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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/P46/012.1

Note

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

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Table of contents

1. Introduction 3

2. Scientific discussion 3

2.1. Information on the development program 3

2.2. Information on the pharmaceutical formulation used in the study 4

2.3. Clinical aspects 4

2.3.1. Introduction 4

2.3.2. Clinical study E2007-G000-307 4

Methods 4

Results 9

2.3.3. Discussion on clinical aspects 23

3. CHMP's overall conclusion and recommendation 23

Fulfilled: 24

Not fulfilled 24

4. Additional clarification requested following preliminary assessment 24

5. Assessment of Applicants Responses 24

Question 1 24

Response 24

Assessment of the Response and Conclusion 25

Question 2A 25

Response 25

Question 2B 26

Response 26

Question 2C 30

Response 30

Question 2D 31

Response 32

Question 2E 32

Response 32

Assessment of the Response and Conclusion 32

6. Additional clarifications required by the CMSs 32

Response 33

Assessment of the Response and Conclusion 33

7. Outstanding Questions 33

1. Introduction

On 17 March 2015, the MAH submitted a completed paediatric study for Fycompa, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. This study is part of PIP.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study E2007-G000-307 [An Open-label Extension Phase of the Double-blind, Placebo-Controlled, Dose Escalation, Parallel-Group Studies to Evaluate the Efficacy and Safety of E2007 (Perampanel) Given as Adjunctive Therapy in Subjects with Refractory Partial Seizures] is part of a clinical development program.

Study E2007-G000-307 (Study 307), an Eisai-sponsored clinical study, was recently completed as part of a clinical development program. This study was open label extension for the three double blind efficacy studies carried out as part of the initial development programme.

Table 1: The Double blind studies in the clinical development programme where the participants were eligible to continue in the open label extension Study 307.

Study ID	No. of study centres/ locations	Design	Study Objective	Study Posology	Sbjs by arm.	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
E2007-G000-304	77; Argentina, Canada, Chile, Mexico, US	RD, DB, PLA-controlled, parallel-group. 3 phases: 6-w pre-randomisation, 19-w DB (6-w titration, 13-w maintenance), 4-w follow-up	Efficacy and safety	PLA PRP 8 mg PRP 12 mg QD at bedtime	121 133 134	54/67 65/68 69/65 36 y	⩾ 12 y Uncontrolled POS receiving up to 3 marketed fixed-dose AEDs	Non-EU: % change in frequency of all POS per 28 days during ttt relative to baseline EU: proportion of 50% responders
E2007-G000-305	84; Australia, EU, India, Israel, Russia, South Africa, US	RD, DB, PLA-controlled, parallel-group. 3 phases: 6-w pre-randomisation, 19-w DB (6-w titration, 13-w maintenance), 4-w follow-up	Efficacy and safety	PLA PRP 8 mg PRP 12 mg QD at bedtime	136 129 121	71/65 65/64 50/71 35.5 y	⩾ 12 y Uncontrolled POS receiving up to 3 marketed fixed-dose AEDs	Non-EU: % change in frequency of all POS per 28 days during ttt relative to baseline EU: proportion of 50% responders

Study ID	No. of study centres/ locations	Design	Study Objective	Study Posology	Sbjs by arm.	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
E2007-G000-306	116; Argentina, Australia, Canada, Chile, China, EU, Hong Kong, India, Malaysia, Philippines, Russia, Serbia, South Korea, Taiwan, Thailand, Ukraine	RD, DB, PLA-controlled, parallel-group. 3 phases: 6-w pre-randomisation, 19-w DB (6-w titration, 13-w maintenance), 4-w follow-up	Efficacy and safety	PLA PRP 2 mg PRP 4 mg PRP 8 mg QD at bedtime	185 180 172 169	95/90 85/95 88/84 77/92 33.8 y	⩾ 12 y Uncontrolled POS receiving up to 3 marketed fixed-dose AEDs	Non-EU: % change in frequency of all POS per 28 days during ttt relative to baseline EU: proportion of 50% responders

2.2. Information on the pharmaceutical formulation used in the study

No additional information has been supplied. The already marketed 2mg and 4mg tablets were used in the study.

2.3. Clinical aspects

2.3.1. Introduction

Perampanel (E2007), 2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1, 2-dihydropyridin-3-yl) benzonitrile hydrate (4:3), an highly selective alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptor antagonist, is an anticonvulsant drug approved internationally as adjunctive therapy in the treatment of partial onset seizures in patients 12 years and older.

Perampanel is currently available on the market in the EU, USA, Canada, Switzerland, and in over 40 other countries, as Fycompa® film-coated tablets (containing 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg perampanel).

CHMP's comment:

The applicant initially proposed that the submitted information did not change the risk benefit balance and did not warrant any change in the product information.

2.3.2. Clinical study E2007-G000-307

AN OPEN-LABEL EXTENSION PHASE OF THE DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE ESCALATION, PARALLEL-GROUP STUDIES TO EVALUATE THE EFFICACY AND SAFETY OF E2007 (PERAMPANEL) GIVEN AS ADJUNCTIVE THERAPY IN SUBJECTS WITH REFRACTORY PARTIAL SEIZURES

Methods

Objectives

The primary objective is to evaluate the safety and tolerability of perampanel (up to12mg/day) given as adjunctive treatment in subjects with refractory partial seizures.

The secondary objective is to evaluate the maintenance of effect of perampanel for the control of refractory partial seizures.

The exploratory objective is to evaluate the potential withdrawal symptoms of perampanel in subjects with refractory partial seizures. (revised per Amendments 02 and 03)

In addition, this study will:

• Evaluate the long-term effect of perampanel on growth and development including sexual staging in adolescents (ie, 12 to 17 years at the time of consent/assent in the preceding double-blind study, in countries where data are available). (added per Amendment 03)

• Determine the pharmacokinetics (PK) of perampanel using a population PK approach and explore the PK/PD relationship in adolescents (in countries where data are available). (added per Amendment 03)

Study design

This was an open-label extension (OLE) study for subjects who completed 1 of the following double-blind (DB), placebo-controlled, Phase 3 studies: E2007-G000-304, E2007-G000-305, or E2007-G000-306 (hereafter referred to as 304, 305, and 306, respectively). This OLE study consisted of 2 phases: an Open-label Treatment Phase (comprised of a 16-week blinded Conversion Period and a 256-week Maintenance Period) and a Follow-up Phase (4 weeks).

The open-label Maintenance Period began at completion of the blinded Conversion Period. During the open-label Maintenance Period, subjects were treated with the perampanel dose that provided the best combination of individual efficacy and tolerability. Subjects who either withdrew from the study prematurely or completed the Maintenance Period returned for a final visit at the end of the 4-week open-label Follow-up Phase.

Subjects entered the OLE study on the concomitant antiepileptic drug (AED) regimen they were on during the core DB study, consisting of at least 1, to a maximum of 3, concomitant AED(s). The dose(s) of the concomitant AED(s) could have been adjusted. Following Amendment 03, the concomitant AED(s) itself could have been discontinued or changed at the investigator's discretion during the OLE study.

The sponsor terminated the study in 2012 following receipt of a positive opinion for perampanel from the Committee for Medicinal Products for Human Use. An end-of-treatment (EOT) visit was scheduled within 2 to 6 weeks for all subjects who remained in the Maintenance Period. If it was the opinion of the treating physician that a subject would benefit significantly from further treatment with perampanel after the trial concluded, perampanel treatment was made available under Eisai's compassionate use policy in accordance with local country legislative provisions until the time that perampanel was commercially available in the country in which the subject resided.

No Follow-up Phase was required for subjects who continued perampanel treatment under an Expanded Access Protocol.

Study population / Sample size

Male and female subjects were eligible for this OLE study if they completed the DB Phase (Visit 8) of Study 304, 305, or 306 and showed compliance with the inclusion and exclusion criteria for that study (other than criteria related to seizure frequency); provided informed consent for participation in the OLE study; were currently receiving treatment with a stable dose of 1 to a maximum of 3 marketed AEDs (on a stable dose of 2 or 3 marketed AEDs in Lithuania); and were considered reliable and able

to record seizure data and report adverse event (AE) information (or have a caretaker able to perform these duties).Planned: Up to 1430 subjects.

Enrolled in OLE study: 1218 subjects, including 124 adolescent subjects, defined as those aged 12 to 17 years at the time of providing informed consent/assent in the core DB study. Treated in OLE study: 1216 subjects.

Treatments

Perampanel was supplied as 2-mg tablets (lot numbers P7Y005ZZB, P7Z002ZZA, P7Z004ZZA, P82002ZZA, P82003ZZA, P86004ZZA, P92003ZZA, P92008ZZA, P92009ZZA, P96004ZZA, P96005ZZA, P99009ZZA, P99010ZZA) or 4-mg tablets (lot numbers P7Y006ZZA, P7Z005ZZA, P83003ZZA, P83005ZZA, P86006ZZA, P99011ZZA, P99012ZZA). Matching placebo 2-mg tablets (lot numbers P7Y003ZZB, P8Z001ZZA, P77005ZZA, P86002ZZA, P92007ZZA,P96003ZZA).

All doses were taken once daily, by mouth, before bedtime, and with food. In the Conversion Period, all titrations were to be based on individual tolerance, as per the investigator's clinical judgment and the subject's willingness to increase the perampanel doses up to 12 mg. During the Maintenance Period, subjects were to be treated with the perampanel dose that provided the best combination of individual safety, tolerability, and efficacy up to a maximum dose of 12 mg/day.

Doses could be down- or up-titrated until the MTD dose was identified for each subject.

Subjects who could not tolerate 2 mg/day were discontinued. Subjects previously assigned to a placebo arm were to be up-titrated in 2-mg increments to a maximum of 12 mg/day in a blinded fashion on the basis of individual tolerance. For subjects who achieved 12 mg/day during the DB study, their dose was to be stably maintained (unless a dose adjustment was necessary). For subjects who achieved perampanel doses below 12 mg, the up-titration was to be made in 2 mg increments in a blinded fashion until an optimal dose was found (up to a maximum of 12 mg) (revised per Amendments 01 and 02).

The planned total duration of treatment during the OLE study was up to 5 years or until the product became available commercially or the study was closed (except in the United Kingdom and India where the total duration was 272 weeks [16 week Conversion Period + 256-week Maintenance Period]).

Outcomes / Endpoints

Efficacy

Efficacy assessments included seizure counts from subject diaries. The key efficacy endpoints included the percent change in seizure frequency (all seizures types) per 28 days during treatment relative to baseline as well as the proportion of subjects who experienced a 50% or greater reduction in seizure frequency during treatment per 28 days relative to baseline (responder).

Safety

Safety assessments included examination of the incidence rates of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), and withdrawals due to AEs; changes in vital signs and body weight and incidence rates of clinically significant vital sign values; changes in laboratory test parameters and incidence of clinically notable laboratory abnormalities; change from baseline in electrocardiogram (ECG) interval values, incidence rates of abnormal QT interval values corrected for heart rate using Fridericia (QTcF) or Bazett (QTcB) formulae, and rates of abnormal ECG interpretations; shift from baseline in withdrawal questionnaire responses; shift from baseline in

Tanner Staging for adolescent subjects; changes from baseline in thyroid hormone and insulin-like growth factor-1 (IGF-1) and change from baseline in body weight and height in adolescent subjects; and rates of concomitant medication use. A TEAE was defined as an AE that either began on or after the date of first dose of perampanel and up to 30 days after the last dose of perampanel, or began before the date of first perampanel dose and increased in severity during the perampanel treatment. For subjects randomized to 1 of the perampanel treatment groups in the preceding core DB study, the first dose date of perampanel is from the core DB study. For subjects randomized to placebo in the preceding core DB study, the first dose date of perampanel was from the OLE study. AEs were classified into standardized terminology from the verbatim description (investigator term) according to the Medical Dictionary for Regulatory Activities (MedDRA™) Coding Dictionary, version 13.1. TEAEs were summarized by System Organ Class (SOC) and MedDRA preferred term.

Statistical Methods

Details concerning the data analyses are specified in the Statistical Analysis Plan (SAP). Efficacy analyses were based on the Full Intent-to-Treat (ITT) Analysis Set, while safety analyses were based on the Safety Analysis Set. The Safety Analysis Set was defined as subjects who provided informed consent for the OLE study, received at least 1 dose of perampanel in the OLE study, and had at least 1 postdose safety assessment in the OLE study (N = 1216 for overall population; N = 124 for adolescent population). Two subjects were enrolled and treated in the OLE study but were not included in the Safety Analysis Set as they did not have any postbaseline safety data after the first OLE dose as of the interim cut-off date.

The Full ITT Analysis Set was defined as subjects who provided informed consent for the OLE, received at least 1 dose of perampanel in the OLE study, and had valid seizure data during the perampanel treatment duration (DB and/or OLE studies) (N = 1217 for overall population; N = 124 for adolescents). As inclusion in the Full ITT Analysis Set for subjects treated in the OLE study was dependent on availability of seizure data during perampanel treatment in the DB and/or OLE studies, the number of subjects in this analysis set was higher than that in the Safety Analysis Set (which required availability of data in the OLE study).

All data analyses were descriptive in nature, with summary statistics presented for continuous endpoints and frequency counts presented for categorical endpoints. Two general approaches were used to analyse efficacy data. The first examined seizure data by maximum perampanel dose received and used the Pre-perampanel Baseline for evaluating change. The second approach examined seizure data as a function of randomised treatment group in the core DB study and used the Pre-randomisation Phase of the core DB study as the baseline for evaluating change.

The Pre-perampanel Baseline was defined as follows unless otherwise specified: (1) for subjects who had been assigned to placebo treatment in the core DB study, the Pre-perampanel Baseline was computed from all data during the core DB study, and (2) for subjects who had been assigned to perampanel in the core DB study, the Preperampanel Baseline was computed from the Pre-randomisation Phase of the core DB study. For all efficacy analyses, the perampanel treatment duration consisted of (1) the DB (Titration + Maintenance Periods) plus the OLE (Conversion + Maintenance Periods) for subjects assigned to perampanel in the core DB study and who had a ≤14-day gap in perampanel exposure between the DB and OLE studies; (2) the OLE Treatment Phase for subjects assigned to perampanel in the core DB study and who had a >14-day gap in perampanel exposure between the DB and OLE studies; or (3) the OLE Treatment Phase for subjects assigned to placebo in the core DB study.

For analyses using the Pre-randomisation Phase of the core DB study for determining baseline seizure frequency, efficacy data were summarised by randomised treatment group in the core DB study for the DB Titration Period, DB Maintenance Period, OLE Conversion Period, and by 13-week intervals during the OLE Maintenance Period.

Additional summaries of the efficacy endpoints were provided for subgroups defined by age (<18, 18-64, and >64 years), sex (male/female), race (White; Asian or Pacific Islander; Other), and number of AEDs (1, 2, 3) at DB Baseline. Summaries of the key efficacy endpoints were also examined for the subgroup of adolescent subjects.

Subgroup analyses were performed using both efficacy analysis approaches (ie, using Pre-perampanel Baseline and Pre-randomisation Phase Baseline). Exploratory efficacy endpoints, and their analyses, are defined in the SAP.

Safety data were summarised by maximum daily dose (defined as <4 mg/day, 4 mg/day, >4 to 8 g/day, and >8 to 12 mg/day) and included data from the entire perampanel treatment duration. The perampanel treatment duration for AE analyses was defined as all exposure to perampanel in the core DB study and current OLE study. The perampanel treatment duration for all other safety endpoints was similar to that specified for the efficacy analyses, except that for subjects assigned to perampanel treatment in the core DB study who had a >14-day gap in exposure between the core and current OLE study, the treatment duration was defined as either the DB or OLE treatment phase, whichever was longer. Safety endpoints were also summarized for the subgroup of adolescent subjects.

Changes in the Conduct of the Study or Planned Analyses

There were 3 global amendments, and 6 country-specific amendments, to the original protocol (dated 15 Feb 2008). The SAP defined ITT analysis set is referred to as the Full ITT Analysis Set.

CHMP's comments:

The primary objective of the study was to examine safety and tolerability of the treatment in the long term administration. In that sense and in view of the design, this study was primarily a safety study. As planned, the study was discontinued once the product became commercially available.

The transition from double blind to open label is acceptable from the point of view of the current study. The acceptability of the conversion from the point of view of the original double blind studies has been assessed and accepted previously.

Significant numbers of patients have been enrolled in the study, but considering that completion of the double blind phase was the entry requirement, the study population in this open label phase does not necessarily reflect the population that will be exposed to the product in the clinical practice.

The basic efficacy assessment measures were appropriate in respect of the objectives of the study. The more extensive safety monitoring was also appropriate in this context.

Statistical methods are well described. All analyses were descriptive in nature which is appropriate for the type of the study.

Results

Recruitment / Number analysed

A total of 1218 subjects provided informed consent, were eligible to participate, and were enrolled in Study 307, including 311 subjects from Study 304 (105 placebo, 206 perampanel), 312 subjects from Study 305 (118 placebo, 194 perampanel), and 595 subjects from Study 306 (157 placebo, 438 perampanel). The enrolment in Study 307 represented between 96% and 97% of subjects who completed the DB Phase of each Phase 3 study (311/320 subjects for Study 304, 312/322 subjects for Study 305, and 595/623 subjects for Study 306). No new subjects have been enrolled since the previous interim synoptic CSR dated 02 May 2011. Two enrolled subjects (12016004, 40046017) were lost to follow-up and did not have any postbaseline safety data after the first OLE dose and were not included in the Safety Analysis Set.

Table below summarises subject disposition for the Safety Analysis Set, 35 of the 1216 subjects in the Safety Analysis Set had completed the study, 1181 (97.1%) subjects had been discontinued from the OLE study.

Table 2: Subject Disposition and Primary Reason for Discontinuation (Safety Analysis Set)

	Maximum Daily Dose Exposed				
Category	<4 mg/day (N=1)	4 mg/day (N=13)	>4 to 8 mg/day (N=75)	>8 to 12 mg/day (N=1127)	Total (N=1216)
Study Completion,[a] n (%)					
Completed	0	0	0	35 (3.1)	35 (2.9)
Discontinued	1 (100)	13 (100)	75 (100)	1092 (96.9)	1181 (97.1)
Ongoing	0	0	0	0	0
Therapy Completion,[b] n (%)					
Completed	0	0	0	35(3.1)	2 (<1)
Discontinued	1 (100)	13 (100)	75 (100)	1092 (96.9)	1181 (97.1)
Ongoing	0	0	0	0	0
Primary Reason for Discontinuation,[c] n (%)					
Adverse event[d]	1 (100)	4 (30.8)	21 (28.0)	168 (14.9)	194 (16.0)
Lost to follow-up	0	0	1 (1.3)	30 (2.7)	31 (2.5)
Subject choice	0	2 (15.4)	21 (28.0)	229 (20.3)	252 (20.7)
Inadequate therapeutic effect	0	2 (15.4)	11 (14.7)	189 (16.8)	202 (16.6)
Administrative/Other	0	5 (38.5)	21 (28.0)	476 (42.2)	502 (41.3)

Percentages based on the total number of subjects in the relevant treatment group.
Of the 502 subjects who were discontinued due to 'Administrative/Other' reasons, 478 were discontinued due study closure, availability of perampanel commercially in their country, or entering Eisai's compassionate use program. These subjects are considered to have completed the study to the extent their participation was allowed.
a: As reported for 'study completion' on the End of Study (Subject Disposition) case report form.
b: As reported for "therapy completion" on the End of Study (Subject Disposition) case report form. Discontinued subjects also include those who discontinued therapy, but had not filled out an End of Study (Subject Disposition) form.
c: Only one primary reason is recorded.
d: Corresponding adverse events leading to withdrawal from therapy were reported on the Adverse Event case report form as applicable.
Source: Table 14.1.2.1

The most common primary reason for discontinuation of perampanel treatment in the OLE study was administrative / other (502 subjects, 41.3%) followed by subject choice (252 subjects, 20.7%). Subjects who discontinued as a result of the study closure, availability of perampanel commercially in their country, or entering Eisai's compassionate use program were removed from the study administratively, and the reason for discontinuation is captured under the Administrative/Other category. A total of 478 of the 502 subjects who were discontinued due to 'Administrative/Other'

reasons were discontinued due to one of these administrative reasons. These subjects are considered to have completed the study to the extent their participation was allowed.

For 194 subjects (16.0%), AEs were the primary reason for withdrawal from the study. This number is lower than the 231 subjects who were reported to have been discontinued from study treatment due to an AE (Table below) due to differences in the data source (End of Study Case Report Form (CRF) page versus AE CRF page). Of the 231 subjects who were discontinued from study treatment due to an AE, 194 subjects had "adverse event" recorded as their primary reason for discontinuation and 39 subjects had "adverse event" recorded as their secondary reason for discontinuation. An additional 5 subjects had "adverse event" recorded as the primary reason for discontinuation per the End of Study CRF), but the investigators did not record these events as having an outcome of discontinuation on the AE CRF. Four of these 5 subjects had a fatal AE (27596005, 51284006, 51284011, and 51394009). The remaining subject (44046004) was withdrawn after 40 days of open-label treatment; all reported AEs during the OLE Conversion Period were mild in severity (gait disturbance, stress, diarrhea, and gastric disorder) and did not have an taken of discontinuation or drug interrupted; the secondary reason for discontinuation was 'Subject choice'.

Because >90% of subjects in Study 307 received a maximum daily dose of >8 to 12 mg/day perampanel, inclusive, comparisons of results across maximum dose groups are not meaningful.

The frequency distribution of reasons for discontinuation in the OLE study was similar for subjects who had received prior treatment with placebo or perampanel.

All of the 124 adolescents included in the Adolescent Safety Analysis Set had been discontinued from perampanel treatment in the OLE study, of which 57 (46.0%) withdrew due to administrative/other reasons. Other common reasons for discontinuation among adolescent subjects were subject choice (n=30, 24.2%), AEs (n=18, 14.5 %), and inadequate therapeutic response (n=17, 13.7%).

CHMP's comments:

The majority of subjects (97.1%) are counted as discontinued. The study was terminated due to the product becoming commercially available and 478 subjects were recorded as discontinued on these grounds. The second largest group of discontinuations comes from the subject choice (252 subjects or 20.7%). AEs were the reason for discontinuation in 231 subjects (19%).

The subject disposition is well described in the report. The study was not designed to detect any safety differences between treatment groups and the results are primarily descriptive.

Baseline data

The demographic characteristics and baseline epilepsy-specific history are summarised for subjects in the Safety Analysis Set in the Table below. The demographic characteristics at DB Baseline were similar for the Enrolled Subjects and Full ITT Analysis Set, and did not differ as a function of previous DB treatment with placebo or perampanel.

Table 3: Demographic and Baseline Characteristics (Safety Analysis Set)

Category	Maximum Daily Dose Exposed <4 mg/day (N=1)	4 mg/day (N=13)	>4 to 8 mg/day (N=75)	>8 to 12 mg/day (N=1127)	Total (N=1216)
Age (Year)[a]					
Mean (SD)	35.0	43.1 (16.78)	36.1 (13.93)	34.1 (13.29)	34.3 (13.39)
Min, Max	35, 35	20, 76	12, 70	12, 73	12, 76
Age Group, n (%)					
<18	0	0	9 (12.0)	115 (10.2)	124 (10.2)
18-64	1 (100)	12 (92.3)	64 (85.3)	997 (88.5)	1074 (88.3)
>64	0	1 (7.7)	2 (2.7)	15 (1.3)	18 (1.5)
Sex, n (%)					
Male	1 (100)	6 (46.2)	30 (40.0)	573 (50.8)	610 (50.2)
Female	0	7 (53.8)	45 (60.0)	554 (49.2)	606 (49.8)
Race, n (%)					
White	1 (100)	8 (61.5)	57 (76.0)	844 (74.9)	910 (74.8)
Black or African American	0	1 (7.7)	1 (1.3)	21 (1.9)	23 (1.9)
Asian/Japanese/Chinese	0	3 (23.1)	17 (22.7)	231 (20.5)	251 (20.6)
Other[b]	0	1 (7.7)	0	31 (2.8)	32 (2.6)
Seizure Type,[c] n (%)					
Simple partial without motor signs	0	6 (46.2)	28 (37.3)	358 (31.8)	392 (32.2)
Simple partial with motor signs	1 (100)	6 (46.2)	25 (33.3)	337 (29.9)	369 (30.3)
Complex partial	0	11 (84.6)	65 (86.7)	964 (85.5)	1040 (85.5)
Complex partial with secondary generalization	0	8 (61.5)	49 (65.3)	803 (71.3)	860 (70.7)

Percentages based on the total number of subjects in the relevant treatment group.
DB = double blind, Max = maximum, Min = minimum, n = number of subjects with characteristic, SD = standard deviation.
a: Age at informed consent to core DB study.
b: Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Other race categories.
c: Seizure types are at baseline in the core DB study.
Source: Table 14.1.3.2.

The mean age among adolescent subjects was 14.9 years (range: 12 to 17 years). Approximately 60% (72/124, 58.1%) of adolescents were less than 16 years of age. Other than age, the demographic and baseline characteristics for the Adolescent Safety Analysis Set were similar to those for the overall Safety Analysis Set.

Treatment Compliance and Concomitant Medications

Diary compliance was ascertained from the days on which valid seizure counts were recorded in the subject diary, and the mean compliance was approximately 98% across the entire OLE study in the Full ITT Analysis Set. Treatment compliance, ascertained from counts of tablets dispensed and tablets returned, averaged approximately 99% during the Conversion Period for the Full ITT Analysis Set, and at least 75.9% of subjects were 100% compliant with study medication at Visits 6 to 22 of the Maintenance Period (i.e., visits for which at least 25 subjects had data).Diary compliance and study medication compliance for the Adolescent Full ITT Analysis Set was consistent with that for the Full ITT Analysis Set.

Overall, 13.3% of the subjects in the Safety Analysis Set were taking 1 AED, 50.4% were taking 2 AEDs, and 36.3% were taking 3 AEDs. The most common AEDs taken at DB Baseline were carbamazepine (34.0%), valproic acid (33.3%), lamotrigine (31.3%), levetiracetam (29.2%), topiramate (20.2%), and oxcarbazepine (17.9%); all other background AEDs were taken by <10% of subjects.

The distribution of concomitant AED use at DB Baseline in the Adolescent Safety Analysis Set was similar to that described for the overall Safety Analysis Set.

CHMP's comment:

The compliance was recorded and it was satisfactory. The concomitant medication was frequently taken, as expected for the type of the study. Considering the safety profiles of these additional medications the use of concomitant medications introduces an important level of complexity to the interpretation of the safety events recorded in this study.

Efficacy results

Table below summarises the median percent change from the Pre-perampanel Baseline in seizure frequency per 28 days by 13-week interval through the end of Year 1, and for Weeks 92-104 (end of Year 2), Weeks 144-156 (end of Year 3), Weeks 196-208 (end of Year 4), Weeks 222-234, and Weeks 248-260 (end of Year 5) for the entire Full ITT Analysis Set; data are shown for all partial seizures, complex partial plus secondarily generalised seizures, and secondarily generalised seizures. These data indicate that the benefit of perampanel is sustained over time, although it should be noted that the number of subjects with available data declined over time. The change in the percent reduction in the frequency of all 3 seizure types during the first 3 to 6 months following initiation of adjunctive perampanel treatment is maintained for 4 years. The largest median percent decrease in seizure frequency was observed in subjects with secondarily generalised seizures. The median percent change in all partial seizures per 28 days by 13-week interval is plotted in the figure below among the subsets of subjects in the Full ITT Analysis Set who received at least 26 weeks, 39 weeks, 1 year, 2 years, 3 years, 4 years, and 5 years of treatment.

Table below also summarises the responder rate by 13-week interval through the end of Year 1, and for Weeks 92-104 (end of Year 2), Weeks 144-156 (end of Year 3), Weeks 196-208 (end of Year 4), Weeks 222-234, and Weeks 248-260 (end of Year 5) by seizure type for the entire Full ITT Analysis Set. These data were consistent with those for percent change in seizure frequency, and showed that the responder rate was generally stable across time from about Week 26 through Week 208 for each seizure type.

Table 4: Summary of Percent Change from Pre-perampanel Baseline in Seizure Frequency per 28 Days and Responder Analysis During Perampanel Treatment Duration – Full ITT Analysis Set

	Seizure Type		
Analysis Window Statistic	Overall	Complex partial plus secondarily generalized	Secondarily generalized
Pre-perampanel – N	1217	1126	510
Median seizure frequency	11.17	7.79	3.28
Perampanel Treatment Duration			
Weeks 1-13 – N	1217	1126	510
Median % change	-29.14	-32.42	-54.95
Responder rate, n (%)	375 (30.8)	392 (34.8)	278 (54.5)
Weeks 14-26 – N	1159	1073	482
Median % change	-38.54	-43.19	-65.69
Responder rate, n (%)	474 (40.9)	466 (43.4)	283 (58.7)
Weeks 27-39 – N	1088	1011	458
Median % change	-42.81	-46.22	-77.47
Responder rate, n (%)	481 (44.2)	478 (47.3)	290 (63.3)
Weeks 40-52 – N	969	903	416
Median % change	-46.22	-49.39	-81.15
Responder rate, n (%)	442 (45.6)	446 (49.4)	282 (67.8)
Weeks 92-104 – N	720	664	313
Median % change	-56.59	-62.11	-90.33
Responder rate, n (%)	412 (57.2)	389 (58.6)	217 (69.3)
Weeks 144-156 – N	517	478	231
Median % change	-61.45	-67.95	-100.00
Responder rate, n (%)	315 (60.9)	299 (62.6)	171 (74.0)
Weeks 196-208 – N	119	111	47
Median % change	-73.30	-80.77	-100.00
Responder rate, n (%)	77 (64.7)	79 (71.2)	40 (85.1)
Weeks 222-234 – N	37	36	11
Median % change	-81.36	-89.02	-99.11
Responder rate, n (%)	27 (73.0)	27 (75.0)	8 (72.7)
Weeks 248-260 – N	5	5	1
Median % change	-97.16	-98.39	-98.39
Responder rate, n (%)	4 (80.0)	5 (100.0)	1 (100)

DB = double blind, ITT = intent-to-treat, N = total number of subjects; n = number of subjects with event, OLE – open-label extension. Week 1 begins on the date of the first dose of perampanel treatment duration. The perampanel treatment duration starts from the first perampanel dose in the DB or OLE study to the last perampanel dose in the OLE study, except for subjects with a gap in perampanel exposure from the DB to the OLE study of >14 days where the perampanel treatment duration is the open-label exposure.

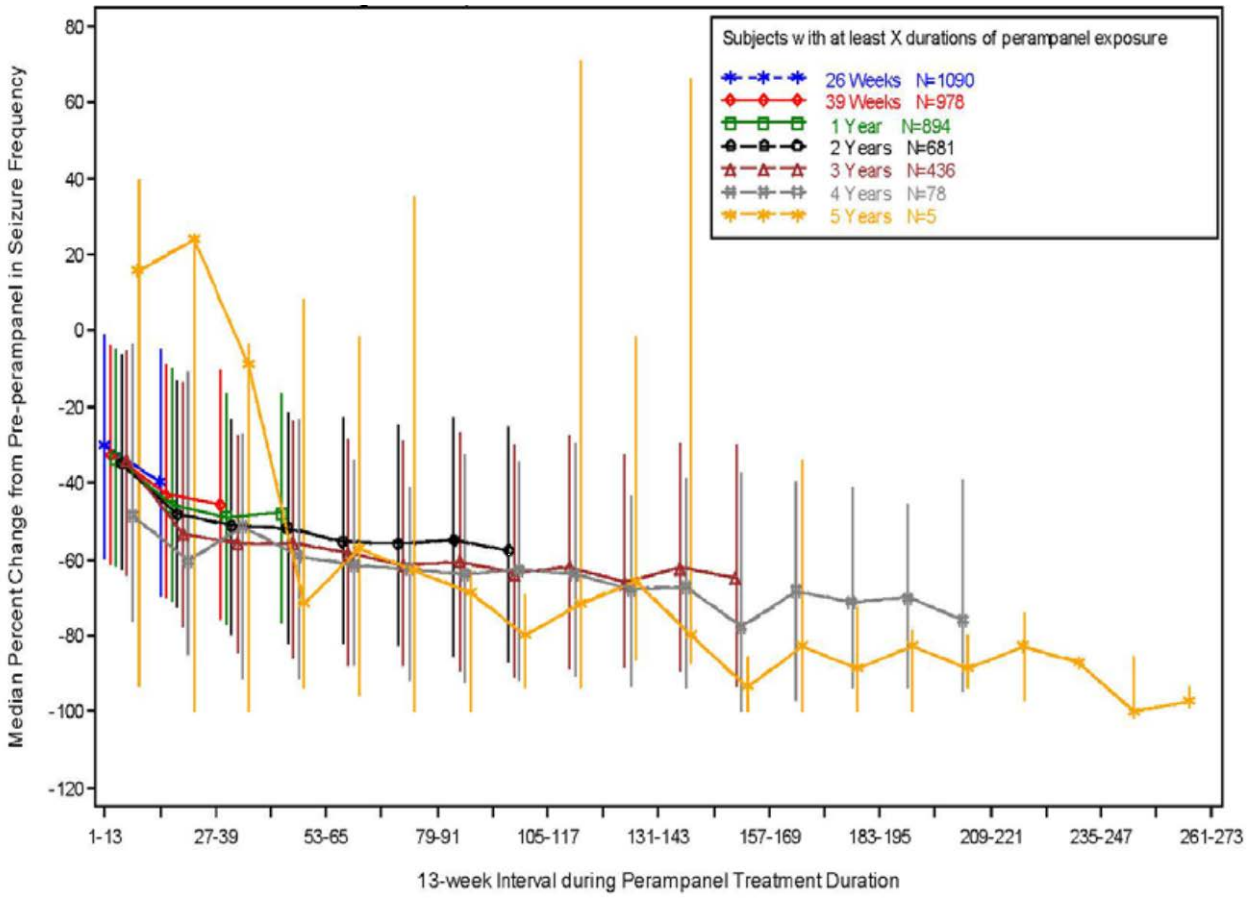

Figure 1: Figure: Median Percent Change from Pre-perampanel Baseline in Seizure Frequency per 28 Days by 13-week Interval During Perampanel Treatment Duration – Full ITT Analysis Set

Among the 1217 subjects in the Full ITT Analysis Set, 8.0% achieved seizure freedom (100% reduction in frequency of all partial-onset seizures) during the Week 27 to 39 analysis window at an optimised dose of perampanel (up to 12 mg/day). Similarly, seizure freedom was achieved during the Weeks 40 to 52 analysis window for 9.4% of the 894 subjects who received at least 1 year of perampanel exposure, and during Weeks 53-104 for 6.9% of the 681 subjects who received at least 2 years of perampanel exposure.

Data for age, sex, and race subgroups were generally consistent with those for the overall population in showing a similar stable pattern over time for improvement in seizure control as reflected by the median percent change in seizure frequency and responder rate. Improvements in seizure control were seen in all subgroups based on the number of background AEDs at DB Baseline. The clinical relevance of these observations is difficult to interpret as changes in background AED therapy, including the addition or removal of AEDs, was permitted during the OLE study.

Table below summarises, by previous DB treatment group (placebo or overall perampanel), the median percent change in total seizure frequency per 28 days and the percentage of responders for the DB Maintenance Period (when dose was stable), the Conversion Period of the OLE study, and by 13-week intervals through Week 208 (end of Year 4) for the Maintenance Period of the OLE study. Among subjects who received prior DB treatment with placebo, both the median percent reduction in total seizure frequency and the responder rate increased to a level similar to that for subjects receiving previous DB treatment with perampanel by the end of the Conversion Period of the OLE study. Efficacy

was maintained over time; a greater reduction in seizure frequency and an increased responder rate was observed with long-term treatment with perampanel.

Table 5: Percent Change from Double-blind Prerandomization Phase in Total Seizure Frequency per 28 days and Responder Rate Through Week 208 of Open-label Study: Full ITT Analysis Set

Analysis Window	Median Percent Change in Total Seizure Frequency		Responder Rate (n, %)	
Parameter	Prior Placebo	Prior Perampanel	Prior Placebo	Prior Perampanel
Seizure Freq. – Prerandomization Phase, n	379	838	379	838
Median	11.45	11.20	--	--
DB Maintenance Period, n	379	838	379	838
Median, % change or responder rate, n (%)	-18.55	-31.70	77 (20.3)	285 (34.0)
Conversion Period – OLE Study, n	379	836	379	836
Median % change or responder rate, n (%)	-44.34	-41.38	168 (44.3)	363 (43.4)
Maintenance Weeks 1-13 – OLE Study, n	303	701	303	701
Median % change or responder rate, n (%)	-48.24	-45.29	146 (48.2)	320 (45.6)
Maintenance Weeks 14-26 – OLE Study, n	280	639	280	639
Median % change or responder rate, n (%)	-48.92	-50.0	137 (48.9)	320 (50.1)
Maintenance Weeks 27-39 – OLE Study, n	262	588	262	588
Median % change or responder rate, n (%)	-53.10	-52.07	136 (51.9)	303 (51.5)
Maintenance Weeks 40-52 – OLE Study, n	247	551	247	551
Median % change or responder rate, n (%)	-53.85	-53.52	134 (54.3)	288 (52.3)
Maintenance Weeks 92-104 – OLE Study, n	178	436	178	436
Median % change or responder rate, n (%)	-67.77	-63.56	117 (65.7)	262 (60.1)
Maintenance Weeks 144-156 – OLE Study, n	78	216	78	216
Median % change or responder rate, n (%)	-72.32	-67.54	53 (67.9)	137 (63.4)
Maintenance Weeks 196-208 – OLE Study, n	17	35	17	35
Median % change or responder rate, n (%)	-69.04	-80.69	12 (70.6)	24 (68.6)

Open-label Maintenance Week 1 begins on the date of first open-label maintenance dose.
DB = double-blind, freq = frequency, ITT = intent-to-treat, n = number of subjects with event, OLE = open-label extension.

By the first year of treatment in the OLE period (ie, OLE Maintenance Weeks 40-52), 11.8% of subjects who had received prior DB treatment with placebo and 11.3% of subjects who had received prior DB treatment with perampanel had achieved seizure freedom (100% reduction in frequency of all partial-onset seizures). During the second year of OLE treatment (OLE Maintenance Weeks 53-104), 8.9% and 8.6% of subjects who had received prior DB treatment with placebo or perampanel, respectively, had achieved seizure freedom.

Because these subgroup analyses were done by DB treatment group, the number of subjects was small (<15) for some of the subgroups. Results were generally consistent for all subgroups in showing improvements in seizure control following initiation of perampanel therapy in the OLE study for subjects who received DB placebo, and sustained improvements in seizure control during the OLE study for subjects who had received DB perampanel.

For the entire Adolescent Full ITT Analysis Set, the median percent change in total seizure frequency per 28 days relative to the Pre-perampanel Baseline (median seizure frequency, 19.36) was -30.72% during Weeks 1 to 13 (n=124), -33.06% during Weeks 14 to 26 (n=115), -45.33% during Weeks 27 to 39 (n=110), -41.79% during Weeks 40 to 52 (n=101), -62.96% during Weeks 92-104 (n=75), and -64.89% during Weeks 144-156 (n=53). The responder rate (all partial seizures) during these same intervals for the Adolescent Full ITT Analysis Set was 29.8%, 38.3%, 47.3%, 39.6%, 60.0%, and 64.2%, respectively. Data were consistent in showing improvements in seizure control following initiation of perampanel therapy in the OLE study for adolescent subjects who received DB placebo, and sustained improvements in seizure control during the OLE study for adolescent subjects who had received DB perampanel.

CHMP's comment:

The numbers presented for the percentage change in the median frequency of seizures and the responder rate do not indicate loss of efficacy over the time.

However, the attrition of participants form the study over the time introduces bias by increasing the number of responders in the remaining patient population. There was no control group and due to the way the doses were selected it is not possible to draw conclusions about comparable efficacy of various dose levels. Furthermore, the changes in the background AED were allowed, so the recorded relative improvements cannot be entirely attributed to the study treatment even if other limitations were not present.

While the recorded improvements seem to level in the "prior-placebo" and the "prior-perampanel" subgroup in the improvement of the frequency of seizures, the responder rate remains consistently higher in the "prior-perampanel" subgroup, indicating that there was a selection bias favouring responders at the time of inclusion into the study.

In view of the significant limitations in the design of the study in regards to investigation of efficacy, it is not possible to draw any reliable conclusions that would change the present assessment of risk and benefit balance in regards to the efficacy.

Safety results

Approximately three quarters of subjects in the Safety Analysis Set (n=889, 73.1%) received more than 52 weeks (1 year) of perampanel treatment, 700 (57.6%) subjects received more than 100 weeks (~2 years) of perampanel treatment, and 401 (33.0%) subjects received more than 160 weeks (~3 years) of perampanel treatment. The mean (SD) cumulative duration of exposure to perampanel for the Safety Analysis Set was 115.41 weeks (range: 1.1, 269.3 weeks). The total exposure to perampanel was 140334 subject weeks (~2699 subject-years).

The mean ± SD dose of perampanel across the entire OLE Treatment Phase, when the dose of perampanel was titrated to maximum individual subject efficacy and tolerability, was 10.15 ± 2.294 mg (range: 1.9, 12.0) for the Safety Analysis Set. The stability of the perampanel dose over the up to ~4-year OLE Treatment Phase is underscored by the similarity of the mean ± SD dose during the initial 16-week Conversion Period (9.85 ± 2.168 mg) and the subsequent Maintenance Period (10.52 ± 2.236 mg). The mean dose across the entire perampanel treatment duration (9.47 ± 2.354 mg) was less than that for the OLE Treatment Phase since it included data from the DB core studies which included a fixed dose DB treatment phase with lower doses.

Among the 124 subjects who comprised the Adolescent Safety Analysis Set, the mean (± SD) cumulative duration of exposure to perampanel was 119.09 (± 70.392) weeks (range: 2.7, 251.6 weeks). No adolescent subject had a gap of >7 days between the double-blind and OLE studies. The mean dose of perampanel across the entire OLE Treatment Phase among adolescent subjects of 10.31 ± 2.353 mg (range: 2.5, 12.0) was similar to that for the overall Safety Analysis Set.

Table below summarises the overall TEAE profile for the Safety Analysis Set. TEAEs included those AEs that occurred from the first day of perampanel administration (in DB and/or OLE study) to 30 days after the last dose of perampanel, or that were present before the first day of perampanel administration but worsened in severity during the study.

Table 6: Adverse Event Summary - Safety Analysis Set

	Maximum Daily Dose Exposed				
	<4 mg/day (N=1) n (%)	4 mg/day (N=13) n (%)	>4 to 8 mg/day (N=75) n (%)	>8 to 12 mg/day (N=1127) n (%)	Total (N=1216) n (%)
TEAE	1 (100)	12 (92.3)	72 (96.0)	1045 (92.7)	1130 (92.9)
Treatment-related TEAE	0	11 (84.6)	70 (93.3)	936 (83.1)	1017 (83.6)
Severe TEAE	0	2 (15.4)	17 (22.7)	245 (21.7)	264 (21.7)
Serious TEAE	0	2 (15.4)	16 (21.3)	270 (24.0)	288 (23.7)
Death	0	0	0	11 (<1)	11 (<1)
Other Serious TEAEs	0	2 (15.4)	16 (21.3)	262 (23.2)	280 (23.0)
Life threatening	0	0	0	17 (1.5)	17 (1.4)
Requires or prolongs hospitalization	0	2 (15.4)	13 (17.3)	249 (22.1)	264 (21.7)
Persistent or significant disability or incapacity	0	0	0	7 (<1)	7 (<1)
Congenital anomaly	0	0	0	0	0
Other important medical event	0	0	4 (5.3)	26 (2.3)	30 (2.5)
TEAE leading to study drug adjustment	1 (100)	11 (84.6)	68 (90.7)	563 (50.0)	643 (52.9)
TEAE leading to study or study drug withdrawal	1 (100)	6 (46.2)	28 (37.3)	196 (17.4)	231 (19.0)
TEAE leading to study or study drug dose reduction	0	8 (61.5)	58 (77.3)	440 (39.0)	506 (41.6)
TEAE leading to study or study drug dose interruption	0	0	3 (4.0)	51 (4.5)	54 (4.4)

TEAE = Treatment-emergent adverse event: An adverse event is treatment emergent if the adverse event started on or after the date of first perampanel dose and prior to or on the day of (Date of Last Dose + 30 days) of open-label treatment.
Percentages are based on the total number of subjects in relevant treatment group.
For each row category, a subject with 2 or more adverse events in that category is counted only once.
Adverse events were summarized across the entire perampanel exposure. For subjects who received perampanel in the preceding double-blind study, the perampanel exposure consisted of the double-blind plus the open-label treatment duration. For subjects who received placebo in the preceding double-blind study, the perampanel exposure consisted of the open-label treatment duration.
Source: Table 14.3.2.1.1.

There were 11 subject deaths during perampanel exposure, 3 of which were previously reported in the previous interim synoptic CSR where the mean cumulative duration of perampanel exposure was 52 weeks. Two of the 11 deaths were classified as a sudden unexplained death in epilepsy (SUDEP). Ten of the 11 deaths occurred within 30 days of the last dose of perampanel (8 occurred while on perampanel or within 2 to 3 days of the last dose). One death occurred more than 30 days after the last dose of perampanel. Ten of the 11 deaths were assessed by the investigator as not related to study treatment; a death due to convulsions in an adolescent subject was assessed as possibly related to study treatment. In addition, there was a pregnancy in a subject which resulted in neonatal death after Caesarian delivery.

A total of 288 (23.7%) subjects in the Safety Analysis Set had SAEs (including fatal events) up through the 5 years of exposure to perampanel across the DB or OLE studies. The most common treatment-emergent SAEs (preferred terms) were those related to epilepsy (convulsion [n=43, 3.5%], status epilepticus [n=16, 1.3%], epilepsy [n=15, 1.2%], grand mal convulsion [n=6, <1%], seizure cluster

[n=6, <1%], partial seizures [n=3, <1%], partial seizures with secondary generalisation [n=3, <1%], drug withdrawal convulsions [n=2, <1%]). Most of these epilepsy-related TEAEs were considered serious because they involved hospitalisation or prolonged hospitalization. Pneumonia (n=13, 1.1%) and aggression (n=14, 1.2%) were the only non-seizure related SAEs reported in >1% of subjects. Those SAEs which occurred in 0.5% to <1.0% (6 to 12 subjects) were head injury (n=12), psychotic disorder (n=8), ankle fracture (n=7), suicidal ideation (n=6), urinary tract infection (n=6), and abortion induced (n=6). All non-fatal SAEs had resolved except in 12 subjects (1.0%) (peripheral sensorimotor neuropathy [24095001], epilepsy [13035002], colitis [25026006], head injury [52015004], iritis [25036001], somnolence [25026010], breast cancer metastatic [28065004], nephrolithiasis [29045003], ataxia [32026006], affective disorder [42045004], carotid artery dissection [34035004], pneumonia and dementia [51284011]). Non-fatal SAEs led to withdrawal of perampanel in 70 (5.0%) subjects.

TEAEs resulting in discontinuation from the study or perampanel treatment occurred in 231 subjects (19 %) in the Safety Analysis Set up through the 5 years of exposure to perampanel in the DB or OLE study (Table 5). For 194 of these subjects, AEs were also the primary reason for withdrawal from the study (Table 1). For 39 of the 231 subjects, the investigator indicated that AEs was the secondary reason for study withdrawal (primary reason of subject choice in 25 subjects, inadequate therapeutic response in 11 subjects, lost to follow-up in 2 subjects, and administrative/other in 1 subject). For 3 subjects who were discontinued from perampanel therapy due to an AE, the primary reason for withdrawal from the study was administrative/other (unable to receive oral drug [10074009], study closing [10074002 and 24035001]) (Listing 16.2.1.2).

Dizziness (n=50, 4.1%) irritability (n=15, 1.2%), and fatigue (n=13, 1.1%) were the only TEAEs (preferred terms) that resulted in the discontinuation of 1% or more of subjects; other TEAEs (preferred terms) that resulted in the discontinuation of 0.5% to <1.0% (6 to 12) of subjects were mainly psychiatric or nervous system disorders (convulsion [n=12], aggression [n=12], somnolence [n=11], ataxia [n=10], abnormal behaviour [n=9], headache [n=8], anger [n=7], depression [n=6], suicidal ideation [n=6], and gait disturbance [n=6]) and also included vertigo (n=7), weight increased (n=8), and diplopia (n=6).

A total of 531 (43.7%) of subjects in the Safety Analysis Set had a TEAE that resulted in interruption of study drug or dose adjustment (i.e., reduction) during exposure to perampanel in the DB or OLE study. The most common of these events (≥2.0% incidence) were dizziness (22.8%), somnolence (8.6%), ataxia (3.6%), fatigue (3.1%), dysarthria (2.3%), headache (2.3%), gait disturbance (2.1%), and vertigo (2.1%). For most subjects, these TEAEs resolved without sequelae and the subject remained on treatment.

TEAEs that the investigators indicated were associated with overdose (by checking a box on the AE page of the CRF) occurred in 25 (2.1%) subjects in the Safety Analysis Set during exposure to perampanel in the DB or OLE study. The most common TEAEs that the investigators indicated were associated with overdose were in the nervous system disorder SOC (n=18, 1.5%), of which dizziness (n=13, 1.1%) was the most common. All but 1 of these TEAEs resolved (somnolence in 1 subject was persisting). For 6 subjects, these TEAEs were serious (mostly due to requiring hospitalisation) (intentional overdose, accidental overdose [n=2], suicide attempt, grand mal seizure, and adjustment disorder).

There were a total of 14 pregnancies in 13 women enrolled in Study 307 (3 subjects had 2 pregnancies, one approximately 6 months apart, one approximately 1 year apart, one subject approximately 18 months apart). Of the 14 pregnancies, 8 resulted in induced abortions (12036009, 21026008, 21026020, 30036001, 51735003, 33014004, 39566001, and 10124004), 3 resulted in a

spontaneous abortion (30036001, 39566001, and 10124006), 2 resulted in the birth of a healthy infant (30026004 and 10124006). The remaining pregnancy (27606003) also resulted in a live birth following Caesarian section at 39 weeks of gestation; however, the neonate died approximately 5-6 hours after birth. The investigator considered the neonatal death to be likely related to aspiration of fluid during birth and not related to study treatment. Perampanel was discontinued in 8 subjects (6 as a result of the positive pregnancy test, 2 for lack of efficacy), including 4 subjects who subsequently had an induced abortion, 2 subjects who subsequently had a spontaneous abortion, 1 subject who delivered a healthy infant, and the 1 subject whose pregnancy resulted in neonatal death after Caesarian delivery. Narratives for the 13 subjects with confirmed pregnancies are provided in Section 14.3.3. Positive pregnancy test results were erroneously recorded on the CRF for 2 subjects (37016004, 51364005); the investigational sites confirmed that these subjects had not been pregnant.

Sixteen (1.3%) subjects in the Safety Analysis Set had an AE related to suicidality during exposure to perampanel in the DB and/or OLE study. For 12 subjects, the event consisted of suicidal ideation, and for 4 subjects, the event was non-fatal suicide attempt. All subjects with suicidal events recovered, and 8 of the 16 subjects remained in the study.

Falls were reported as a TEAE for 118 (9.7%) of subjects during perampanel exposure during the DB or OLE study. Few of these events were serious (n=5) or resulted in withdrawal of perampanel treatment (n=5).

Aggression events (aggression, anger, paranoia) were reported as TEAEs for 85 (7.0%) subjects during perampanel exposure during the DB or OLE study (Table 6). Most of these events were non-serious and did not result in treatment discontinuation. For 14 subjects (1.2%), aggression was serious, and for 12 subjects (<1%), this event resulted in withdrawal of perampanel treatment. Most events of aggression that were serious or resulted in discontinuation of study treatment resolved.

Mood disorders and disturbances were the most common AE category of special interest, reported for 263 (21.6%) subjects. The most common of these events was irritability (n=158, 13.0%). Irritability generally did not result in treatment discontinuation (n=1, <1%) and was considered serious in only 1 subject.

At least 1 TEAE occurred in 1130 (92.9%) subjects in the Safety Analysis Set during exposure to perampanel in the DB and/or OLE study. The following table presents common TEAEs, i.e., those with an incidence of ≥5.0%.

Table 7: Treatment-emergent Adverse Events: Most Common (≥5% in Total Safety Population) - Safety Analysis Set and Adolescent Safety Analysis Set

	Total Subjects (N=1216) n (%)	Adolescent Subjects (N=124) n (%)
Dizziness	592 (48.7)	38 (30.6)
Somnolence	268 (22.0)	29 (23.4)
Headache	246 (20.2)	29 (23.4)
Fatigue	183 (15.0)	14 (11.3)
Weight increased	161 (13.2)	11 (8.9)
Irritability	160 (13.2)	16 (12.9)
Nasopharyngitis	142 (11.7)	30 (24.2)
Fall	118 (9.7)	14 (11.3)
Nausea	117 (9.6)	8 (6.5)
Convulsion	113 (9.3)	19 (15.3)
Upper respiratory tract infection	107 (8.8)	14 (11.3)
Vomiting	95 (7.8)	17 (13.7)
Back pain	87 (7.2)	3 (2.4)
Depression	87 (7.2)	5 (4.0)
Insomnia	87 (7.2)	11 (8.9)
Ataxia	86 (7.1)	7 (5.6)
Diarrhoea	84 (6.9)	11 (8.9)
Gait disturbance	80 (6.6)	5 (4.0)
Pyrexia	80 (6.6)	18 (14.5)
Anxiety	79 (6.5)	9 (7.3)
Vertigo	78 (6.4)	2 (1.6)
Balance disorder	74 (6.1)	7 (5.6)
Influenza	71 (5.8)	9 (7.3)
Laceration	69 (5.7)	8 (6.5)
Aggression	66 (5.4)	25 (20.2)
Diplopia	64 (5.3)	4 (3.2)
Contusion	62 (5.1)	4 (3.2)
Dysarthria	62 (5.1)	2 (1.6)

An adverse event is treatment emergent if the adverse event started on or after the date of first perampanel dose and prior to or on the day of (Date of Last Dose + 30 days) of open-label treatment.
Percentages are based on the total number of subjects in relevant treatment group.
A subject with 2 or more adverse events in the same preferred term is counted only once for that preferred term.
Adverse events were summarized across the entire perampanel exposure. For subjects who received perampanel in the preceding double-blind study, the perampanel exposure consisted of the double-blind plus the open-label treatment duration. For subjects who received placebo in the preceding double-blind study, the perampanel exposure consisted of the open-label treatment duration.

The TEAE profile for adolescents receiving perampanel in the DB and/or OLE study was generally similar to that for the entire Safety Analysis Set. The following common TEAEs in the total Safety Analysis Set (≥5%) appeared to be reported at an approximately 2-fold higher frequency in adolescent subjects receiving perampanel compared to the total population: nasopharyngitis (24.2% vs. 11.7%), aggression (20.2% vs. 5.4%), vomiting (13.7% vs. 7.8%), and pyrexia (14.5% vs. 6.6%) (Table above). The following common TEAEs in the total Safety Analysis Set were at least 2-fold less frequent among adolescents receiving perampanel compared to the total population: back pain (2.4% vs 7.2%), vertigo (1.6% vs 6.4%), and dysarthria (1.6% vs 5.1%). Of note, irritability occurred in similar rates for the total and adolescent Safety Analysis Sets (13.2% and 12.9%, respectively).

One death occurred in an adolescent subject (death due to convulsion in Subject 51815001). Rates for the following events in adolescents were similar to those for the total Safety Analysis Set: SAEs (29.0% vs 23.7%, respectively), AEs leading to discontinuation from the study or perampanel (18.5% vs 19.0%, respectively), and TEAEs leading to dose reduction (34.7% vs 41.6%, respectively). SAEs reported in 2% or more of adolescent subjects were convulsions (n=11, 8.9%), aggression (n=5, 4.0%), and status epilepticus (n=3, 2.4%) was the most common SAE among adolescent subjects.

There were no clinically important mean changes in haematology or clinical chemistry laboratory values during exposure to perampanel in the DB and/or OLE study for the Safety Analysis Set. Similarly, shift analysis revealed no shifts of clinical concern for haematology or clinical chemistry parameters. The most common markedly abnormal haematology value was low neutrophils (n=86, 7.2%), while the most common markedly abnormal clinical chemistry value was low sodium (n=62, 5.2%) and high gamma glutamyl transferase (n=71, 5.9%). The clinical laboratory safety profile for the 124 adolescent subjects was similar to that described for the overall Safety Analysis Set.

There were no clinically important mean changes in vital signs during perampanel exposure in the DB and/or OLE study for the Safety Analysis Set; mean changes from baseline to the EOT in blood pressure and heart rate were less than ± 2 mmHg or bpm, respectively. The pattern of results for vital sign measurements during perampanel exposure for the Adolescent Safety Analysis Set was similar to that for the total Safety Analysis Set. As expected, there was a progressive increase in body weight and height over time for both male and female subjects. The mean ± SD change from baseline to the EOT in body weight and height were 7.63 ± 9.933 kg (n=72) and 5.71 ± 8.677 cm (n=49), respectively, among male adolescent subjects and 6.23 ± 7.995 kg (n=51) and 3.41 ± 3.536 cm (n=36), respectively, among female adolescent subjects. In this adolescent population, a weight increase of >7% was observed in 67.7% of adolescents (9.7% had weight decrease of >7%).

There were no clinically important changes in mean ECG parameters. Shifts from baseline to each visit in ECG interpretation also showed no shifts of clinical concern. The ECG results for the Adolescent Safety Analysis Set were consistent with those for the total Safety Analysis Set.

With implementation of Amendment 03, Tanner staging was to have been done and blood samples were to have been collected and analysed for thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), and IGF-1 at Week 16 and 40 among adolescent subjects. There was no appreciable difference in the mean or median values for TSH, fT3, fT4, and IGF-1 at Weeks 16 and 40.

Tanner staging data were available for 13 adolescents (6 male, 7 female). All but 1 of these subjects were at Tanner Stage IV or V at OLE Baseline (one female subject was in Tanner Stage III), and either remained at the same stage or had increased to the next stage at the last available assessment. There were too few adolescent subjects to allow meaningful interpretation of these data.

CHMP's comment:

Despite the length of the study and the total number of recruited patients, the exposure was relatively modest - 889 patients exposed to one year and considerably fewer for longer periods. The mean dose 10.15mg can be regarded as reflective of what average will be used in the clinical practice. 124 subjects who comprised the adolescent safety analysis set had the cumulative duration of exposure of 119.09 (+/-70.392) weeks, the mean dose was marginally higher than in adults 10.31.

Total 1017 treatment emergent adverse events occurred during the study. Of those 288 were described as serious. There were 11 deaths and of those one was in an adolescent due to convulsions assessed as possibly related to the study medication. In an additional case a pregnancy resulted in neonatal death following Caesarean delivery birth. The investigator considered the neonatal death to be likely related to aspiration of fluid during birth and not related to the study treatment. The reported cases of death are not seen as additional safety concern.

Drug treatment was interrupted in 531 subjects due to TEAE of which the most common was dizziness. In majority of cases the treatment was continued after the AE resolved. TEAEs associated with overdose occurred in 25 subjects. In one subject the overdose related AE, somnolence, remain persistent. None of these safety events is unexpected or substantially different to what is seen with the product in past.

Of the 14 pregnancies during the study, 8 resulted in induced abortions, 3 resulted in a spontaneous abortion and 2 in birth to a healthy infant. In addition, as already mentioned, one infant died after birth by Caesarean section. There are no clear safety signals from cases of pregnancies in this trial.

Aggression events (aggression, anger, paranoia) were reported as TEAEs for 85 (7.0%) subjects. For 14 subjects (1.2%), aggression was serious, and for 12 subjects (<1%), this event resulted in withdrawal of perampanel treatment.

Of the TEAEs Dizziness, Somnolence and Headache are the most frequently recorded events. Headache, however, does not appear in the list of AEs in the current product information. Following the request for the additional information, the justification for leaving it out based on the similarity of the rates in those on placebo and those on perampanel in the placebo controlled studies was accepted.

Aggression appeared in 20.2% of the adolescent subjects compared to 5.4% in the overall study population. In addition the safety profile in the overall population does not appear entirely similar to that in the patients younger than 18.

Table 8: Table: Comparison of the treatment emerging AEs in overall study population and in the adolescent subset

Overall Study Population		Adolescents	
TEAE	**Percentage of Patients**	**TEAE**	**Percentage of Patients**
Dizziness	48.7	Dizziness	30.6
Somnolence	22.0	Nasopharyngitis	24.2
Headache	20.2	Somnolence	23.4
Fatigue	15.0	Headache	23.4
Weight-increased	13.2	Aggression	20.2
Irritability	13.2	Convulsion	15.3
Nasopharyngitis	11.7	Pyrexia	14.5
Fall	9.7	Vomiting	13.7
Nausea	9.6	Irritability	12.9
Convulsion	9.3	Fatigue	11.3
Upper-respiratory-tract-infection	8.8	Fall	11.3
Vomiting	7.8	Upper-respiratory-tract-infection	11.3

Back-pain	7.2	Weight-increased	8.9
Depression	7.2	Insomnia	8.9
Insomnia	7.2	Diarrhoea	8.9
Ataxia	7.1	Anxiety	7.3
Diarrhoea	6.9	Influenza	7.3
Gait-disturbance	6.6	Nausea	6.5
Pyrexia	6.6	Laceration	6.5
Anxiety	6.5	Ataxia	5.6
Vertigo	6.4	Balance-disorder	5.6
Balance-disorder	6.1	Depression	4.0
Influenza	5.8	Gait-disturbance	4.0
Laceration	5.7	Diplopia	3.2
Aggression	5.4	Contusion	3.2
Diplopia	5.3	Back-pain	2.4
Contusion	5.1	Vertigo	1.6
Dysarthria	5.1	Dysarthria	1.6

The table above illustrates that there are certain differences in the safety profiles in overall study population compared to the adolescent subgroup. The differences are likely to be more pronounced if the adult subgroup rather than the overall population was compared to the adolescent subgroup. Originally proposed wording of the product information did not indicate that there was any difference in the safety profile of the product when used in the adults compared to the paediatric patients.

Following the supplemental information on occurrence of aggression in adolescents, this was included in the product literature. The information on any other possible differences in the safety profile for adults and adolescents will be considered as part of the PSUR process.

2.3.3. Discussion on clinical aspects

As part of this procedure the data from one study have been submitted. This was an open label extension in which patients from pivotal blinded randomised placebo controlled studies were enrolled and followed for loss of efficacy and for safety.

There was no evidence of loss of efficacy, but due to the limitations in the design of the study, reliable conclusions about the efficacy in long term use cannot be made.

Safety has also been assessed and the presented data generally match the known safety related issues for perampanel. However, further clarifications were requested in regards to the safety in the overall population compared to the safety in adolescents. The applicant has provided this information and the product literature has been amended to reflect the identified issues.

3. CHMP's overall conclusion and recommendation

The additional data submitted with this procedure is primarily focused on the longer term safety of the product. No reliable conclusions regarding the efficacy can be made based on the submitted data.

Generally, the presented data confirm the known safety profile of perampanel and the risk benefit balance can also be regarded as positive. Following further clarification regarding the adverse event "aggression" in adolescents, the product information has been amended accordingly.

A further, thorough comparison of the safety in adults and paediatric patients is needed. Since the product is already marketed, the post marketing information together with the trail data should be presented and analysed for any such differences during the next PSUR cycle.

☒ **Fulfilled:**

☐ **Not fulfilled**

4. Additional clarification requested following preliminary assessment

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

The timetable is a 30 day response timetable with clock stop.

1. Headache was recorded in 20.2% of subjects on this study. However, this does not appear in the section 4.8 of the SmPC. Please provide justification or amend the SmPC and PIL accordingly.
2. The safety profile as recorded in this study in the overall study population does not appear to closely match that of the adolescents. Further information is needed:
    a. Please provide TEAE frequencies for adults (as opposed to the overall study population) and compare this to the TEAE frequencies in adolescents.
    b. Please provide TEAE frequencies for the serious AEs in adults compared to the serious TEAE in paediatric patients.
    c. Please integrate all safety results, the existing data and data recorded in E2007-G000-307 and present the comparison of the integrated safety profile of adults to that of the paediatric patients.
    d. Please provide evidence based justification of the SmPC statements that the safety profile in adolescents is expected to be similar to that of the adults, or alternatively amend the product information to reflect the differences.
    e. Please justify the omission in SmPC and PIL of the information on increased rate of aggression in adolescent patients compared to adults or amend the product information accordingly.

5. Assessment of Applicants Responses

Question 1

Question 1

Headache was recorded in 20.2% of subjects on this study. However, this does not appear in the section 4.8 of the SmPC. Please provide justification or amend the SmPC and PIL accordingly.

Response

The adverse reactions in Section 4.8 of the SmPC were based on a review of the double blind Phase 3 partial-onset seizure (POS) epilepsy studies (304, 305, and 306). In the POS submission which included the Epilepsy Phase 3 Double-blind pool, headache occurred in 11.3% of subjects on placebo and 11.4% of total subjects on perampanel. In the integrated data of controlled clinical studies of both POS and primary generalized tonic-clonic (PGTC) seizures (Studies 304, 305, 306, and 332), headache

occurred in 11.1% of subjects on placebo and 11.9% of subjects on perampanel. Headache was not considered an adverse reaction and was therefore not included in Section 4.8. Headache is a fairly common symptom across the patient population, as demonstrated by the placebo rate in the controlled clinical trials. The incidence rate of headaches would be expected to go up in longer duration studies, such as the open-label extension 307 study, as it happens for most adverse events (AEs), even in the absence of a drug effect. Therefore, it is considered that the incidence rate of 20.2% in Study 307 after long-term open-label treatment does not change the conclusion of the analysis of the controlled clinical trial data that headache is not an adverse drug reaction for perampanel.

Assessment of the Response and Conclusion

The rates of headache compared to placebo are marginally higher than for those on active treatments in the placebo controlled studies. The applicant's justification for not including headache is accepted.

Point resolved.

Question 2A

Please provide TEAE frequencies for adults (as opposed to the overall study population) and compare this to the TEAE frequencies in adolescents.

Response

The incidence of the most common TEAEs for adults compared to those in paediatric patients are found in Table 1 below. The incidence of all TEAEs can be found in Appendix 1. Table 1 shows that the incidences of the majority of the TEAEs are comparable between adults and adolescents, although there is a higher incidence of aggression in adolescents (20.2%) compared to adults (3.8%). It is worth noting that higher incidence of aggression in adolescents was also observed in the phase 3 double-bind, placebo-controlled studies. In addition, the incidence of nasopharyngitis, pyrexia, pharyngitis, abdominal pain and rhinitis is also higher (more than 2 times) in adolescents than in adults, although this is not unexpected in this age group.

Table 1 Treatment-emergent Adverse Events: Most Common (≥5% in Any Population) - Safety Analysis Set Study 307

	Overall Subjects (N=1216) n (%)	Adult Subjects (N=1092) n (%)	Adolescent Subjects (N=124) n (%)
Dizziness	592 (48.7)	554 (50.7)	38 (30.6)
Somnolence	268 (22.0)	239 (21.9)	29 (23.4)
Headache	246 (20.2)	217 (19.9)	29 (23.4)
Fatigue	183 (15.0)	169 (15.5)	14 (11.3)
Weight increased	161 (13.2)	150 (13.7)	11 (8.9)
Irritability	160 (13.2)	144 (13.2)	16 (12.9)
Nasopharyngitis	142 (11.7)	112 (10.3)	30 (24.2)
Fall	118 (9.7)	104 (9.5)	14 (11.3)
Nausea	117 (9.6)	109 (10.0)	8 (6.5)
Convulsion	113 (9.3)	94 (8.6)	19 (15.3)
Upper respiratory tract infection	107 (8.8)	93 (8.5)	14 (11.3)

Table 1 Treatment-emergent Adverse Events: Most Common (≥5% in Any Population) - Safety Analysis Set Study 307

	Overall Subjects (N=1216) n (%)	Adult Subjects (N=1092) n (%)	Adolescent Subjects (N=124) n (%)
Vomiting	95 (7.8)	78 (7.1)	17 (13.7)
Back pain	87 (7.2)	84 (7.7)	3 (2.4)
Depression	87 (7.2)	82 (7.5)	5 (4.0)
Insomnia	87 (7.2)	76 (7.0)	11 (8.9)
Ataxia	86 (7.1)	79 (7.2)	7 (5.6)
Diarrhoea	84 (6.9)	73 (6.7)	11 (8.9)
Gait disturbance	80 (6.6)	75 (6.9)	5 (4.0)
Pyrexia	80 (6.6)	62 (5.7)	18 (14.5)
Anxiety	79 (6.5)	70 (6.4)	9 (7.3)
Vertigo	78 (6.4)	76 (7.0)	2 (1.6)
Balance disorder	74 (6.1)	67 (6.1)	7 (5.6)
Influenza	71 (5.8)	62 (5.7)	9 (7.3)
Laceration	69 (5.7)	61 (5.6)	8 (6.5)
Aggression	66 (5.4)	41 (3.8)	25 (20.2)
Diplopia	64 (5.3)	60 (5.5)	4 (3.2)
Dysarthria	62 (5.1)	60 (5.5)	2 (1.6)
Contusion	62 (5.1)	58 (5.3)	4 (3.2)
Head injury	60 (4.9)	53 (4.9)	7 (5.6)
Decreased appetite	58 (4.8)	49 (4.5)	9 (7.3)
Cough	54 (4.4)	46 (4.2)	8 (6.5)
Oropharyngeal pain	43 (3.5)	36 (3.3)	7 (5.6)
Pharyngitis	36 (3.0)	27 (2.5)	9 (7.3)
Abdominal pain upper	33 (2.7)	26 (2.4)	7 (5.6)
Rhinitis	19 (1.6)	10 (0.9)	9 (7.3)

An Adverse Event is Treatment Emergent if the Adverse Event started on or after the Date of First Perampanel Dose and prior to or on the day of (Date of Last Dose + 30 days) of open-label treatment.
Percentages are based on the total number of subjects in relevant treatment group
A subject with two or more adverse events in the same preferred term is counted only once for that preferred term
Adverse events were summarized across the entire perampanel exposure. For subjects who received perampanel in the preceding double-blind study, the perampanel exposure consisted of the double-blind plus the open-label treatment duration. For subjects who received placebo in the preceding double-blind study, the perampanel exposure consisted of the open-label treatment duration.

Question 2B

Please provide TEAE frequencies for the serious AEs in adults compared to the serious TEAE in paediatric patients.

Response

TEAE incidence for serious AEs in adults compared to serious TEAEs in adolescent patients for events in ≥2 subjects in any population are found in Table 2 below. The incidence of all TEAEs can be found in Appendix 2. The result shows higher incidence of epilepsy related SAEs (convulsion and status epilepticus), as well as aggression in adolescents compared to adults.

Table 2 Serious Treatment-emergent Adverse Events: (≥2 Subjects in Any Population) Safety Analysis Set Study 307

	Overall Subjects (N=1216) n (%)	Adult Subjects (N=1092) n (%)	Adolescent Subjects (N=124) n (%)
Convulsion	43 (3.5)	32 (2.9)	11 (8.9)
Status epilepticus	16 (1.3)	13 (1.2)	3 (2.4)
Epilepsy	15 (1.2)	13 (1.2)	2 (1.6)
Aggression	14 (1.2)	9 (0.8)	5 (4.0)
Pneumonia	13 (1.1)	12 (1.1)	1 (0.8)
Head injury	12 (1.0)	11 (1.0)	1 (0.8)
Psychotic disorder	8 (0.7)	8 (0.7)	0
Ankle fracture	7 (0.6)	7 (0.6)	0
Dizziness	6 (0.5)	6 (0.5)	0
Seizure cluster	6 (0.5)	6 (0.5)	0
Suicidal ideation	6 (0.5)	6 (0.5)	0
Urinary tract infection	6 (0.5)	6 (0.5)	0
Abortion induced	6 (0.5)	5 (0.5)	1 (0.8)
Grand mal convulsion	6 (0.5)	5 (0.5)	1 (0.8)
Affective disorder	5 (0.4)	5 (0.5)	0
Depression	5 (0.4)	5 (0.5)	0
Osteoarthritis	5 (0.4)	5 (0.5)	0
Road traffic accident	5 (0.4)	5 (0.5)	0
Toxicity to various agents	5 (0.4)	5 (0.5)	0
Fall	5 (0.4)	4 (0.4)	1 (0.8)
Appendicitis	5 (0.4)	3 (0.3)	2 (1.6)
Acute psychosis	4 (0.3)	4 (0.4)	0
Cholelithiasis	4 (0.3)	4 (0.4)	0
Contusion	4 (0.3)	4 (0.4)	0
Facial bones fracture	4 (0.3)	4 (0.4)	0
Suicide attempt	4 (0.3)	4 (0.4)	0
Angina pectoris	3 (0.2)	3 (0.3)	0
Ataxia	3 (0.2)	3 (0.3)	0
Atrial fibrillation	3 (0.2)	3 (0.3)	0

Table 2 Serious Treatment-emergent Adverse Events: (≥2 Subjects in Any Population) Safety Analysis Set Study 307

	Overall Subjects (N=1216) n (%)	Adult Subjects (N=1092) n (%)	Adolescent Subjects (N=124) n (%)
Craniocerebral injury	3 (0.2)	3 (0.3)	0
Disorientation	3 (0.2)	3 (0.3)	0
Dyspnoea	3 (0.2)	3 (0.3)	0
Gastritis	3 (0.2)	3 (0.3)	0
Hyponatraemia	3 (0.2)	3 (0.3)	0
Lumbar vertebral fracture	3 (0.2)	3 (0.3)	0
Nausea	3 (0.2)	3 (0.3)	0
Paranoia	3 (0.2)	3 (0.3)	0
Partial seizures	3 (0.2)	3 (0.3)	0
Foot fracture	3 (0.2)	2 (0.2)	1 (0.8)
Partial seizures with secondary generalisation	3 (0.2)	1 (0.1)	2 (1.6)
Abnormal behaviour	2 (0.2)	2 (0.2)	0
Accidental overdose	2 (0.2)	2 (0.2)	0
Agitation	2 (0.2)	2 (0.2)	0
Back pain	2 (0.2)	2 (0.2)	0
Bradycardia	2 (0.2)	2 (0.2)	0
Brain contusion	2 (0.2)	2 (0.2)	0
Cerebral haemorrhage	2 (0.2)	2 (0.2)	0
Cerebrovascular accident	2 (0.2)	2 (0.2)	0
Cholecystitis	2 (0.2)	2 (0.2)	0
Clavicle fracture	2 (0.2)	2 (0.2)	0
Colon cancer	2 (0.2)	2 (0.2)	0
Device related infection	2 (0.2)	2 (0.2)	0
Drug withdrawal convulsions	2 (0.2)	2 (0.2)	0
Dysarthria	2 (0.2)	2 (0.2)	0

Table 2 Serious Treatment-emergent Adverse Events: (≥2 Subjects in Any Population) Safety Analysis Set Study 307

	Overall Subjects (N=1216) n (%)	Adult Subjects (N=1092) n (%)	Adolescent Subjects (N=124) n (%)
Extradural haematoma	2 (0.2)	2 (0.2)	0
Fibula fracture	2 (0.2)	2 (0.2)	0
Gait disturbance	2 (0.2)	2 (0.2)	0
Hand fracture	2 (0.2)	2 (0.2)	0
Hemiparesis	2 (0.2)	2 (0.2)	0
Humerus fracture	2 (0.2)	2 (0.2)	0
Hypertension	2 (0.2)	2 (0.2)	0
Hypoaesthesia	2 (0.2)	2 (0.2)	0
Laceration	2 (0.2)	2 (0.2)	0
Muscular weakness	2 (0.2)	2 (0.2)	0
Nephrolithiasis	2 (0.2)	2 (0.2)	0
Pain	2 (0.2)	2 (0.2)	0
Pneumonia aspiration	2 (0.2)	2 (0.2)	0
Rib fracture	2 (0.2)	2 (0.2)	0
Somnolence	2 (0.2)	2 (0.2)	0
Subdural haematoma	2 (0.2)	2 (0.2)	0
Syncope	2 (0.2)	2 (0.2)	0
Tibia fracture	2 (0.2)	2 (0.2)	0
Tooth abscess	2 (0.2)	2 (0.2)	0
Wound infection staphylococcal	2 (0.2)	2 (0.2)	0
Abortion spontaneous	2 (0.2)	1 (0.1)	1 (0.8)
Dysfunctional uterine bleeding	2 (0.2)	1 (0.1)	1 (0.8)
Jaw fracture	2 (0.2)	1 (0.1)	1 (0.8)
Lower limb fracture	2 (0.2)	1 (0.1)	1 (0.8)
Postoperative wound infection	2 (0.2)	1 (0.1)	1 (0.8)
Traumatic intracranial haemorrhage	2 (0.2)	1 (0.1)	1 (0.8)

An Adverse Event is Treatment Emergent if the Adverse Event started on or after the Date of First Perampanel Dose and prior to or on the day of (Date of Last Dose + 30 days) of open-label treatment.

Percentages are based on the total number of subjects in relevant treatment group

A subject with two or more adverse events in the same preferred term is counted only once for that preferred term

Adverse events were summarized across the entire perampanel exposure. For subjects who received perampanel in the preceding double-blind study, the perampanel exposure consisted of the double-blind plus the open-label treatment duration. For subjects who received placebo in the preceding double-blind study, the perampanel exposure consisted of the open-label treatment duration.

Question 2C

Please integrate all safety results, the existing data and data recorded in E2007-G000- 307 and present the comparison of the integrated safety profile of adults to that of the paediatric patients.

Response

The incidence of the most common TEAE for adults compared to those for paediatric patients in the pooled data from three open label extension (OLE) studies are found in Table 3 below. The incidence of all TEAEs can be found in Appendix 3.

Table 3 shows that the incidence of the majority of the TEAEs is comparable between adults and adolescents, although there is a higher incidence of aggression in adolescents (12.5%) compared to adults (3.3%), while the incidence of dizziness, weight increased, nausea, back pain, depression, gait disturbance, vertigo, ataxia, and contusion is higher (more than 2 times) in adults than in adolescents. This observation based on the pooled data from three OLE studies is consistent with that in Study 307 alone. It should be noted that a higher overall incidence is expected for most adverse events, due to the longer exposure in the OLE compared to double blind studies, however the qualitative profile remains similar between the five double blind studies (Table 4) compared to the OLE.

Table 3 Treatment-emergent Adverse Events: Most Common (≥5% in Any Population) - Safety Analysis Set - Extension Studies (235 Ext, 332 Ext, and 307)

Preferred Term	Overall Subjects (N=1468) n (%)	Adult Subjects (N=1211) n (%)	Adolescent Subjects (N=257) n (%)
Dizziness	548 (37.3)	496 (41.0)	52 (20.2)
Somnolence	218 (14.9)	182 (15.0)	36 (14.0)
Headache	211 (14.4)	183 (15.1)	28 (10.9)
Weight increased	172 (11.7)	157 (13.0)	15 (5.8)
Fatigue	148 (10.1)	130 (10.7)	18 (7.0)
Irritability	143 (9.7)	125 (10.3)	18 (7.0)
Nasopharyngitis	140 (9.5)	101 (8.3)	39 (15.2)
Upper respiratory tract infection	124 (8.4)	107 (8.8)	17 (6.6)
Convulsion	116 (7.9)	87 (7.2)	29 (11.3)
Fall	104 (7.1)	89 (7.3)	15 (5.8)
Nausea	102 (6.9)	96 (7.9)	6 (2.3)
Back pain	89 (6.1)	85 (7.0)	4 (1.6)
Vomiting	88 (6.0)	67 (5.5)	21 (8.2)
Insomnia	86 (5.9)	74 (6.1)	12 (4.7)
Depression	84 (5.7)	78 (6.4)	6 (2.3)
Gait disturbance	83 (5.7)	77 (6.4)	6 (2.3)
Laceration	78 (5.3)	69 (5.7)	9 (3.5)
Vertigo	77 (5.2)	70 (5.8)	7 (2.7)

Table 3 **Treatment-emergent Adverse Events: Most Common (≥5% in Any Population) - Safety Analysis Set - Extension Studies (235 Ext, 332 Ext, and 307)**

Preferred Term	Overall Subjects (N=1468) n (%)	Adult Subjects (N=1211) n (%)	Adolescent Subjects (N=257) n (%)
Diarrhoea	77 (5.2)	65 (5.4)	12 (4.7)
Pyrexia	77 (5.2)	55 (4.5)	22 (8.6)
Balance disorder	76 (5.2)	68 (5.6)	8 (3.1)
Ataxia	74 (5.0)	67 (5.5)	7 (2.7)
Aggression	72 (4.9)	40 (3.3)	32 (12.5)
Contusion	64 (4.4)	60 (5.0)	4 (1.6)

Table 4 **Treatment-emergent Adverse Events: Most Common (≥5% in Any Population) - Safety Analysis Set - Double Blind Studies (304, 305, 306, 235 Core, and 332 Core)**

	Placebo Subjects			FYCOMPA Subjects		
Preferred Term	Overall (N=572) n (%)	Adult (N=470) n (%)	Adolescent (N=102) n (%)	Overall (N=1204) n (%)	Adult (N=1008) n (%)	Adolescent (N=196) n (%)
Dizziness	52 (9.1)	40 (8.5)	12 (11.8)	344 (28.6)	297 (29.5)	47 (24.0)
Somnolence	37 (6.5)	32 (6.8)	5 (4.9)	172 (14.3)	143 (14.2)	29 (14.8)
Headache	65 (11.4)	48 (10.2)	17 (16.7)	138 (11.5)	113 (11.2)	25 (12.8)
Fatigue	27 (4.7)	22 (4.7)	5 (4.9)	108 (9.0)	96 (9.5)	12 (6.1)
Irritability	16 (2.8)	13 (2.8)	3 (2.9)	88 (7.3)	75 (7.4)	13 (6.6)
Nausea	24 (4.2)	21 (4.5)	3 (2.9)	61 (5.1)	54 (5.4)	7 (3.6)
Nasopharyngitis	28 (4.9)	21 (4.5)	7 (6.9)	61 (5.1)	45 (4.5)	16 (8.2)
Fall	16 (2.8)	15 (3.2)	1 (1.0)	55 (4.6)	52 (5.2)	3 (1.5)
Upper respiratory tract infection	20 (3.5)	17 (3.6)	3 (2.9)	49 (4.1)	39 (3.9)	10 (5.1)
Aggression	3 (0.5)	2 (0.4)	1 (1.0)	25 (2.1)	10 (1.0)	15 (7.7)

TEAE frequencies for the serious AEs in adults compared to the serious TEAE for adolescent patients in the pooled data from three OLE studies are found in Appendix 4. The result shows higher incidence of convulsion, as well as aggression in adolescents compared to adults. This observation based on the pooled data from three OLE studies is consistent with that in Study 307 alone.

Question 2D

Please provide evidence based justification of the SmPC statements that the safety profile in adolescents is expected to be similar to that of the adults, or alternatively amend the product information to reflect the differences.

Response

Based on the clinical trial database of 196 adolescents from double-blind studies (Studies 304, 305, 306, 235, and 332) for partial onset seizures and PGTC seizures, as well as database of 257 adolescents from long-term open-label extension studies (307, 235 extension, and 332 extension), the safety profile in adolescents is similar to that of the adults. Aggression, while common in both adults and adolescents, was observed more commonly in adolescents than in adults.

Question 2E

Please justify the omission in SmPC and PIL of the information on increased rate of aggression in adolescent patients compared to adults or amend the product information accordingly.

Response

The pivotal POS studies had demonstrated increased frequency of aggression in adolescents compared to adults but the sample size of adolescents compared to adults was small. We propose the following wording in Section 4.8 of the SmPC.

Paediatric population

~~*Based on the clinical trial database of 165 adolescents, the frequency, type and severity of adverse reactions in adolescents are expected to be the same as in adults.*~~

Based on the clinical trial database of 196 adolescents from double-blind studies for partial onset seizures and primary generalized tonic-clonic seizures, the overall safety profile in adolescents was generally similar to that of the adults. Aggression, while common in both adults and adolescents, was observed more frequently in adolescents than in adults.

Assessment of the Response and Conclusion

The applicant has provided the requested information. The data shows that aggression, convulsion, status epilepticus, rhinitis, pharyngitis, nasopharyngitis, pyrexia and abdominal pain appeared more frequently in the study.

The applicant is changing the SmPC to include the warning regarding the higher incidence of aggression in adolescents. The other AEs reported higher in this study have occurred in relatively small number of trial participants and reliability of conclusions covering those in the context of the current variation would be limited. Considering that the post marketing data would be of particular interest here, the other differences in safety profiles of adolescents and adults should be revisited and addressed through the PSUR process.

Point can be considered resolved.

6. Additional clarifications required by the CMSs

The Rapporteur's assessment and conclusions are supported. However we would like to propose a rewording of the Paediatric population statement in SmPC section 4.8.

A rewording of the Paediatric population statement in SmPC section 4.8 was proposed by the MAH and considered acceptable by the CHMP. We would like to propose to amend the wording as indicated below (deletions crossed, additions underlined):

Paediatric population

Based on the clinical trial database of 196 adolescents from double-blind studies for partial onset seizures and primary generalized tonic-clonic seizures, the overall safety profile in adolescents was ~~generally~~ similar to that of ~~the~~ adults.~~ Aggression, while common in both adults and adolescents~~, except for aggression, which was observed more frequently in adolescents than in adults.

Response

The applicant confirmed their agreement with the proposed wording with a minor addition as outlined below bold and underscored text:

Paediatric population

*Based on the clinical trial database of 196 adolescents **exposed to perampanel** from double-blind studies for partial onset seizures and primary generalized tonic-clonic seizures, the overall safety profile in adolescents was ~~generally~~ similar to that of ~~the~~ adults. ~~Aggression, while common in both adults and adolescents,~~ except for aggression, which was observed more frequently in adolescents than in adults.*

Assessment of the Response and Conclusion

The proposed wording:

Paediatric population

Based on the clinical trial database of 196 adolescents exposed to perampanel from double-blind studies for partial onset seizures and primary generalized tonic-clonic seizures, the overall safety profile in adolescents was similar to that of adults, except for aggression, which was observed more frequently in adolescents than in adults.

Is in line with the data and requested changes and it is, therefore, acceptable.

Point resolved.

7. Outstanding Questions

None. A variation should be submitted within 60 days.