28 January 2021
EMA/114809/2021
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/P46/019

Note

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

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1. Introduction

Perampanel is a highly selective non-competitive AMPA-type glutamate receptor antagonist. In the EU, Fycompa (perampanel), following the recent 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 pediatric 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.

With this post-authorisation measure (PAM) EISAI is hereby submitting final study results and report related to paediatric population in line with Article 46 of paediatric regulation 1901/2006 for Study E2007-M065-411 (Study 411). Study 411 was a Phase 4, observational, open-label, post marketing, non-interventional drug monitoring study, to collect data on the use of Fycompa in actual clinical settings. The study was conducted in the hospitals of participating physicians/investigators in Taiwan. Male and female subjects (aged 12 years and older) who were diagnosed to have POS with or without SGS and who were appropriate to receive Fycompa according to the investigator, were eligible to enroll in this study. The purpose of Study 411 was to evaluate the safety and efficacy of Fycompa as an adjunctive treatment of POS with or without SGS in subjects with epilepsy aged 12 years and older.

On 27 October 2020, the MAH submitted a completed paediatric study for Fycompa (perampanel), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. This study E2007-M065-411 (Study 411) which was completed on 03 July 2017, was implemented as a Taiwan post-marketing, observational study following comments from the review of the marketing authorisation application by the Taiwan Food and Drug Administration (TFDA). The TFDA requested a post-marketing, safety monitoring study instead of a bridging study.

The submission of the final clinical study report for Study 411 is being made to the European Medicines Agency to fulfil the obligation to present data from any MAH-sponsored study in a pediatric population.

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 411 was FYCOMPA as film-coated tablets of 2, 4 and 8 mg.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for Study E2007-M065-411 (hereafter referred to as Study 411), a Phase 4, observational, open-label, post marketing, non-interventional drug monitoring study to evaluate the safety and efficacy of Fycompa as an adjunctive treatment of POS with or without SGS in subjects with epilepsy aged 12 years and older

2.3.2. Clinical study

Description

The study was conducted in the hospitals of the participating physician/investigators in Taiwan to collect data on the use of Fycompa in actual clinical settings.

Methods

Objectives

The objectives of the study are to evaluate the safety and efficacy of Fycompa in patients with the adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

Study design

Study 411 has been designed to evaluate the safety profile of Fycompa prescribed as add-on therapy in patients with epilepsy in Taiwan. The anti-epileptic drugs (AEDs) were prescribed by the physician according to current and best medical practice. The study protocol did not prescribe or advise any drug or treatment for the study patients and they were given treatment according to investigators' routine practice. There was no control group in the study. Figure 1 below represents the study design:

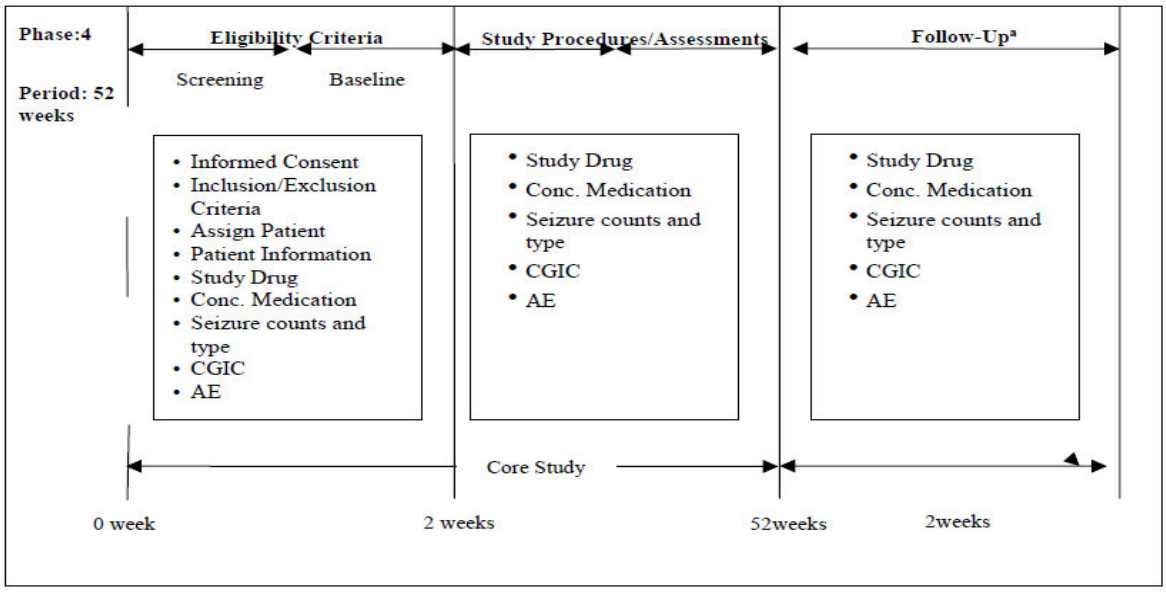

Figure 1 Study Design

a: Required only for patients who discontinue prior to Week 52 (in whom Early Termination visit has been performed).
CGIC: Clinical Global Impression of Change

CHMP comment:

On Visit 0, there was the screening/baseline visit, conducted in Week-0 of the study, and the eligibility criteria were carried out, in particular the seizure count(s) in the past 4 weeks.

On treatment phase, the patients received Fycompa in addition to their current AED; the treatment with Fycompa was initiated with a dose of 2 mg/day once daily before bedtime. During treatment, the maintenance dose ranged between 4 and 12 mg daily.

The following assessments / procedures were carried out during the 50 weeks treatment period:
- Recording seizure count(s) and seizure type(s) experienced by patient.
- Collecting and recording concomitant drug treatment details of patient in the eCRF.
- Examining and recording number and details of AE(s) experienced by patient.

The Follow-Up visit was only performed for patients who discontinued prior to Week-52 and it had been conducted after 2 weeks of ET (Early Termination) visit. The same assessments and procedures as mentioned above were carried out during the 50 weeks treatment period.

Study population /Sample size

The study planned to enrol 100 patients (60 evaluable). Subjects were eligible for participation in the study if they were aged 12 years and older with a diagnosis of partial-onset seizures with or without secondarily generalized seizures.

CHMP comment:

The patients were selected to receive Fycompa as an adjunctive treatment starting at Visit 0 and according to investigator's judgment.

Treatments

Fycompa was taken as a single oral dose taken once daily before bedtime. Treatment was initiated with a dose of 2 mg/day as approved in the PIL.

CHMP comment:

The dose was increased based on clinical response and tolerability by increments of 2 mg/day to a maintenance dose of 4 mg/day to 12 mg/day.

Outcomes/endpoints

- Safety:

All Adverse Events (AEs) including Serious Adverse Events (SAEs).

Adverse Events of Special Interest (AESI) such as Medication Errors, Lack of Therapeutic Efficacy, Overdose, Abuse, Misuse, Off Label Use, Pregnancy and exposure to drug during breast feeding.

- Efficacy :

Change from Baseline in 28-day seizure count at the End of treatment.

Response rate at Week 12, Week 24 and Week 52. Response was defined as >=50% reduction in 28-day seizure frequency from Baseline.

CHMP comment:

Safety is the primary endpoint and efficacy the secondary.

Statistical Methods

- Safety aspects: the number and percentage of patients with AEs/SAE and frequency/incidence of each type of AE/SAE were calculated.
- Efficacy aspects: the mean change from baseline in 28-day seizure frequency at the end of the treatment and the 50% response rate after 12, 24 and 52 weeks of treatment were calculated.

CHMP comment:

As this is an open-label, post marketing, non-interventional drug monitoring study, there are no statistical methods *per se*. The results are only observational.

Results

Recruitment/ Number analysed

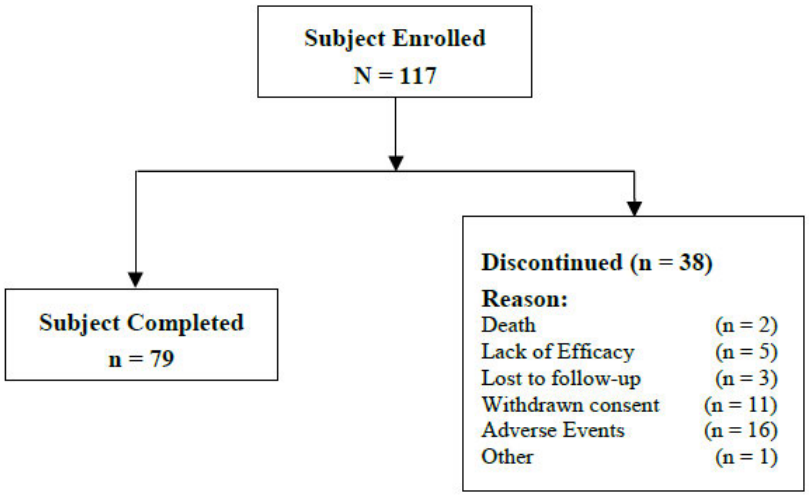

Figure 2 Subject Disposition and Primary Reason for Discontinuation from Study Treatment

Source: Table 14.1.1

CHMP comment:

This study was conducted between 11 Apr 2016 and 03 Jul 2017 at 3 study sites in Taiwan.

117 subjects were enrolled into the study. Of these, 79 subjects completed the study (= 67.5% of all patients) and 38 discontinued (= 32.5% of all patients).

The main reasons for discontinuation are: death (n=2; 1.7%), lack of efficacy (n= 5; 4.3%), lost to FUp (n= 3; 2.6%), withdrawn consent (n= 11; 9.4%) and AE (n= 16; 13.7%).

Baseline data

Table 1

Table 11-1 Demography, Baseline Age, Height and Weight – All Enrolled Subjects

Category	Fycompa® (N=117) n (%)
Age (year)[a]	
n	117
Mean (SD)	32.8(13.7)
Median	31.0
Min, Max	(13.0,65.0)
Age group, n (%)	
12 to 17 Years	13(11.1)
18 to 60 Years	99(84.6)
>60 Years	5(4.3)
Sex, n (%)	
Male	69(59.0)
Female	48(41.0)

CHMP comment:

The mean age of patients is 32.8 years. The median (minimum, maximum) age of the enrolled subjects was 31.0 (13.0, 65.0) years. There were 69 (59.0%) male subjects and 48 (41.0%) female subjects in the study.

Around 20 % of subjects were taking 1 concomitant AED, nearly 1/3 of subjects were taking 2 concomitant AED, and almost 1/3 of subjects were taking 3 concomitant AED.

Among the 117 subjects, only 13 (11.1%) subjects were 12 to 17 years of age, 99 (84.6%) subjects were 18 to 60 years of age and 5 (4.3%) subjects were above 60 years of age. The low amount of paediatrics in this study do not provide enough further safety data in this specific population.

The paediatrics (12 to 17 years of age) are underrepresented, which undermines the validity of the study in this age cohort. No firm conclusion concerning this age group is therefore possible.

Efficacy results

During this study, efficacy assessments were evaluated as secondary endpoints and included percentage change in 28-day seizure frequency from baseline and 50% responder rate (50% or greater reduction in seizure frequency compared to baseline).

Table 2

Table 11-5 Analysis of Change from Baseline in 28-day Seizure Count (All Enrolled Subjects)

	Fycompa® (N= 117)
Baseline	
N	177
Mean (SD)	9.39 (26.65)
Median	2.00
(Min, Max)	(0.00, 285.00)
Week 52	
N	132
Mean (SD)	5.55 (16.18)
Median	0.67
(Min, Max)	(0.00, 134.33)
Change from Baseline	
N	114
Mean (SD)	-1.78 (15.93)
(95% CI)	(-4.74,1.17)
Median	-0.84
(Min, Max)	(-62.33, 133.33)
p-value*	0.2342

n - Represents the various types of seizures reported by subjects
One Subject can have more than one Seizure Count
Change = Visit value - Baseline value, SD = Standard deviation, CI = Confidence interval
*Using paired t-test
Source: Table 7 of Statistical output

CHMP comment:

Regarding the percentage change in 28-day seizure frequency from baseline, the mean ± SD seizure count at baseline was 9.39±26.65 seizures, with a mean ± SD change from baseline at Week 52 of –1.78±15.93 seizures (P=0.2342). This is not a significant result however no firm conclusion can be drawn from these efficacy data and do not challenge the known efficacy results for perampanel in the studied population, mainly in adults.

Table 3

Table 11-6 Response Rate at Week 12, Week 24 and Week 52 (All Enrolled Subjects)

	Fycompa® (N= 117)			
	Total	**n**	**(%)**	**(95% CI)**
Week 12	165	17	(10.30)	(0.0612, 0.1598)
Week 24	149	15	(10.07)	(0.0574, 0.1606)
Week 52	132	41	(31.06)	(0.2330, 0.3970)

One Subject has more than one Seizure Count
Source: Table 9 of Statistical output

CHMP comment:

Regarding the 50% responder rate (defined as 50% or greater reduction in 28-day seizure frequency from baseline), it concerned 10.30% (17/165) subjects at Weeks 12, 10.07% (15/149) subjects at Weeks 24, and 31.06% (41/132) subjects at Weeks 52. This endpoint is that recommended in EU by the guidelines. The study design do not lead to put in question the known efficacy results.

Safety results

Extent of Exposure

Table 4

Table 1 Summary of Exposure to Study Drug – All Enrolled Subjects

	Fycompa (N=117)			
Parameter	**4 mg**	**8 mg**	**12 mg**	**Total**
Based on last dose taken by the subject during the study period				
Number of subjects	67 (57.3)	41 (35.0)	9 (7.7)	117 (100.0)
Mean (SD)	2.87 (1.01)	7.22 (0.99)	10.44 (0.88)	4.97 (2.15)
Median	2	8	10	4
Min-Max	1 – 4	6 – 8	10 – 12	1 – 12
Based on maximum dose taken by the subject during the study period				
Number subjects	47 (38.5)	53 (47.0)	17 (14.5)	117 (100.0)
Mean (SD)	3.09 (1.00)	7.40 (0.93)	10.47 (0.87)	6.11 (1.58)
Median	4	8	10	6
Min-Max	1 – 4	6 – 8	10 – 12	1 – 12

CHMP comment:

Subjects received Fycompa for up to 52 weeks. The mean daily dose during the study was 4.97±2.15 mg/day and the mean daily dose based on the maximum dose taken by the subject during the study was 6.11±1.58 mg/day, respectively.

The mean daily dose is in accordance with the dosing recommendation already approved in the SmPC for children above 12 years of age and adults for the treatment of POS, in conjunction with other AED.

Summary of TEAE

Table 5

Table 2 Overview of Treatment-Emergent Adverse Events – All Enrolled Subjects

	Fycompa (N=117)			
Parameter	**4 mg (N=45)**	**8 mg (N=55)**	**12 mg (N=17)**	**Total (N=117)**
All TEAEs	28 (62.2)	37 (67.3)	13 (76.5)	78 (66.7)
Treatment-related TEAEs	24 (53.3)	26 (47.3)	12 (70.6)	62 (53.0)
Severe TEAEs	5 (11.1)	2 (3.6)	0	7 (6.0)
Serious TEAEs	8 (17.8)	6 (10.9)	4 (23.5)	18 (15.4)
Deaths	2 (4.4)	0	0	2 (1.7)
Other SAEs	7 (15.6)	6 (10.9)	4 (23.5)	17 (14.5)
Life threatening	0	0	0	0
Required inpatient hospitalization or prolongation of existing hospitalization	7 (15.6)	6 (10.9)	2 (11.8)	15 (12.8)
Persistent or significant disability or incapacity	1 (2.2)	0	0	1 (0.9)
Congenital anomaly/birth defect	0	0	0	0
Important medical events	0	0	2 (11.8)	2 (1.7)

A total of 232 treatment emergent adverse events (TEAEs) were reported in 78 (66.67%) subjects with 47 (40.17%) subjects reporting AEs in the nervous system disorder SOC.

There were 38 serious adverse events (SAE) reported in the study by 18 (15.4%) subjects of which a total of **8 SAEs were reported by 2 subjects between the ages of 12 and 17 years**. The majority of subjects (15 out of 18 i.e. 12.8%) with serious TEAE required hospitalization or prolongation of existing hospitalization.

A total of 12 SAEs were reported in the SOC of nervous system disorders by a total of 9 (7.69%) subjects and 5 SAEs were reported in the SOC psychiatric disorders by a total of 2 (1.71%) subjects.

The other SAEs were of renal and urinary disorders, neoplasms benign, malignant and unspecified (including cysts and polyps) ie, 3 events each.

Of the SAEs, 9 events were considered possibly related to the study drug and the remaining SAEs were all considered not related to the study drug.

For 36 subjects (30.8%), the occurrence of TEAE led to study drug dose adjustment in 15 subjects (33.3%) of the 4mg group and in 16 subjects (29.1%) of the 8mg group. For 23 subjects the TEAE led to study drug dose reduction and for 16 subjects the TEAE led to study or study drug withdrawal.

There were two deaths in the 4mg group reported in the present study (see below for more details).

CHMP comment:

The most frequent SOC is related to nervous system disorders and psychiatric disorders in accordance with the known safety profile of perampanel.

From these data, no further safety conclusion could be drawn regarding the paediatrics for the following reasons: they represent only 11% of the overall included patients and the MAH did not provide separate data for patients aged 12 to 17 years, as the data are mixed for the overall included patients. This issue is a flaw of this study not pursued.

As detailed recently in the PSUSA for perampanel, available post marketing data since the marketing authorization in July 2012 did not show additional risks associated with long-term use of perampanel. Nevertheless, post-marketing studies are ongoing and long term safety in adolescents and adults should remain a missing information in the PSUR.

TEAE by SOC and PT for all enrolled subjects

Among the 232 events in 78 subjects, the most frequent AE occurring in more than 10% of the subjects implied MedDRA SOC Nervous System Disorders.

Indeed, seventy-four (74) subjects showed AE within this SOC: 31 events of dizziness and 15 events of headache which were common AEs in this SOC.

The other common AEs were psychiatric disorders (40 events) mostly irritability with 16 events, infections and infestations (31 events) mostly upper respiratory tract infections with 19 events, general disorders (17 events) mostly malaise with 6 events, injury poisoning and procedural complications (14 events) mostly wounds with 5 events.

Table 6

Table 3 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – All Enrolled Subjects

MedDRA System Organ Class Preferred Term	Fycompa (N=117) n (%)	 Events
Cellulitis	1 (0.85)	1
Influenza	1 (0.85)	1
Nasopharyngitis	4 (3.42)	4
Otitis externa	1 (0.85)	1
Pharyngitis	1 (0.85)	1
Pneumonia	2 (1.71)	2
Subcutaneous abscess	1 (0.85)	1
Upper respiratory tract infection	12 (10.26)	19
Injury, poisoning and procedural complications	11 (9.40)	14
Contusion	2 (1.71)	2
Eyelid Injury	1 (0.85)	1
Fall	1 (0.85)	1
Head injury	2 (1.71)	2
Lip injury	1 (0.85)	1
Skin abrasion	1 (0.85)	1
Spinal column injury	1 (0.85)	1
Wound	3 (2.56)	5
Investigations	2 (1.71)	2
Weight decreased	2 (1.71)	2
Metabolism and nutrition disorders	6 (5.13)	7
Diabetes mellitus	1 (0.85)	1
Hyperkalemia	1 (0.85)	1
Hyponatremia	1 (0.85)	1
Increased appetite	2 (1.71)	2
Obesity	1 (0.85)	1
Polydipsia	1 (0.85)	1
Musculoskeletal and connective tissue disorders	2 (1.71)	2
Arthralgia	1 (0.85)	1
Back pain	1 (0.85)	1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.85)	3
Myeloproliferative disorder	1 (0.85)	1
Neoplasm malignant	1 (0.85)	1
Tumour associated fever	1 (0.85)	1
Nervous system disorders	47 (40.17)	74
Altered state of consciousness	1 (0.85)	1

Table 7

Table 3 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – All Enrolled Subjects

MedDRA System Organ Class Preferred Term	Fycompa (N=117)	
	n (%)	Events
Ataxia	5 (4.27)	5
Cerebral haemorrhage	1 (0.85)	1
Cerebral infarction	1 (0.85)	1
Dizziness	24 (20.51)	31
Epilepsy	2 (1.71)	2
Headache	13 (11.11)	15
Hydrocephalus	1 (0.85)	1
Lethargy	4 (3.42)	4
Loss of consciousness	1 (0.85)	1
Memory impairment	1 (0.85)	1
Poor quality sleep	3 (2.56)	3
Seizure	2 (1.71)	2
Somnolence	4 (3.42)	5
Status epilepticus	1 (0.85)	1
Psychiatric disorders	27 (23.08)	40
Adjustment disorder	1 (0.85)	1
Affect lability	1 (0.85)	1
Aggression	5 (4.27)	4
Agitation	4 (3.42)	4
Anger	1 (0.85)	1
Anxiety	1 (0.85)	1
Emotional disorder	3 (2.56)	3
Insomnia	3 (2.56)	3
Irritability	16 (13.68)	16
Major depression	1 (0.85)	1
Obsessive-compulsive disorder	1 (0.85)	1
Paranoid personality disorder	1 (0.85)	1
Psychiatric symptom	1 (0.85)	1
Sleep disorder	1 (0.85)	1

CHMP comment:

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, somnolence and ataxia. For the MedDRA SOC Psychotic Disorders, the most common AE are irritability, aggression and agitation.

The AE headache which is one of the most frequent AE from SOC Nervous System Disorders is not stated in the SmPC nor mentioned in the recent PSUSA AR.

Events reported in patients who had medical history of suicidal behaviours were consistent with the known safety profile of perampanel or could be related to the medical history of the patients.

Severity of AE and relationship to study drug /outcome

Of the 232 TEAEs, there were 151 mild AEs, 67 moderate and 14 severe AEs reported during the study.

The study drug dosage was decreased due to 30 TEAEs.

The study drug was discontinued due to 26 TEAEs.

Concomitant medication was given for 94 AEs, non-drug treatment was given for 33 AEs and no action was taken for 49 AEs.

The relationship to study drug was reported as probably related for 55 TEAEs and possibly related for 59 TEAEs. There were 118 TEAEs which were not related to the study drug.

Regarding the outcome, a total of 178 AEs were recovered/resolved without sequelae, 2 were recovered/resolved with sequelae and 27 AEs were reported as not recovered.

CHMP comment:

The most frequently reported TEAEs that led to discontinuation were irritability (6 [5.1%] subjects with 6 events) and dizziness (3 [2.6%] subjects with 3 events) which are AE from the SOC Nervous System Disorders. In the SmPC, it is stated: "The adverse reactions most commonly (≥ 1% in the total perampanel group and greater than placebo) leading to discontinuation were dizziness and somnolence". Therefore, this is overall in line with what was observed in controlled phase 3 studies assessing the efficacy and safety of perampanel when given for the treatment of POS in adjunction to other AED. Regarding the AE irritability, it is tabulated in section 4.8 as common (≥ 1/100 to < 1/10) and the frequency in study 411 is slightly higher with 13.68%. This is in the same range however no formal comparison is possible.

Deaths during the study

There were two deaths reported during this study.

Table 8

Table 12-2 Listing of All Deaths – All Subjects

Subject ID Age (yr), Sex, Race	Date of Death/ Study Day of Death[a]	Last Dose Before Death	Cause of Death (Investigator Term/ Preferred Term)	AE Start Date Study Day	Relationship to Study Drug	Duration of Treatment[b]	Day of Death in Relation to Last Dose[c]
EXXXX							
[redacted]	[redacted] 2017	[redacted] 2017	General Disorders And Administration Site Conditions/Drowning/Drowning	[redacted]2 017/318	Possibly Related	FROM [redacted]2016	0
[redacted]	[redacted] 2017	[redacted] 2017	Cardiac Disorders/Cardiac Failure/Heart Failure Due To Multiple Liver Malignant Tumors	[redacted]20 17/331	Not Related	FROM [redacted]2016	0

MedDRA Version 18.1
Age is age at informed consent, yr = year
F = Female, M = Male.
AE = adverse event.
a: Study Day of Death = date of death – date of first dose of study drug +1
b: Duration of treatment = date of last dose of study drug – date of first dose of study drug +1
c: Number of days between end of study drug and death.
Source: Listing 8 of Statistical output

CHMP comment:

There was one drowning considered possibly related to the study drug and one heart failure due to multiple liver malignant tumors considered not related to the study drug.

No death was reported for subjects aged between 12 and 17 years.

Other safety findings

The study was an observational study and vital signs were not recorded during the study. There was no other observation apart from AEs and SAEs monitored in the study.

2.3.3. Discussion on clinical aspects

The aim of this study was to evaluate the safety and efficacy of Fycompa (perampanel) in patients with adjunctive treatment of partial-onset seizures, with or without secondary generalized seizures.

Fycompa was taken as a single oral dose once daily. The drug was taken at doses of 4 mg/day to 12 mg/day to be effective therapy in partial-onset seizures. The drug was initiated with a dose of 2 mg/day as per the approved package insert. The dose was increased based on clinical response and tolerability by increments of 2 mg/day to a maintenance dose of 4 mg/day to 12 mg/day.

The primary endpoint for this observational study is safety assessment.

Regarding the safety, the AEs described in Study 411 are overall consistent with the known safety profile for Fycompa described in the SmPC. The safety results of the study reported that 17 (14.52%) subjects experienced at least one SAEs. Most common AEs and SAEs were reported in the nervous

system disorders, including dizziness, headache and ataxia among others. In some cases, the dose decrease was an option to continue the treatment. In other cases, the subjects discontinued the study or study treatment. No deaths were reported for subjects aged between 12 and 17 years.

There were no significant changes in the frequency and severity of previously identified adverse reactions apart from the AE headache.

On the basis of the review of the AEs and TEAEs in this study, no additional changes to the safety information of the SmPC are requested by the Applicant which is acceptable. However the AE "headache" may be possibly added to the SmPC in the future (15 events in 13 patients, frequency of 11.11% which could be categorized as very common). Of note, this AE is not yet discussed in the recent PSUSA and needs to be kept in mind and further explored.

Regarding efficacy, which is the secondary endpoint in this study, there is a non-significant change from baseline in seizure count at week 52 [-1.78 (15.93), p = 0.2342]. This is not a significant result however no firm conclusion can be drawn from these efficacy data and do not challenge the known efficacy results for perampanel in the studied population, mainly in adults. Response rate was not high possibly explained by the studied population.

3. Rapporteur's CHMP overall conclusion and recommendation

The MAH submitted the results of study 411 in order to fulfil the requirement of reporting paediatric data as outlined in accordance with Article 46 of regulation (EC) no 1901/2006, as amended. Only a small number of paediatric patients were included in this study (i.e. 11% of the patients).

The MAH determines that the benefit-risk ratio for Fycompa remains unchanged and positive despite the non-significant efficacy result at 52 weeks, which is hardly disputable regarding the study design (open-labelled, uncontrolled). Indeed the results of this study could only be considered as supportive of the known safety profile and efficacy results of perampanel in adults and adolescents above 12 years of age and do not allow to draw any further robust conclusion.

The MAH does not propose any changes of the currently approved SmPC based on the present data, which is supported. However, the AE "headache" needs to be kept in mind and further explored for its potential addition in the SmPC.

☒ **Fulfilled:**

No regulatory action required.