460 patients)
- Duration of seizure, 45.41% (208/458 patients)
- Activity level of daily living, 37.08% (175/472 patients)
- Overall improvement, 50.63% (240/474 patients)

Table 12: Overall improvement

Item	Category	At Week 12 of administration			At Week 24 of administration			At the time of final evaluation		
		Number of patients	(%)	Number of effective cases Efficacy rate (%) (95% confidence interval)	Number of patients	(%)	Number of effective cases Efficacy rate (%) (95% confidence interval)	Number of patients	(%)	Number of effective cases Efficacy rate (%) (95% confidence interval)
Seizure intensity	Number of patients evaluated	399			360			482		
	Markedly improved	32	(8.02)	215	36	(10.00)	210	62	(12.86)	232
	Considerably improved	53	(13.28)	(55.84)	61	(16.94)	(60.17)	74	(15.35)	(50.43)
	Slightly improved	130	(32.58)	(50.73,60.87)	113	(31.39)	(54.82,65.35)	96	(19.92)	(45.77,55.10)
	Unchanged	165	(41.35)		132	(36.67)		196	(40.66)	
	Slightly worsened	3	(0.75)		5	(1.39)		25	(5.19)	
	Considerably worsened	2	(0.50)		2	(0.56)		5	(1.04)	
	Markedly worsened	0	(0.00)		0	(0.00)		2	(0.41)	
	Not assessable	14	(3.51)	-	11	(3.06)	-	22	(4.56)	-
Duration of seizure	Number of patients evaluated	399			360			482		
	Markedly improved	31	(7.77)	185	34	(9.44)	190	63	(13.07)	208
	Considerably improved	43	(10.78)	(48.43)	54	(15.00)	(54.91)	68	(14.11)	(45.41)
	Slightly improved	111	(27.82)	(43.32,53.57)	102	(28.33)	(49.50,60.24)	77	(15.98)	(40.79,50.10)
	Unchanged	194	(48.62)		147	(40.83)		232	(48.13)	
	Slightly worsened	3	(0.75)		7	(1.94)		14	(2.90)	
	Considerably worsened	0	(0.00)		2	(0.56)		3	(0.62)	
	Markedly worsened	0	(0.00)		0	(0.00)		1	(0.21)	
	Not assessable	17	(4.26)	-	14	(3.89)	-	24	(4.98)	-
Daily activity	Number of patients evaluated	399			360			482		
	Markedly improved	16	(4.01)	145	22	(6.11)	150	45	(9.34)	175
	Considerably improved	44	(11.03)	(36.62)	52	(14.44)	(41.78)	52	(10.79)	(37.08)
	Slightly improved	85	(21.30)	(31.86,41.57)	76	(21.11)	(36.63,47.07)	78	(16.18)	(32.71,41.61)
	Unchanged	228	(57.14)		191	(53.06)		243	(50.41)	
	Slightly worsened	20	(5.01)		13	(3.61)		35	(7.26)	
	Considerably worsened	3	(0.75)		4	(1.11)		16	(3.32)	
	Markedly worsened	0	(0.00)		1	(0.28)		3	(0.62)	
	Not assessable	3	(0.75)	-	1	(0.28)	-	10	(2.07)	-
Overall improvement	Number of patients evaluated	399			360			482		
	Markedly improved	31	(7.77)	229	32	(8.89)	221	57	(11.83)	240
	Considerably improved	69	(17.29)	(57.83)	81	(22.50)	(61.90)	75	(15.56)	(50.63)
	Slightly improved	129	(32.33)	(52.79,62.74)	108	(30.00)	(56.65,66.97)	108	(22.41)	(46.03,55.22)
	Unchanged	157	(39.35)		123	(34.17)		172	(35.68)	
	Slightly worsened	7	(1.75)		9	(2.50)		49	(10.17)	
	Considerably worsened	3	(0.75)		3	(0.83)		10	(2.07)	
	Markedly worsened	0	(0.00)		1	(0.28)		3	(0.62)	
	Not assessable	3	(0.75)	-	3	(0.83)	-	8	(1.66)	-

CHMP comment:

A multivariate analysis was performed for the overall improvement and 3 factors were found to have a statistically significant impact on their results.

The efficacy rate of overall improvement was lower:

- in patients for which duration of disease was 5 years or longer (47.59% vs 58.82 [<5 years]) likely due to the refractory conditions associated with longer duration of disease.

- in patients with psychiatric symptoms (aggression…) or suicide-related actions within 2 years before the start of administration of perampanel compared to patients without these symptoms (33.33% vs 52.93%).

- in patients with concomitant use of antiepileptics that were EIAEDs; it could be suspected that patients receiving EIAEDs may have had decreased blood levels of perampanel, which could have affected the results. However, blood samples for pharmacokinetic analysis were not collected in this study to confirm this assumption.

Overall, the incidence of ADRs was higher in patients with a history of psychiatric symptoms (61.43%) than those without (38.97%), even whether the specific contributing factors were unknown.

Safety results

- Extent of Exposure

Most patients in the overall safety analysis set received an initial perampanel dose of 2 mg/day (318/505 [62.97%] patients) of which 98/149 (65.77%) patients received concomitant EIAEDs (ie, carbamazepine, phenytoin).

The mean total treatment period of perampanel (excluding an interruption period) in the overall safety analysis set was 70.16 weeks and for patients receiving EIAEDs it was 65.57 weeks.

The average of the mean daily dose in the overall safety analysis set was 4.42 mg and the average of maximum daily dose was 5.95 mg. For patients receiving EIAEDs, the average of the mean daily dose was 4.86 and the average of maximum daily dose was 6.62 mg.

About half of the patients completed the study (255/505 [50.50%]) with 250/505 [49.50%]) discontinuing. Most common reasons for discontinuation were AEs (121/250 [48.40%]) and inadequate response (117/250 [46.80%]).

Table 13: Presence of discontinuation, reason for discontinuation, and presence of withdrawal symptoms

Item	Item	CRF (1) (from start of administration to Week 52)				CRF (1) (2) (from start of administration to Week 104)			
		Patients in the safety analysis set		Patients in the efficacy analysis set		Patients in the safety analysis set		Patients in the efficacy analysis set	
		Number of patients	%	Number of patients	%	Number of patients	%	Number of patients	%
Number of patients analyzed		505		484		505		484	
Presence of discontinuation of Fycompa treatment	No	324	(64.16)	311	(64.26)	255	(50.50)	245	(50.62)
	Yes	181	(35.84)	173	(35.74)	250	(49.50)	239	(49.38)
Reason for discontinuation[a] (Duplicate count)	Stop visiting the hospital halfway	12	(6.63)	12	(6.94)	30	(12.00)	30	(12.55)
	Inadequate response	81	(44.75)	80	(46.24)	117	(46.80)	113	(47.28)
	Adverse events	104	(57.46)	97	(56.07)	121	(48.40)	114	(47.70)
	Symptoms improved	1	(0.55)	1	(0.58)	2	(0.80)	2	(0.84)
	Other	6	(3.31)	6	(3.47)	8	(3.20)	8	(3.35)
Presence of withdrawal symptoms[b]	No	166	(98.22)	158	(98.14)	215	(97.73)	204	(97.61)
	Yes	1	(0.59)	1	(0.62)	2	(0.91)	2	(0.96)
	Unknown	2	(1.18)	2	(1.24)	3	(1.36)	3	(1.44)

a: The denominator is the number of patients who discontinued.
b: The denominator is the number of patients excluding the patients whose reason for discontinuation is death caused by adverse events, and the patients who discontinued treatment with the reason of "stop visiting the hospital halfway."

- Adverse events

In the overall safety analysis set, 388 AEs occurred in 242 patients (242/505 [47.92%]).

Table 14: Occurrence of adverse events by seriousness

Number of patients analyzed	505		
Seriousness	Serious	Non-serious	Total
Number of patients with events	26	216	242
Number of events	47	341	388
Incidence	5.15%	42.77%	47.92%

A total of 213 patients (213/505 [42.18%]) reported 288 AEs that were considered ADRs.

Table 15: Occurrence of adverse reactions by seriousness

Number of patients analyzed	505		
Seriousness	Serious	Non-serious	Total
Number of patients with events	9	204	213
Number of events	15	273	288
Incidence	1.78%	40.40%	42.18%

The most common types of ADRs (by system organ class [SOC] with incidence ≥10.00%), were nervous system disorders (110/505 [21.78%]) and psychiatric disorders (99/505 [19.60%]).

Common ADRs (by preferred term [PT] with incidence ≥ 5.00%), included somnolence (68/505 [13.47%]), irritability (43/505 [8.51%]), and dizziness (26/505 [5.15%]).

Table 16:

Nervous system disorders	4 (0.79)	106 (20.99)	110 (21.78)
Altered state of consciousness	1 (0.20)	0 (0.00)	1 (0.20)
Amnesia	0 (0.00)	1 (0.20)	1 (0.20)
Ataxia	0 (0.00)	1 (0.20)	1 (0.20)
Atonic seizures	0 (0.00)	1 (0.20)	1 (0.20)
Coma	1 (0.20)	0 (0.00)	1 (0.20)
Dizziness	0 (0.00)	26 (5.15)	26 (5.15)
Drop attacks	0 (0.00)	1 (0.20)	1 (0.20)
Drug withdrawal convulsions	0 (0.00)	1 (0.20)	1 (0.20)
Epilepsy	1 (0.20)	15 (2.97)	16 (3.17)
Headache	0 (0.00)	4 (0.79)	4 (0.79)
Hypersomnia	0 (0.00)	2 (0.40)	2 (0.40)
Somnolence	2 (0.40)	66 (13.07)	68 (13.47)
Status epilepticus	1 (0.20)	0 (0.00)	1 (0.20)
Psychiatric disorders	1 (0.20)	98 (19.41)	99 (19.60)
Aggression	0 (0.00)	12 (2.38)	12 (2.38)
Agitation	1 (0.20)	23 (4.55)	24 (4.75)
Anger	0 (0.00)	8 (1.58)	8 (1.58)
Enuresis	0 (0.00)	1 (0.20)	1 (0.20)
Euphoric mood	0 (0.00)	1 (0.20)	1 (0.20)
Impulsive behaviour	0 (0.00)	1 (0.20)	1 (0.20)
Insomnia	0 (0.00)	3 (0.59)	3 (0.59)
Intentional self-injury	0 (0.00)	3 (0.59)	3 (0.59)
Irritability	0 (0.00)	43 (8.51)	43 (8.51)
Mood altered	0 (0.00)	1 (0.20)	1 (0.20)
Poriomania	0 (0.00)	1 (0.20)	1 (0.20)
Restlessness	0 (0.00)	2 (0.40)	2 (0.40)
Stereotypy	0 (0.00)	1 (0.20)	1 (0.20)
Suicidal ideation	0 (0.00)	3 (0.59)	3 (0.59)
Affect lability	0 (0.00)	4 (0.79)	4 (0.79)
Dysphemia	0 (0.00)	1 (0.20)	1 (0.20)
Abnormal behaviour	0 (0.00)	1 (0.20)	1 (0.20)
Psychiatric symptom	0 (0.00)	2 (0.40)	2 (0.40)
Persistent depressive disorder	0 (0.00)	1 (0.20)	1 (0.20)
Obsessive-compulsive symptom	0 (0.00)	2 (0.40)	2 (0.40)

CHMP comment:

According to the Applicant, the incidence of ADRs in this study (42.18%) was lower than the incidence rate of ADRs reported in the studies conducted at the time of approval (620/860 [72.09%]).

Table 2-10 Comparison of incidence of adverse reactions between at the time of approval and in this study

	Number of patients	Number of patients with adverse reactions	Incidence of adverse reactions
Clinical Study (At the time of approval)	860	620	72.09%
This study	505	213	42.18%

The adverse reactions with higher incidence at the time of approval (with the incidence of ≥5.00%) include "dizziness" in 40.47% (348/860), "somnolence" in 20.23% (174/860), and "irritability" in 6.16% (53/860). In this study, the 3 most frequently reported adverse reactions were overall the same even whether irritability is observed with a slightly higher frequency in this study (8.51% vs 6.16%). The overall under-notification is not unexpected and rather common for products that are on the market since some years.

A total of 142 AEs leading to discontinuation of study drug administration were reported in 122 patients (122/505 [24.16%]), of which the most common AEs reported included psychiatric disorders (66/505 [13.07%]) and nervous system disorders (47/505 [9.31%]).

Table 17: Occurrence of adverse events leading to discontinuation of administration

Number of patients analyzed	505		
Seriousness	Serious	Non-serious	Total
Number of patients with events	8	114	122
Number of events	12	130	142
Incidence	1.58%	22.57%	24.16%

The proportion of "patients discontinuing Fycompa" decreased when the initial titration interval became longer, and significant differences were observed in odds ratio for "≥ 4 weeks" (OR=0.211, P<0.001) compared to "< 2 weeks."

The proportion of patients with "occurrence of adverse reactions" decreased when the initial interval of dose escalation increased. Significant differences were observed for "≥ 2 to < 4 weeks" (OR=0.441, P=0.029) and "≥ 4 weeks" (OR=0.298, P<0.001) compared to "< 2 weeks."

Table 18: Interval of initial dose increase, rate of discontinuation, and incidence of adverse reactions for Fycompa

Item	Factor	Category	Number of patients	Number of patients who discontinued treatment	Proportion of discontinuation (%)	Odds ratio	95% CI for odds ratio	*P* value
Discontinuation of Fycompa treatment	Initial dose	< 2 mg/day	185	89	(48.11)			
		≥ 2 mg/day	320	161	(50.31)	1.092	(0.760,1.569)	0.633
	Interval of initial dose titration	< 2 weeks	45	33	(73.33)			
		≥ 2 weeks and < 4 weeks	90	53	(58.89)	0.521	(0.238,1.140)	0.102
		≥ 4 weeks	308	113	(36.69)	0.211	(0.105,0.424)	<0.001
Item	Factor	Category	Number of patients	Occurrence of adverse reactions Number of patients	Adverse reactions Incidence (%)	Odds ratio	95% CI for odds ratio	*P* value
Development of adverse reactions	Initial dose	< 2 mg/day	185	80	(43.24)			
		≥ 2 mg/day	320	133	(41.56)	0.933	(0.647,1.346)	0.712
	Interval of initial dose titration	< 2 weeks	45	29	(64.44)			
		≥ 2 weeks and < 4 weeks	90	40	(44.44)	0.441	(0.211,0.924)	0.029
		≥ 4 weeks	308	108	(35.06)	0.298	(0.155,0.573)	<0.001

CHMP comment:

In patients who had their perampanel dose increased at least once in the safety analysis set, the proportion of patients discontinuing perampanel decreased when the initial titration interval became longer, with a significant difference observed after 4 weeks compared to under 2 weeks.

Also, the proportion of patients with adverse reactions decreased when the initial interval of dose escalation increased, a significant difference was observed after 2 weeks upwards.

This observation confirms that the most appropriate mode of administration to ensure safety is a personalized increasing dose in a smooth dose escalation manner conducted on a sufficient titration interval.

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

There were 3 deaths reported for this study; however, 1 of the 3 deaths (endotracheal haemorrhage that could not be arrested) was outside of the 2-year study observation period. Of the 2 deaths that were within the 2-year study observation period, 1 patient died of unknown causes (AE reported term of "death") and 1 patient died from the reported AE of "influenza pneumonia".

A total of 47 serious adverse events (SAEs) occurred in 26 patients (26/505 [5.15%]). Common SAEs (by SOC with the incidence of ≥2.00%), included infections and infestations (15/505 [2.97%]). Common SAEs (by PT with the incidence of ≥1.00%), included pneumonia (10/505 [1.98%]).

A total of 15 serious ADRs occurred in 9 patients (9/505 [1.78%]). Common types of serious ADRs (by SOC, with incidence ≥0.50%), included nervous system disorders (4/505 [0.79%]), and respiratory, thoracic, and mediastinal disorders (3/505 [0.59%]). Common serious ADRs (by PT, with incidence ≥ 0.40%), included somnolence (2/505 [0.40%]).

Occurrence of AEs related to dizziness, balance disorder, ataxia, and muscle relaxation and occurrence of falls caused by these AEs as well as occurrence of AEs related psychiatric symptoms (aggression…) were considered as AEs of important interest in this study.

In addition, unexpected ADRs (defined as ADRs which is not listed in the Japanese perampanel PI) were also evaluated:

- A total of 32 unexpected ADRs occurred in 24 patients (24/505 [4.75%]), most of which were non-serious and each PT occurred in less than 0.6% of patients.
- A total of 31 AEs of dizziness occurred in 27 patients (27/505 [5.35%]) of which 30 in 26 patients (26/505 [5.15%]) were considered ADRs. No serious events occurred.
- There was no occurrence of AEs or ADRs of balance disorder.
- A total of 1 ataxia-related AE occurred in 1 patient (1/505 [0.20%]). This event was considered an ADR. No serious events occurred.
- A total of 6 muscle relaxation-related AEs occurred in 6 patients (6/505 [1.19%]), of which 5 events in 5 patients (5/505 [0.99%]) were considered to be ADRs. No serious events occurred.
- A total of 1 fall and injury-related AE resulting from AEs related to dizziness, balance disorder, ataxia, and muscle relaxation occurred in 1 patient each (1/505 [0.20%]). This event was considered an ADR. No serious events occurred.
- A total of 105 hostility- and aggression-related AEs occurred in 96 patients (96/505 [19.01%]) of which 3 events in 3 patients (3/505 [0.59%]) were SAEs; 100 of these events in 93 patients (93/505 [18.42%]) were considered ADRs and 1 of these ADRs in 1 patient (1/505 [0.20%]) was a SAE.

CHMP comment:

The three reported deaths in this study are not considered related to the perampanel treatment.

In addition to the SAE and AESI, unexpected ADRs (defined as ADRs which is not listed in the Japanese perampanel package insert) were also assessed. For more details regarding the specific ADR, see later on in the AR. Most AE were ADR and non-serious. Overall, no new or unexpected AE is raised during this study.

- ➢ Other safety findings

- Presence of abuse/dependency

No SAEs of abuse or dependency occurred.

- Occurrence of psychiatric disorder-related adverse events

A total of 120 psychiatric disorder-related AEs occurred in 102 patients (102/505 [20.20%]). A total of 3 SAEs occurred in 3 patients (3/505 [0.59%]). Of these, 115 events in 99 patients (99/505 [19.60%]) were considered ADRs of which 1 serious ADR (agitation) occurred in 1 patient (1/505 [0.20%]).

Furthermore, a higher incidence in psychiatric disorder-related AEs were also reported for patients with recorded psychiatric symptoms (aggression…) or suicide-related actions within 2 years before the start of administration of perampanel. The possible reason for this being that these AEs may occur more easily in the presence of history of psychiatric symptoms.

- Occurrence of suicide-related adverse events

Table 19: Occurrence of suicide-related adverse reactions

Number of patients analyzed	505		
Seriousness	Serious	Non-serious	Total
Number of patients with events	0	6	6
Number of events	0	6	6
Incidence	0.00%	1.19%	1.19%
SOC/PT	Number of patients with events (incidence, %) by SOC/PT		
Psychiatric disorders	0 (0.00)	6 (1.19)	6 (1.19)
Intentional self-injury	0 (0.00)	3 (0.59)	3 (0.59)
Suicidal ideation	0 (0.00)	3 (0.59)	3 (0.59)

When the same event occurred more than once in a patient, it was counted as 1 event. MedDRA/J version (24.0)
When both serious and non-serious events with the same term occur in a patient, the serious one is counted as 1 event.

Table 20: Occurrence of suicide-related adverse events by patient background factor (multivariate)

Factor	Category	Number of patients	Number of patients with events	Incidence (%)	Odds ratio	95% CI for odds ratio	*P* value
Gender	Male	300	4	(1.33)			
	Female	205	2	(0.98)	-	-	-
Age (years)	< 15	265	3	(1.13)			
	15≤	240	3	(1.25)	-	-	-
Body weight (kg) (at the start of administration of Fycompa)	< 30	97	0	(0.00)			
	30≤ < 50	194	3	(1.55)	-	-	-
	50≤	120	1	(0.83)	-	-	-
Seizure type (Type of seizures that was observed at the start of administration of Fycompa)[d]	Partial seizures (including secondary generalized seizures)[ab]	361	4	(1.11)	-	-	-
	Tonic-clonic seizure[ab]	79	1	(1.27)	-	-	-
Classification of epilepsy (Idiopathic/symptomatic)	Idiopathic[ab]	66	2	(3.03)	-	-	-
	Symptomatic[ab]	405	3	(0.74)	-	-	-
Duration of disease (years)	< 5	88	1	(1.14)			
	5≤	415	5	(1.20)	-	-	-
Psychiatric symptoms (aggression, etc.) or suicide-related actions within 2 years before the start of administration of Fycompa	No	426	2	(0.47)			
	Yes	70	4	(5.71)	17.632	(1.802,172.469)	0.013
Presence of developmental disorder or cognitive impairment	No	121	2	(1.65)			
	Yes	379	4	(1.06)	-	-	-
Concomitant use of antiepileptics that enhance metabolism of perampanel	No	363	5	(1.38)			
	Yes	142	1	(0.70)	-	-	-
Number of major concomitant oral antiepileptics[c] (at the start of administration of Fycompa)	1	79	1	(1.27)			
	2≤	425	5	(1.18)	-	-	-

a: Duplicate count.
b: Compared with patients not classified to each category.
c: When drugs with the same generic name are used in a patient, they are counted as one drug.
d: Data were tallied by type of seizures observed within 4 weeks before the start of treatment.

A total of 6 suicide-related AEs occurred in 6 patients (6/505 [1.19%]), including 3 patients with intentional self-injury and 3 patients with suicidal ideation. All these events were considered to be ADRs. No serious events occurred.

The higher incidence of ADRs in patients with a history of psychiatric symptoms (aggression…) or suicide-related behaviour within 2 years before the start of administration of perampanel (61.43% versus 38.97%) is explained by the fact that patients with a history of psychiatric symptoms were more likely to develop adverse reactions of psychiatric symptoms.

As a result of multivariate analysis, the following factors showed a significant difference with OR >1: For the factor of "psychiatric symptoms (such as aggression) or suicide-related behaviors within 2 years before the start of administration of Fycompa," a significant difference was observed in the patients with the condition versus those without the condition (OR=17.632, P=0.013).

- Occurrence of central nervous system adverse events

A total of 138 central nervous system AEs occurred in 120 patients (120/505 [23.76%]). Common AEs (by PT with the incidence of ≥3.00%) included somnolence (71/505 [14.06%]), dizziness (27/505 [5.35%]), and epilepsy (20/505 [3.96%]). A total of 10 SAEs occurred in 8 patients (8/505 [1.58%]); the most common SAEs were status epilepticus (3/505 [0.59%]) and somnolence (2/505 [0.40%]).

Table 21: Occurrence of central nervous system adverse events

Number of patients analyzed	505		
Seriousness	Serious	Non-serious	Total
Number of patients with events	8	112	120
Number of events	10	128	138
Incidence	1.58%	22.18%	23.76%
SOC/PT	Number of patients with events (incidence, %) by SOC/PT		
Nervous system disorders	8 (1.58)	112 (22.18)	120 (23.76)
Altered state of consciousness	1 (0.20)	0 (0.00)	1 (0.20)
Amnesia	0 (0.00)	1 (0.20)	1 (0.20)
Ataxia	0 (0.00)	1 (0.20)	1 (0.20)
Atonic seizures	0 (0.00)	1 (0.20)	1 (0.20)
Coma	1 (0.20)	0 (0.00)	1 (0.20)
Dizziness	0 (0.00)	27 (5.35)	27 (5.35)
Drop attacks	0 (0.00)	1 (0.20)	1 (0.20)
Drug withdrawal convulsions	0 (0.00)	1 (0.20)	1 (0.20)
Encephalopathy	1 (0.20)	0 (0.00)	1 (0.20)
Epilepsy	1 (0.20)	19 (3.76)	20 (3.96)
Generalised tonic-clonic seizure	0 (0.00)	1 (0.20)	1 (0.20)
Headache	0 (0.00)	5 (0.99)	5 (0.99)
Hypersomnia	0 (0.00)	2 (0.40)	2 (0.40)
Somnolence	2 (0.40)	69 (13.66)	71 (14.06)
Status epilepticus	3 (0.59)	0 (0.00)	3 (0.59)
Focal dyscognitive seizures	1 (0.20)	0 (0.00)	1 (0.20)

When the same event occurred more than once in a patient, it was counted as 1 event. MedDRA/J version (24.0)
When both serious and non-serious events with the same term occur in a patient, the serious one is counted as 1 event.

CHMP comment:

The Applicant is asked to provide the narratives and outcomes of the three cases of status epilepticus.

A total of 124 central nervous system ADRs occurred in 110 patients (110/505 [21.78%]). Common ADRs (by PT with the incidence of ≥3.00%) included somnolence (68/505 [13.47%]), dizziness (26/505 [5.15%]), and epilepsy (16/505 [3.17%]). A total of 6 serious ADRs occurred in 4 patients (4/505

[0.79%]); of which somnolence (2/505 [0.40%]) was the only serious ADR reported by more than 1 patient.

Table 22:

Number of patients analyzed	505		
Seriousness	Serious	Non-serious	Total
Number of patients with events	4	106	110
Number of events	6	118	124
Incidence	0.79%	20.99%	21.78%
SOC/PT	Number of patients with events (incidence, %) by SOC/PT		
Nervous system disorders	4 (0.79)	106 (20.99)	110 (21.78)
Altered state of consciousness	1 (0.20)	0 (0.00)	1 (0.20)
Amnesia	0 (0.00)	1 (0.20)	1 (0.20)
Ataxia	0 (0.00)	1 (0.20)	1 (0.20)
Atonic seizures	0 (0.00)	1 (0.20)	1 (0.20)
Coma	1 (0.20)	0 (0.00)	1 (0.20)
Dizziness	0 (0.00)	26 (5.15)	26 (5.15)
Drop attacks	0 (0.00)	1 (0.20)	1 (0.20)
Drug withdrawal convulsions	0 (0.00)	1 (0.20)	1 (0.20)
Epilepsy	1 (0.20)	15 (2.97)	16 (3.17)
Headache	0 (0.00)	4 (0.79)	4 (0.79)
Hypersomnia	0 (0.00)	2 (0.40)	2 (0.40)
Somnolence	2 (0.40)	66 (13.07)	68 (13.47)
Status epilepticus	1 (0.20)	0 (0.00)	1 (0.20)

When the same event occurred more than once in a patient, it was counted as 1 event. MedDRA/J version (24.0)
When both serious and non-serious events with the same term occur in a patient, the serious one is counted as 1 event.

- Occurrence of coordinated movement-related adverse events

A total of 1 coordinated movement-related AE occurred in 1 patient (0.20% [1/505]). This event was considered an ADR. No serious events occurred.

- Occurrence of cardiovascular adverse events

There was no occurrence of cardiovascular AEs.

- Occurrence of adverse events related to eyes, skin, blood vessels, or aortas

A total of 5 AEs related to eyes, skin, blood vessels, or aortas occurred in 5 patients (5/505 [0.99%]). Of these, a total of 2 events (pruritus and rash) in 2 patients (2/505 [0.40%]) were considered ADRs related to eyes, skin, blood vessels, or aortas. No serious events occurred.

- Occurrence of blood disorder-related adverse events

A total of 4 blood disorder-related AEs occurred in 3 patients (3/505 [0.59%]) of which 2 were SAEs that occurred in 1 patient (1/505 [0.20%]). A total of 2 blood disorder-related ADRs (white blood cell count decreased and platelet count decreased; 1 patient each) occurred in 2 patients (2/505 [0.40%]) of which 1 SAE (platelet count decreased) occurred in 1 patient (1/505 [0.20%]).

- Occurrence of endocrine system-related adverse events

No endocrine system-related AEs occurred.

- Occurrence of abnormal lipid metabolism-related adverse events

A total of 1 abnormal lipid metabolism-related AE (carnitine deficiency) occurred in 1 patient (1/505 [0.20%]). This event was not serious and was not considered an ADR.

- Occurrence of increased weight adverse events

A total of 7 increased weight AEs occurred in 7 patients (7/505 [1.39%]) of which 5 events (weight increased, 4/505 [0.79%]; and obesity, 1/505 [0.20%]) in 5 patients (5/505 [0.99%]) were considered ADRs. No serious events occurred.

- Influence of perampanel on worsening developmental disorder or cognitive dysfunction

Of the 121 patients without developmental disorder or cognitive dysfunction at the start of administration of Fycompa, there was no patient with the influence of Fycompa (worsening). Of the 59 patients who discontinued Fycompa treatment, none of them was with the "presence of influence (worsening)" of Fycompa.

Of the 379 patients with developmental disorder or cognitive dysfunction at the start of administration with Fycompa, 0.26% (1/379) patients had the influence of Fycompa (worsening) at Week 52, and 0.00% (0/379) at Week 104 of administration with Fycompa. Of the 188 patients who discontinued Fycompa treatment, 3.72% (7/188) patients had the influence of Fycompa (worsening) at the time of discontinuation, and 0.53% (1/188) at 4 weeks after discontinuation.

Table 23: Presence of influence (worsening) of Fycompa on development disorder or cognitive dysfunction

Presence of developmental disorder or cognitive impairment at the start of treatment			No		Yes		Unknown	
			121		379		5	
			Number of patients	%	Number of patients	%	Number of patients	%
Presence of influence (worsening) of Fycompa on developmental disorder or cognitive dysfunction	At Week 12 of administration	No	63	(52.07)	226	(59.63)	2	(40.00)
		Yes	0	(0.00)	4	(1.06)	0	(0.00)
		Not evaluated/Unknown	45	(37.19)	121	(31.93)	2	(40.00)
		Not entered	13	(10.74)	28	(7.39)	1	(20.00)
	At Week 24 of administration	No	51	(42.15)	206	(54.35)	1	(20.00)
		Yes	0	(0.00)	5	(1.32)	0	(0.00)
		Not evaluated/Unknown	43	(35.54)	106	(27.97)	2	(40.00)
		Not entered	27	(22.31)	62	(16.36)	2	(40.00)
	At Week 52 of administration	No	46	(38.02)	180	(47.49)	2	(40.00)
		Yes	0	(0.00)	1	(0.26)	0	(0.00)
		Not evaluated/Unknown	42	(34.71)	103	(27.18)	2	(40.00)
		Not entered	33	(27.27)	95	(25.07)	1	(20.00)
	At Week 76 of administration	No	39	(32.23)	142	(37.47)	2	(40.00)
		Yes	0	(0.00)	1	(0.26)	0	(0.00)
		Not evaluated/Unknown	35	(28.93)	83	(21.90)	1	(20.00)
		Not entered	47	(38.84)	153	(40.37)	2	(40.00)
	At Week 104 of administration	No	34	(28.10)	131	(34.56)	1	(20.00)
		Yes	0	(0.00)	0	(0.00)	0	(0.00)
		Not evaluated /Unknown	36	(29.75)	83	(21.90)	2	(40.00)
		Not entered	51	(42.15)	165	(43.54)	2	(40.00)
Patients who discontinued treatment			59		188		3	
Presence of influence (worsening) of Fycompa on developmental disorder or cognitive dysfunction	At discontinuation	No	31	(52.54)	83	(44.15)	1	(33.33)
		Yes	0	(0.00)	7	(3.72)	0	(0.00)
		Not evaluated/Unknown	27	(45.76)	95	(50.53)	2	(66.67)
		Not entered	1	(1.69)	3	(1.60)	0	(0.00)
	At 4 weeks after discontinuation	No	21	(35.59)	75	(39.89)	2	(66.67)
		Yes	0	(0.00)	1	(0.53)	0	(0.00)
		Not evaluated/Unknown	38	(64.41)	105	(55.85)	1	(33.33)
		Not entered	0	(0.00)	7	(3.72)	0	(0.00)

There were 15 ADRs reported for worsening of developmental disorder or cognitive dysfunction by perampanel in 13 patients (13/505 [2.57%]) of which 2 were serious ADRs (agitation and coma, 1 patient each) that occurred in 2 patients (2/505 [0.40%]).

Table 24: Occurrence of adverse reactions reported to be due to the influence of Fycompa on development disorder or cognitive dysfunction (worsening) by the physician

Number of patients in the safety analysis set	505		
Seriousness	Serious	Non-serious	Total
Number of patients with events	2	11	13
Number of events	2	13	15
Incidence	0.40%	2.18%	2.57%
SOC/PT	Number of patients with events (incidence, %) by SOC/PT		
Psychiatric disorders	1 (0.20)	11 (2.18)	12 (2.38)
Aggression	0 (0.00)	1 (0.20)	1 (0.20)
Agitation	1 (0.20)	7 (1.39)	8 (1.58)
Impulsive behaviour	0 (0.00)	1 (0.20)	1 (0.20)
Irritability	0 (0.00)	2 (0.40)	2 (0.40)
Psychiatric symptom	0 (0.00)	2 (0.40)	2 (0.40)
Nervous system disorders	1 (0.20)	0 (0.00)	1 (0.20)
Coma	1 (0.20)	0 (0.00)	1 (0.20)

When the same event occurred more than once in a patient, it was counted as 1 event. MedDRA/J version (24.0)
When both serious and non-serious events with the same term occur in a patient, the serious one is counted as 1 event.

CHMP comment:

It seems that perampanel did not worsen the condition of any of the patients that were without developmental disorder or cognitive dysfunction at the start of administration of perampanel, including patients who discontinued perampanel treatment.

For patients with developmental disorder or cognitive dysfunction at the start of administration with Fycompa, 0.26% (1/379) patients had the influence of Fycompa (worsening) at Week 52, and 0.00% (0/379) at Week 104 of administration with Fycompa. Of the 188 patients who discontinued Fycompa treatment, 3.72% (7/188) patients had the influence of Fycompa (worsening) at the time of discontinuation, and 0.53% (1/188) at 4 weeks after discontinuation.

The methodology of the study did not allow to impute (or not) the worsening of Fycompa on developmental disorder or cognitive dysfunction. It is however reassuring to observe that there is no worsening of developmental and cognitive condition during the study in patients without these kind of disorders at the start of administration.

- Occurrence of memory and learning-related adverse events

A total of 1 memory and learning-related AE occurred in 1 patient (1/505 [0.20%]) which was considered an ADR (amnesia). No serious events occurred.

2.3.3. Discussion on clinical aspects

EISAI submitted final study results and report related to paediatric population for Study E2007-M081-503 (referred to as Study 503). This study 503 was a specified Japanese prospective post-marketing observational study following approval of Fycompa Tablets 2 mg and 4 mg by the Japan Pharmaceuticals and Medical Devices Agency (PMDA). The purpose of Study 503 was to evaluate the long-term safety and efficacy of perampanel oral tablets in real-world adolescent epileptic patients, aged 12 to 17 years, with partial seizures (including secondary generalized seizures) or tonic-clonic seizures. No adult patients participated in this study.

The study enrolled 507 subjects (planned 500 subjects, 50 of which would have tonic-clonic seizures) all of whom were less than 18 years of age and treated with perampanel in the study.

The results of this prospective post-marketing observational study shows that perampanel remains generally well tolerated, safe, and efficacious in the long-term treatment of adolescent epileptic patients with POS (including SGS). A clarification is asked regarding the PGTCS. Indeed, the MAH is asked to clarify to what extent the 50% responder rate on PGTCS in study 332 in the 8 mg perampanel group (64.2%) could be considered similar to the 50% responder rate on PGTCS in study 503 in the overall perampanel group (41.56%). Moreover, according to the provided results, the 50% responder rate on PGTCS in study 503 (41.56%) is even rather similar to the 50% responder rate on PGTCS in study 332 in the placebo group (39.50%).

The AEs described in Study 503 are consistent with the known safety profile for perampanel in the age population studied (12 to 17 years), and as seen in the epilepsy population. A review of these AEs does not suggest new or unexpected information. A clarification is asked regarding the narratives and outcomes of the three cases of status epilepticus.

A total of 32 unexpected ADRs occurred in 24 patients (24/505 [4.75%]), most of which were non-serious and each PT occurred in less than 0.6% of patients.

On the basis of a review of the AEs and AESIs in Study 503, no additional changes to the 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.

3. Rapporteur's CHMP overall conclusion and recommendation

☐ **Fulfilled:**

☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide satisfactory response to the clarification as part of this procedure. (see section "Request for supplementary information")

4. Request for supplementary information

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

1. In spite of knowledge that such an indirect comparison has no robust value, the MAH is asked to clarify to what extent the 50% responder rate on PGTCS in study 332 in the 8 mg perampanel group (64.2%) could be considered "similar" (according to the Applicant) to the 50% responder rate on PGTCS in study 503 in the overall perampanel group (41.56%). Moreover, according to the provided results, the 50% responder rate on PGTCS in study 503 (41.56%) is even rather similar to the 50% responder rate on PGTCS in study 332 in the placebo group (39.50%).
2. The Applicant is asked to provide the narratives and outcomes of the three cases of status epilepticus.

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

MAH responses to Request for supplementary information

Following receipt of the Day 30 preliminary Assessment Report and Request for Supplementary Information (EMA/CHMP/400031/2023) received on 14 September 2023, the MAH provided the responses to the Request for Supplementary Information on 19 September 2023.

Question 1

In spite of knowledge that such an indirect comparison has no robust value, the MAH is asked to clarify to what extent the 50% responder rate on PGTCS in study 332 in the 8 mg perampanel group (64.2%) could be considered "similar" (according to the Applicant) to the 50% responder rate on PGTCS in study 503 in the overall perampanel group (41.56%).

Moreover, according to the provided results, the 50% responder rate on PGTCS in study 503 (41.56%) is even rather similar to the 50% responder rate on PGTCS in study 503 [sic; believe should be Study 332] in the placebo group (39.50%).

Applicant's Response

The word "comparable" in the translated CSR (pg 116) was not the most appropriate choice of word to use in the translation from Japanese to English in this case. In the Japanese original report for Study 503, the sentence was written as "… which was consistent to the 50% responder rate of seizure frequency at the time of approval". We would like to clarify that this phrase was intended as an overall statement encompassing both partial seizures and PGTCS collectively, but not narrowly referring to PGTCS alone.

When examining by seizure types, 50% responder rate for total partial seizures was 48.00% in Study 503 which is in alignment of the 50% responder rate observed in Study 335 (23.0% [4 mg], 36.0% [8 mg], 43.3% [12 mg]). For PGTCS, we acknowledge that the 50% responder rate reported in Study 503 (41.56%) appears to be lower than that reported in Study 332 (64.2%). One plausible explanation for this apparent difference is that the mean daily dose administered in Study 503 was 3.97 ± 2.18 mg for tonic-clonic seizures, which is approximately half of the fixed dose of 8 mg evaluated in Study 332. Of note, unlike Study 332 which was a controlled, interventional study with a fixed prespecified dose of perampanel under investigation, Study 503 was conducted as an observational study based on electronic data capture that reflected clinical practice in real world setting where prescription of perampanel including its dosage was at independent discretion of the treating physician.

We agree with the assessor that such indirect comparison between interventional and non-interventional studies has its limitations.

CHMP comment:

The MAH's justification is acceptable and this confirms that such indirect comparison is not recommended. ***Issue solved.***

Question 2

The Applicant is asked to provide the narratives and outcomes of the three cases of status epilepticus.

Applicant's Response

The CIOMS form and/or AE report for the three subjects with status epilepticus are attached in Appendix 1. See response document for more details.

The outcomes of the 3 cases were as follows: all 3 patients (all male, age ranged from 12 to 17 years) recovered from status epilepticus without sequelae.

Latency of event from perampanel treatment initiation to event onset ranged from 163 days to approximately 1.5 year. Perampanel treatment and dose were maintained in two cases (negative dechallenge), and were maintained initially in one case but eventually discontinued (positive dechallenge). In this latter case, fosphenytoin treatment and adjustments to other concomitant antiseizure medications (ASMs) may have resulted in event resolution.

There was no case with a positive rechallenge.

Of the 3 cases, 1 patient had a history of status epilepticus reported prior to perampanel treatment initiation. Causality was assessed to be possibly related to perampanel (dose at onset, 6 mg/day) and co-suspect phenytoin in a patient with a history of status epilepticus in 1 case, not related to perampanel (dose at onset, 8 mg/day) with alternate cause being underlying disease (epilepsy) in 1 case, and not related (dose at onset, 3 mg/day) given the event occurred during dose adjustments to the patient's other ASMs (co-suspects) and given the patient's underlying disease (epilepsy).

CHMP comment:

The MAH provided the narratives and outcomes of the three cases of status epilepticus that occurred in male adolescents aged between 12 and 17 years old. All three recovered without sequelae. The causality was assessed to be possibly related to perampanel in one case and not related in the two other cases where confounding factors are present, in particular the underlying disease epilepsy itself. ***Issue solved.***

5. CHMP overall conclusion and recommendation

☒ **Fulfilled:**