17 September 2020
EMA/695418/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fycompa

International non-proprietary name: perampanel

Procedure No. EMEA/H/C/002434/II/0047

Note

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

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List of abbreviations

ABNAS	Aldenkamp–Baker Neuropsychological Assessment Schedule
AE	Adverse Event
AED	antiepileptic drug
ADR	adverse drug reaction
ALAG1	Lag time
ALT	alanine aminotransferase
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ASF	Average Seizure Frequency
ATC	Anatomical Therapeutic Chemical
AUCss	Area under the Curve, at steady-state
BMI	Body Mass Index
BP	Blood Pressure
BPR	Blood Plasma Ratio
BSV	Between subject variability
Cav,ss	Concentration average, at steady-state
CBCL	Child Behavior Check List
CBZ	Carbamazepine
CGI	Clinical Global Impression
CGIC	Clinical Global Impression of Change
CHMP	Committee for Medicinal Products for Human Use
CL/F	Apparent Clearance
Cmaxss	Concentration maximal, at steady-state
CNS	Central Nervous System
C-SSRS	Columbia-Suicide Severity Rating Scale
CWRES	Conditional weighted residual
DBS	Dried Blood Spot
EAP	Extended Access Program
EEG	electroencephalogram
EIAED	Enzyme-Inducing Antiepileptic Drug
EMA	European Medicines Agency
EOT	end of treatment
ERA	Environmental Risk Assessment
FAS	Full Analysis Set
GGT	Gamma Glutamyl Transferase
GLP	Good Laboratory Practice
GOF	Goodness Of Fit
IGE	Idiopathic Generalized Epilepsy

IGF	Insulin-like Growth Factor
IIV	Inter-Individual Variability
ILAE	International League Against Epilepsy
IOV	Inter-Occasion Variability
ISO	International Standardization Organisation
ISR	Incurred Samples Reanalysis
Ka	Absorption constant
LC-MS/MS	Liquid Chromatography coupled to tandem mass spectrometry
LGPT	Lafayette Grooved Pegboard Test
LLOQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
LTPB	Log-transformed percentage change from baseline
MedDRA	Medical Dictionary for Regulatory Activities
MOA	Mechanism of Action
OECD	Organization for Economic Co-operation and Development
OFV	Objective Function
OXC	Oxcarbazepine
PcVPC	Predicted corrected Visual Predictive Check
PD	Pharmacodynamic(s)
PGTC	Primary Generalized Tonic-Clonic
PGTCS	Primary Generalized Tonic-Clonic Seizures
PK	pharmacokinetic
PopPKPD	Population PK/PD
POS	Partial-Onset Seizures
PRED	Population Prediction
PT	Preferred Term
QC	Quality control
QD	once daily
Q/F	Apparent inter-compartmental clearance
QTc	QT interval corrected for heart rate
RSE	Relative Standard Error
RUV	Residual unexplained Variability
SAE	Serious Adverse Event
SAWP	Scientific Advice Working Party
SD	Standard Deviation
SF	Seizure Frequency
SGTC	Secondarily Generalized Tonic-Clonic
SMQ	Standardized MedDRA Query
SOC	System Organ Class

TAD	Time After Dose
TEAE	Treatment-Emergent Adverse Event
TOP	Topiramate
ULOQ	Upper Limit of Quantification
V2/F	Apparent central Volume of distribution
V3/F	Apparent peripheral Volume of distribution
VAS	Visual Analog Scale
VNS	Vagal Nerve Stimulator
VPC	Visual Predictive Check

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eisai GmbH submitted to the European Medicines Agency on 28 August 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of Indication to include the paediatric patients from 2 to 11 years of age for the adjunctive treatment of Partial-Onset Seizures with or without secondary generalisation and Primary Generalised Tonic-Clonic Seizures with idiopathic generalised epilepsy for Fycompa.
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 4.3 has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0217/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-000467-PIP01-08 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 25 January 2018 (EMEA/H/SA/608/10/2017/PED/II). The Scientific Advice pertained to clinical aspects and in relation to paediatric development of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	28 August 2019
Start of procedure:	14 September 2019
CHMP Rapporteur Assessment Report	14 November 2019
PRAC Rapporteur Assessment Report	19 November 2019
PRAC Outcome	28 November 2019
CHMP members comments	4 December 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	6 December 2019
Request for supplementary information (RSI)	12 December 2019
CHMP Rapporteur Assessment Report	31 March 2020
PRAC Rapporteur Assessment Report	31 March 2020
PRAC members comments	8 April 2020
Updated PRAC Rapporteur Assessment Report	14 April 2020
PRAC Outcome	17 April 2020
CHMP members comments	23 April 2020
Updated CHMP Rapporteur Assessment Report	24 April 2020
Request for supplementary information (RSI)	30 April 2020
Responses to RSI by	10 July 2020
CHMP Rapporteur Assessment Report	19 August 2020
PRAC Rapporteur Assessment Report	19 August 2020
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	3 September 2020
CHMP members comments	7 September 2020
Updated CHMP Rapporteur Assessment Report	11 September 2020
Opinion	17 September 2020

2. Scientific discussion

2.1. Introduction

Fycompa includes the active substance perampanel, a potent, non-competitive, and highly selective antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxzaoleproprionic acid (AMPA) glutamate receptor. It was approved in the European Union (EU) through the centralised procedure in July 2012 as adjunctive therapy for the treatment of partial-onset seizures (POS) with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older, and as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures (PGTCS) in adult and adolescent patients aged 12 years and older with idiopathic generalized epilepsy (IGE) in Jun 2015. The precise mechanism by which perampanel exerts its antiepileptic effect has not yet been fully elucidated.

Fycompa is available as film-coated tablets (2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg) and 0.5 mg/mL oral suspension. Treatment should be initiated by titrating the dose from 2mg/day to a maintenance dose of 4 to 8 mg/day, which may be further increased to a maximum dose of 12 mg/day. Fycompa should be given once daily at bedtime.

In the current submission, the MAH proposes to extend the approved indications to children aged 2 years and older. The proposed changes are supported through extrapolation of adult and adolescent efficacy and paediatric pharmacokinetic (PK) data derived from 2 open-label studies: an exploratory Phase 2 study (Study E2007-G000-232 or Study 232) which included data from subjects from patients with epilepsy from 2 to <12 years of age and a pivotal long-term open-label Phase 3 study (Study E2007-G000-311 or Study 311) in paediatric patients aged 4 to < 12 years old with inadequately controlled POS and PGTC seizures.

2.1.1. The development programme/compliance with CHMP guidance/scientific advice

The MAH received scientific advice from the CHMP on 25 January 2018 (MEA/H/SA/608/10/2017/PED/II). The scientific advice pertained to clinical aspects in relation to the paediatric development of the dossier.

The main points addressed during the CHMP scientific are summarized hereafter:

- The CHMP considers that there is no sound evidentiary basis to establish the proposed extrapolation concept (that matching PK, PK/PD in children and adults can predict efficacy in children).
  That said, it is recognized that only limited efficacy data will be available across relevant strata of the target population and so work in this direction is encouraged. PK and PD data in paediatric patients with PGTCS of IGE across age groups are needed in sufficient numbers to support PK/PD modelling.
  In addition, the proposed PK model needs to be further substantiated, with early samples in paediatric patients across the age classes that will be included in any indication. The latter may be obtained from children with POS. It is not precluded that an improved extrapolation exercise together with clinical data from study 311 might suffice for assessment of efficacy and risk-benefit in children.

- The lower limit of age in study 311 is 4 years. No children aged <2 years were included in the meta-analysis. Before 2 years of age, the hyperexcitability of the immature brain have significant consequences on the PK and PD resulting in greater variability. Between 2- 4 years, the variability in PD response may still remain. Thus, no efficacy data was gained in the claimed indication of PGTCS of IGE in the 2-4 age group, consequently, there appears to be no robust basis to extrapolate down to 2 years of age. Nevertheless, this is ultimately an assessment issue.

- The youngest population is considered the most difficult population to support adequately for extrapolation. PK and PD need to be specifically assessed in the youngest children. A ratio of a total sample size is a poor basis from a scientific perspective on which to discuss the adequacy of the proposed sample size. The CHMP emphasizes that a sufficient number of children aged 4-7 need to be included to provide information on PK and PD in that age range so that robust conclusions can be drawn. It is appreciated that feasibility is also an issue for consideration at PDCO.

During the scientific advice, the following points were discussed:

- Efficacy: the similarity of therapeutic response cannot be ensured, especially in the youngest children, as the brain is maturing until 7 years of age with different hyper or hypoexcitability

thresholds depending on the area considered. In addition, the youngest children may also have differences in PK. Consequently, the similarity of the exposure/response relationships between adults and the different paediatric age class considered (2-4, 4-7 and 7-11) needs to be demonstrated by the relevant data.

- Safety: The most common IGE in children is Childhood Absence Epilepsia (CAE), in which the most common seizure types are absences, followed by myoclonia, however PGTCS can also, albeit rarely, be encountered in CAE. Isolated PGTCS are very rare in children as opposed to being common in adults.

- In children PGTCS appears within more complex syndromes associating different seizure types, the effect of perampanel on these other seizure types should be assessed within the safety assessment, at least to rule out a detrimental effect (or quantify it to integrate it into the overall benefit/risk assessment). The effect of perampanel on neuropsychological aspects in a developing brain and on growth should also be specifically assessed in the paediatric population. Consequently, safety cannot be extrapolated.

  In addition, the guideline on clinical investigation of medicinal products in the treatment of epileptic disorders highlights (CHMP/EWP/566/98 Rev.2/Corr) is taken in consideration for the assessment of the paediatric extension of indication, with in particular:

- Focal epilepsies especially cryptogenic and symptomatic, and idiopathic generalized epilepsies, with absences, myoclonic and/or generalized convulsive seizures, where the efficacy of AEDs seems to be comparable in childhood and adulthood. Focal epilepsies in children older than 4 years old have a similar clinical expression to focal epilepsies in adolescents and adults. In refractory focal epilepsies, the results of efficacy trials performed in adults could to some extent be extrapolated to children provided the dose is established.

- From the safety view point, a minimum of 100 children treated by the study drug should be followed for at least one year. Moreover short term and long-term studies should be designed to detect possible impact on brain development, learning, intelligence, growth, endocrine functions and puberty. Some of these studies may require continuation in the post marketing period. (See Guideline on clinical investigation of medicinal products in children (CPMP/EWP/462/95).

2.2. Non-clinical aspects

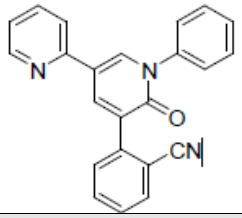
No new non-clinical data other than an updated environmental risk assessment (ERA), have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment was updated, including a Phase II estimation of exposure:

Summary of environmental risk assesment

Substance (INN/Invented Name): perampanel
Chemical name (IUPAC): 2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile hydrate (4:3)
CAS-number: 380917-97-5
Molecular/structural formula & stability :



• $3/4H_2O$

The stability of perampanel drug substance in solutions (pH 2 – 12) was investigated after storage at 25 °C (light shielded and light irradiated at 1000 lux) and 60 °C (light shielded) for 2 weeks. The residual percentage of perampanel drug substance did not change in solutions stored at 25 °C and 60 °C under light shielded conditions. In contrast, when exposed to light, degradation of perampanel drug substance was observed in solutions of various pH values.

PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.86	No potential for PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.86	No potential for PBT
	BCF		
Persistence	DT50 or ready biodegradability		
Toxicity	NOEC or CMR		
PBT-statement :	The compound is not considered as PBT		

Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00096	µg/L	>0.01 threshold (N)
Other concerns (e.g. chemical class)			No other concnern

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106; EC 2001/59, C.19	Koc and log Koc values of perampanel at pH 7.5, based on soil and sewage sludge adsorption-reference data, are 5.1 x 10^2 and 2.71.	
Ready Biodegradability Test	OECD 301; EC 92/69/EEC, Part C; ISO 9439	The relative degradation values calculated from the measurements performed during the test period of 28 days revealed no significant degradation of perampanel (1% to 2%). In the toxicity control, perampanel was found not to inhibit microbial activity.	Not readily biodegradable *See further data from * Phase II Tier A and Tier B assessment.*
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Compartment / DT_{50} (days) / DT_{90} (days) SL water: 7.9 / 67.2 SL total system: 879.2 / >1000 SW water: 6.0 / 65.1 SW total system: 730.4 / >1000 $DT_{50/90}$ = degradation/dissipation time for 50%/90% removal, SL = Swiss Lake, SW = Schoonrewoerdsewie -91% to 93% recovered in 2 water-sediment systems, of which 7% was recovered in the water layer and 84% to 85% was recovered in the sediment extract. -No organic volatiles were detected and mineralization to CO2 was low (<1%) in both systems. -No transformation products were formed. -No degradation of perampanel in the sediment layers within 97 days of incubation	

Phase II Tier A Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algal growth inhibition test	OECD 201; EEC directive 92/69, art C.3,1; ISO 8692; OECD 23	NOEC	>1200	µg/L	*Pseudo-kirchneriella subcapitata*
Daphnia magna acute toxicity test	OECD 211; ISO 10706:2000	EC_{50}	1000	µg/L	

Daphnia magna reproduction test		NOEC	220	µg/L	
Toxicity test on egg and sac-fry stages of fathead minnow	OECD 210; EPA 850. 1400 ; EPA 712-C-96-121	LC_{50} NOEC	>1300 40	µg/L	Pimephales promelas
Fish early life stage test using fathead minnow		NOEC LOEC	60 160	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209; EEC Directive 67/ 548 amended 87/30; ISO Standard 8192	EC_{50}	>100,000	µg/L	
Ratio	**PEC (µg/L)**	**PNEC (µg/L)**	**PEC/PNEC**	**Trigger**	**Remarks**
$PEC_{SURFACEWATER}/PNEC_{WATER}$	0.00096	6	0.00016	1	- recovery ~85% in the sediments of 2 water sediment systems. - sediment dwelling organism study required
$PECS_{URFACEWATER}/PNEC_{MICROORGANISM}$	0.00096	10,000	0.000000096	0.1	
$PEC_{GROUNDWATER}/PNEC_{GROUNDWATER}$	0.00024	22	0.000011	1	
Phase II Tier A and Tier B assessment					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
sediment-water Chironomid (midge) toxicity test	OECD 308 & 218	28-day overall NOEC (for emergence ratio and development rate) 28-day overall EC_{50} (for emergence ratio and development rate)	820 >820	(mg/kg d.w.) (mg/kg d.w.)	Chironomus riparius
Ratio PEC (µg/kg)	**PNEC (µg/L)**	**PNEC (µg/L)**	**PEC/PNEC**	**Trigger**	**Remarks**
$PEC_{SEDIMENT}/PNEC_{SEDIMENT}$	0.011	82	0.00013	1	risk to sediment dwelling organisms is negligible.

EC50 = half maximal effective concentration; LC50 = lethal concentration, median; NOEC = no observed effect concentration, LOEC = lowest-observed effect concentration; PEC = predicted environmental concentration, PNEC = predicted no effect concentration; d.w. = dry weight.

In view of both the indication and the extended population, the CHMP agrees that perampanel is not expected to pose a risk to the environment.

2.2.2. Discussion on non-clinical aspects

In view of both the indication and the extended population, the CHMP agrees that perampanel is not expected to pose a risk to the environment.

2.2.3. Conclusion on the non-clinical aspects

Based on the available data, perampanel is not expected to pose a risk to the environment. No further non-clinical data were considered necessary by the CHMP to support this application.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies:

Table 2.7.3–3 Summary of Clinical Efficacy Studies

Study	Study Dates	Number of Sites/Countries	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments	No. Subjects by Arm	Efficacy Endpoint(s)
E2007-G000-311	16 Nov 2016 to 20 Jul 2018	Total of 80 sites enrolled subjects in: Belgium (4), France (6), Hungary (4), Japan (23), Korea (5), Latvia (1), Poland (3), Spain (6), and United States of America (28).	Multicenter, open-label, single-arm study with an Extension Phase. Three study phases: 4-week Pretreatment Phase, 23- to 25-week Treatment Phase, 33-week Extension Phase.	Subjects ≥4 to <12 years with diagnosed epilepsy with POS with or without secondarily generalized seizures or PGTCS according to the ILAE Classification of Epileptic Seizures and receiving stable doses of 1 to 3 AEDs.	Subjects on concomitant EIAED Perampanel oral suspension 4 mg/day up to 16 mg/day. For Japan only 2 mg/day up to 12 mg/day. Subjects not on concomitant EIAED: Perampanel oral suspension 2 mg/day up to 12 mg/day.	As of 20 Jul 2018, Core Study: 180 (149 POS/31 PGTCS [54 subjects in SGTC subset of POS cohort; 24 subjects in PGTC of IGE subset of PGTC cohort]) Extension Phase A: 136 (116 POS/20 PGTCS [43 subjects in SGTC subset of POS cohort; 15 subjects in PGTC of IGE subset of PGTC cohort]) Extension Phase B: 1*	Percent change in 28-day seizure frequency. Responder rate, defined as the proportion of subjects with a 50% decrease in 28-day seizure frequency. Seizure-free rate. CGI at EOT.
E2007-G000-232	Jan 2012 to May 2014 (Core Study) Feb 2015 (Extension Phase)	Core Study: 22 sites initiated and 15 sites enrolled subjects in the United States of America. Extension Phase: 14 sites in the United States of America.	Multicenter, multiple ascending dose, open-label study with an Extension Phase. Three study phases: 2-week Pretreatment Phase, 11-to 15-week Treatment Phase, 45-week Extension Phase.	Subjects ≥2 to <12 years with diagnosed epilepsy with any type of seizure according to the ILAE Classification of Epileptic Seizures and receiving stable doses of 1 to 3 AEDs.	Perampanel oral suspension 0.015 mg/kg up to 0.18 mg/kg. Perampanel given QD by mouth at bedtime.	Core Study: 50 (any seizure type); of these, 3 had PGTC of IGE Extension Phase: 41 (any seizure type); of these, 3 had PGTC of IGE	Percent change in 28-day seizure frequency Responder rate, defined as the proportion of subjects with a 50% decrease in 28-day seizure frequency. Seizure-free rate CGIC at EOT

AED=antiepileptic drug, CGI=Clinical Global Impression, CGIC=Clinical Global Impression of Change, EIAED=enzyme-inducing antiepileptic drug, EOS=End of Study, EOT=End of Treatment, IGE=idiopathic generalized epilepsy, ILAE=International League Against Epilepsy, No.=number, PGTC=primary generalized tonic-clonic, PGTCS=primary generalized tonic-clonic seizures, POS=partial-onset seizures, QD=once daily.

* As of 20 Jul 2018, 1 subject had entered Extension B but was enrolled in error as the subject was over 12 years of age. Drug was dispensed at Visit 12 and the subject's participation in the study was terminated at the next visit (EOS).

2.3.2. Pharmacokinetics

From the initial MAA dossier, the pharmacokinetic (PK) properties of Fycompa (E2007) in adults and adolescents are well known and the key properties are summarized below:

- E2007 absorption is rapid and complete (F near 100%) with negligible first-pass metabolism
- E2007 is highly bound to plasma proteins (95%), Vd in healthy volunteers average 77 L and blood to plasma ratio was 0.55-0.59

- E2007 is extensively metabolized via primary oxidation and sequential glucuronidation. The metabolism is mediated primarily by CYP3A. Average t1/2 of perampanel was 105 hours, when dosed in combination with the strong inducer carbamazepine, the average t1/2 was 25h.
- E2007 exhibit dose linearity between 2 to 12 mg.

In order to support the proposed paediatric extension of indication, using an extrapolation of adult and adolescent efficacy to patients aged 2 years and older, the MAH conducted 2 open-label studies:

- an exploratory Phase 2 study (Study E2007-G000-232 or Study 232) which included data from subjects from patients with epilepsy from 2 to <12 years of age and,

- a pivotal long-term open-label Phase 3 study (Study E2007-G000-311 or Study 311) in paediatric patients aged 4 to < 12 years old with inadequately controlled POS and PGTC seizures

Summary of clinical pharmacology studies in paediatric subjects

Study Number	Study Title
E2007-G000-232	An Open-Label Pilot Study With an Extension Phase to Evaluate the Pharmacokinetics, and to Generate Preliminary Safety, Tolerability, and Efficacy of Perampanel (E2007) Oral Suspension When Given as an Adjunctive Therapy in Pediatric Subjects From 2 to Less Than 12 Years of Age With Epilepsy
E2007-G000-311	An Open-Label, Multicenter Study with an Extension Phase to Evaluate the Safety, Tolerability, and Exposure-Efficacy Relationship of Perampanel Oral Suspension when Administered as an Adjunctive Therapy in Pediatric Subjects (Age 4 to less than 12 years) with Inadequately Controlled Partial-Onset Seizures or Primary Generalized Tonic-Clonic Seizures

One population PK (popPK) model was developed using all available PK data of perampanel (adult, adolescent, paediatric and POS or PGTC indications).

In addition, two population PK/PD (PopPKPD) models (efficacy) were developed for each indication (POS and PGTC) apart. For safety, graphical PK/PD exploration was first performed followed by logistic regression analysis.

Methods

LC-MS/MS method (Study 311)

The determination of E2007 in human plasma (sodium heparine) was done using an LC-MS/MS method (BTM-1717-R0), similar to the method BTM-1076-R0 using at the time of the initial MAA submission. Except the sample volume (25 µL) performance of the validated method BTM-1717-R0 were similar to that of the initial BTM-1076-R0 method in terms of accuracy, precision, selectivity, dilution integrity, reproducibility, matrix effect and stability. The LLOQ was set at 1.0 ng/mL and the ULOQ at 500 ng/mL. Five QC levels were considered for the validation method at 1, 3, 50, 380 and 3800 ng/mL, however only three were considered for the determination of perampanel PK data from Study 311 (QC at 3, 5, 380 ng/mL). For samples above ULOQ a 10-fold dilution was applied. Long term stability was demonstrated for at least 636 days stored at -20°C. Incurred sample reanalysis was performed and showed satisfactory results.

Blood Biological matrix (Study 232)

A bioanalytical method using dried blood spot (DBS) was developed for the quantification of perampanel blood concentration. The blood sample was put on 2 DBS cards (1 original and 1 back-up card). On each card there were 4 spots, each was filled with approximately 20µL, giving a total of 80 µL per card. One dry blood sample spot (20µL) per time point was analysed using a validated DBS method with LC/MS-MS method to determine blood concentration. Blood plasma perampanel concentrations were converted to plasma concentrations using a blood/plasma ratio of 0.88.

Performance of the developed method are provided in the table 'Summary of perampanel analytical method validation in human blood' hereafter. LLOQ and ULOQ were set at 1 and 500 ng/mL respectively. Four QC levels were considered, at 1, 3, 250 and 400 ng/mL with particularly good performance, intra-run precision (CV%) less than 15% for LLOQ and less than 7% for the others QC; and inter-run precision (CV%) less than 10%. Long term stability was demonstrated at 363 days at room temperature.

Summary of perampanel analytical method validation in human blood

Reference compound	perampanel			
Internal standard	[$^{13}C_6$]-perampanel			
Species Matrix (anticoagulant)	Human blood (sodium heparin)			
Extraction method	DBS Extraction with MeOH/UHQ water (90/10, v/v)			
Detection method	LC-MS/MS			
Concentration range	From 1 to 500 ng/mL			
Regression (weighting)	Linear ($1/x^2$)			
Sample volume	20 µL			
	Tested concentration (ng/mL)			
	1	**3**	**250**	**400**
Intra-run precision (CV%)	13.00 3.88 6.38	5.04 4.31 6.65	3.59 3.34 4.22	2.66 2.56 5.00
Intra-run deviation (%)	0.0 3.0 -6.0	-7.3 0.7 0.3	0.7 -0.8 -3.5	4.1 -2.6 -2.3
Inter-run precision (CV%) n=18	9.09	6.46	3.93	4.62
Inter-run deviation (%) n=18	-1.0	-2.0	-1.2	-0.3
Specificity	Interference ≤ 10.2% was observed for perampanel and ≤ 0.2% for IS			
Carry over	3 S0 (i.e., blanks) need to be injected after the ULOQ and before each predose samples			
IS contribution	Mean interference ≤ 6.3% of the LLOQ was observed for perampanel Mean interference was ≤ 0.2% for IS			
2-fold dilution factor	Validated, provided a specific dilution process is used.			
Matrix effect	Between 0.9 and 1 for perampanel and IS.			
Recovery	Between 77.9% and 88.5% for perampanel and between 87.5% and 94.7% for IS			

Incurred sample reanalysis showed satisfactory results according to the applicant with 72% of the ISR which met the acceptance criteria (+/- 20%);

Population Pharmacokinetic/Pharmacodynamic analysis

Population PK (PopPK) and PK/PD (PopPKPD) analysis were performed with Nonmem® software (version 7.3.0). The analyses consisted of a PopPK model for perampanel on data from all subjects (paediatric, adolescent and adult populations) whatever the indication (POS or PGTC), and several continuous PopPKPD model developed for each indication.

Analysis were conducted using the FOCEI (PopPK model) and FOCE or Laplacian method (PopPKPD models). Covariate selection was based on a standard stepwise forward/backward procedure. Final model

evaluation consisted of several GOF (Goodness of fit) plots, predictive performance was evaluated using VPC, pc-VPC and model validation using a bootstrap analysis.

However since the extrapolation exercise is based on PK only, results from the PopPK/PD models for both indication POS and PGTC are not presented hereafter.

Pharmacokinetics in target population

Study 232

This was a multicenter, multiple ascending dose, open-label study with an Extension Phase conducted to evaluate the PK and to generate preliminary safety, tolerability, and efficacy data for perampanel oral suspension when given as an adjunctive therapy in paediatric subjects from 2 to <12 years of age with epilepsy. Subjects were enrolled into 2 cohorts depending upon age at the time of consent/assent: Cohort 1 consisted of subjects from 7 to <12 years of age and Cohort 2 consisted of subjects from 2 to <7 years of age (please also refer to 2.4.1. Clinical efficacy/Main Studies for additional details).

Study 311

This was a multicenter, open-label single-arm study in children (aged 4 to <12 years) with inadequately controlled POS or PGTC seizures. The study consisted of a Core Study and Extension Phase (Extension A) for subjects globally with an additional Extension Phase (Extension B) available for subjects enrolled in Japan and countries where an extended access program could not be implemented. Subjects were stratified by age (≥4 to <7 years, 7 to <12 years) with at least 30% of subjects planned to be enrolled in the ≥4 to <7 year age group for each seizure type (ie, at least 36 with POS and at least 12 with PGTC seizures). (please also refer to 2.4.1. Clinical efficacy/Main Studies for additional details).

Population Pharmacokinetic Model

Two Pop PK model reports, CPMS-E2007-007R-v1 and CPMS-E2007-015R-v2, were provided. Since CPMS-E2007-007R-v1 have been reviewed twice following EMA/CHMP/SAWP/330293/2015, EMA/CHMP/SAWP/330294/2015 and EMA/CHMP/SAWP/17398/2018 from which several issues were highlighted, the MAH performed a new PopPK model in CPMS-E2007-015R-v2 which was subsequently updated in CPMS-E2007-015-v3 which is detailed here after.

PK dataset

A summary of the PK dataset is presented in following table, where PK data from Study 232 were not accounted for due to analytical issues.

Summary of number of subjects and observation records in Population PK dataset

Study	Population	Subjects (n)	Observation Records Included (n)	Observation Records Excluded (n)
20 Phase 1 Studies (Adults)	Healthy Subjects	706	17548	28
235 (Adolescents)	Refractory POS	78	339	3
304 (Adolescents & Adults)	POS	193	1090	0
305 (Adolescents & Adults)	POS	183	1047	0
306 (Adolescents & Adults)	POS	394	2259	0
311 (Paediatrics)	POS	130	373	0
311 (Paediatrics)	PGTCS	26	73	0
332 (Adolescents & Adults)	PGTCS	73	205	7
335 (Adolescents & Adults)	POS	511	1331	21

POS=Partial onset seizure; PGTCS= primary generalized tonic-clonic seizure

For the paediatric population (Study 311), PK data consisted of sparse PK sampling at several occasions, 1 blood sample for the determination of plasma perampanel concentrations during Visits 7, (Week 15), 8 (Week 19), and 9 (Week 23) and at early discontinuation.

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For studies performed in the adult and adolescent population, PK data consisted of rich PK sampling (20 Phase 1 studies) performed in healthy subjects and sparse PK sampling at steady state at several occasions (Studies 235, 304, 305, 306, 332 and 335).

Therefore, for:

- the POS indication, paediatric PK information consisted of n=373 observations from 130 paediatric subjects vs n =6415 observations from 1359 adult and adolescent subjects.
- the PGTC indication, paediatric PK information consisted of n=73 observations from 26 paediatric subjects vs n =205 observations from 73 adult and adolescent subjects.

Healthy subjects account for n= 17548 observations for 706 subjects.

The table below presents a summary of the baseline characteristics of the studied populations. Only n=4 paediatric subjects were aged 2 to < 4 years (Study 232), n= 59 aged 4 to < 7 years, and n=135 aged 7 to < 12 years against n=1432 aged > 12 years.

Summary of the baseline characteristics of the studied patient's population

	Patients (N=1630)		
Covariate (unit)	**Mean (SD)**	**Median**	**Range (Min-Max)**
Age (years)			
2 to < 4 (n=4)	2.75 (0.50)	3.00	2.0-3.0
4 to < 7 (n= 59)	5.62 (0.71)	5.00	4.0-6.0
7 to < 12 (n=135)	9.10 (1.39)	9.00	7.0-11.0
12 to < 18 (n=226)	14.65 (1.75)	15.0	12.0-17.0
18 and older (n=1206)	23.1 (3.05)	23.0	18.0-28
Overall (n=1630)	29.5 (15.0)	28	2-74
Weight (kg)			
2 to < 4 (n=4)	15.7 (1.92)	15.4	13.8-18.3
4 to < 7 (n= 59)	21.3 (4.81)	20.1	12.2-39.5
7 to <12 (n=135)	33.3 (12.7)	28.7	16.3-90.9
12 to < 18 (n=226)	55.4 (16.1)	52.0	21.0-125
18 and older (n=1206)	64.6 (16.8)	61.0	27.8-160
Overall (n=1630)	62.6 (21.6)	61.5	12.2-160
Alanine transaminase (IU/L)	20.4 (14.0)	17	4-184
Aspartate transaminase (IU/L)	21.9 (9.36)	20	7-141
Creatinine Clearance (mL/min)	116.5 (32.3)	112.6	19.5 – 340.2
Seizure Type	POS = 1523; PGTCS = 107		
Dose	Range: 0.5-16mg		
Sex	Females = 829; Males = 801		
Race	Caucasian = 804; Black/Afro-American = 25; Asian = 320; Japanese = 240; Chinese=204, American Indian/Alaskan/Other/Missing=37		

More than half of the patient dataset were treated with an AEDs inducers (carbamazepine, oxcarbazepine and phenytoin) as shown in the following table.

Summary of co-administered AEDs

	All Subjects (N = 2336)		Patients (N = 1630)	
AED	n	%	n	%
Carbamazepine	540	23.1	540	33.1
Levetiracetam	571	24.4	571	35.0
Lamotrigine	486	20.8	486	29.8
Oxcarbazepine	247	10.6	247	15.2
Topiramate	331	14.2	331	20.3
Valproic acid	567	24.3	567	34.8
Clobazam	206	8.82	206	12.6
Phenytoin	130	5.57	130	8.0
Phenobarbital	96	4.11	96	5.9
Primidone	17	0.73	17	1.0
Zonisamide	136	5.82	136	8.3
Inducers*	917	39.3	917	56.3

*Inducers include carbamazepine, oxcarbazepine and phenytoin..

Results

A population PK model for perampanel was previously developed using pooled data from 20 Phase 1 studies in healthy subjects. Perampanel was best described by a 2 compartment model with first order absorption and linear elimination parameterized in terms of CL/F, V2/F, Q/F and V3/F, Ka and ALAG1 (lag-time in absorption). Since HS received the tablet or the suspension formulation in the presence/absence of food, Ka was parameterized accordingly. IIV were estimated on all PK parameters except ALAG1. RUV was modelled using a combined error model (proportional and additive). Results of the PK parameter estimates are provided in following**Error! Reference source not found.**.

Base Phase 1 Population PK model estimates of perampanel (Phase 1 studies)

Parameter	Point Estimate	%RSE	95% CI
Apparent clearance: CL/F			
Basal CL/F (L/h)	0.625	2.10	0.599 – 0.651
Apparent central volume of distribution: V2/F			
Basal V2/F (L)	27.6	3.66	25.6 – 29.6
Inter-compartment Clearance: Q/F			
Basal Q/F (L/h)	8.81	3.75	8.16 – 9.46
Apparent peripheral volume of distribution: V3/F			
Basal V3/F (L)	46.5	2.15	44.5 – 48.5

Ka (1/h)			
Ka for tablet fasted (1/h)	4.23	6.24	3.71 – 4.75
Ka for tablet fed (1/h)	0.431	6.64	0.375 0.487
Ka for suspension fasted (1/h)	3.26	6.38	2.85 – 3.67
Ka for suspension fed (1/h)	0.316	6.77	0.274 – 0.358
ALAG1			
ALAG1 (Θ_5; h)	0.229	0.0686	0.229 – 0.229
Inter-individual variability(%CV)			
CL/F	51.0	6.35	-
V2/F	58.9	4.81	-
Q/F	55.4	5.99	-
V3/F	40.1	6.46	
Ka	120	6.65	-
Residual variability			-
Proportional (%CV)	21.8	0.463	-
Additive (ng/mL)	1.36	2.05	-

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100;
CL/F = apparent clearance; V2/F = apparent central volume of distribution; Q/F=inter-compartment clearance; Ka = first order absorption rate constant; V3/F = apparent peripheral volume of distribution; ALAG1 = lag time in absorption; L = litre; h = hour; WGT = body weight; CI = confidence interval; %CV = Square root of variance *100.

In the current analysis, this PK model was used as a starting point for PK model development with pooled data from all the available clinical studies (Phase 1, 2 and 3). Several steps were considered to build the Base PK model (all data), implementation of IOV on CL/F and fixed allometric scaling coefficient of 0.75 for CL/F for patients under 18 years old as shown in the following table.

Summary of base PK model building for perampanel (All data)

Model	Model Description	OFV	Comments
PK_Base1_All_FixedKa_NoIOV	**Base PK model for all data with fixed values for Ka, ALAG1 and IIV on Ka from base model from Phase 1 data, no IOV on CL and with a combined RV model**	**186653.195**	**Reference Model**
PK_Base2_All_FixedKa_IOVCL	Base PK model for all data with fixed values for Ka and ALAG1 from base model from Phase 1 data, with IOV on CL and a combined RV model	186128.549	IOV on CL resulted in significant reduction in OFV
PK_All_FixedScalAll	Fixed scaling of 0.75 on CL and Q and 1 for V2 and V3	186142.256	Fixed scaling on all parameters resulted in an increase in OFV compared to model PK_Base2_All_FixedKa_IOVCL
PK_All_FixedScalingAge17	Fixed scaling of 0.75 for Q and 1 for V2 and V3, fixed scaling of 0.75 for CL for subjects aged < 18 years and no scaling on CL for subjects aged ≥ 18 years	185936.983	No scaling on CL for subjects aged ≥ 18 years and fixed scaling of 0.75 on CL for subjects < 18 years resulted in significant reduction in OFV **Model selected as intermediate PK model for subsequent covariate analysis**

Ka = first order absorption rate constant; V3/F = apparent peripheral volume of distribution; ALAG1 = lag time in absorption; IIV = inter-individual variability; IOV = inter-occasion variability; RV = residual variability.

According to the MAH, since eta-shrinkage on CL/F was particularly low (-6.41 %) but above 50% for other parameters, covariate-parameter relationships were only tested on CL/F with all available covariates.

Using univariate analysis following graphical exploration of ETA-CL/F vs covariates, gender, , black-african race, type of seizure (POS or PGTC) and population (healthy vs patient) were first tested prior to the evaluation of the effect of concomitant AED administration on CL/F. Then after backward elimination the effects of gender and phenobarbital/topiramate, phenytoine/oxcarbazepine and carbamazepine was retained in the final model. Final PK parameter estimates are provided in the following table.

Final population PK parameter estimates of perampanel- All data

Parameter	Point Estimate	%RSE	95% CI
Apparent clearance: $CL/F=\Theta_{CL}$			
Basal CL/F for Subjects Aged ≥ 18 Years (L/h)	0.646	1.63	0.625 – 0.667
Apparent clearance: $CL/F=\Theta_{CL}*(WGT/44.95)^{0.75}$			
Basal CL/F for Subjects Aged < 18 Years (L/h)	0.613	2.69	0.581 – 0.645
Effect of phenobarbital or topiramate on CL/F (ratio)	1.22	2.75	1.15 – 1.29
Effect of phenytoin or oxcarbazepine on CL/F (ratio)	1.97	2.79	1.86 – 2.08
Effect of carbamazepine on CL/F (ratio)	3.04	1.97	2.92 – 3.16
Effect of sex on CL/F (ratio)	0.815	2.02	0.783 – 0.847
Apparent central volume of distribution: $V2/F= \Theta_{V2}*(WGT/67.2)$			
Basal V2/F (L)	25.2	3.46	23.5 – 26.9
Inter-compartment Clearance: $Q/F= \Theta_{Q}*(WGT/67.2)^{0.75}$			
Q (L/h)	8.37	3.26	7.83 – 8.91
Apparent peripheral volume of distribution: $V3/F= \Theta_{V3}*(WGT/67.2)$			
Basal V3/F (L)	43.8	1.88	42.2 – 45.4
Absorption Rate Constant: Ka			
Ka for tablet fasted (1/h)	4.23	Fixed	-
Ka for tablet fed (1/h)	0.431	Fixed	-
Ka for suspension fasted (1/h)	3.26	Fixed	-
Ka for suspension fed (1/h)	0.316	Fixed	-

Lag Time in Absorption: ALAG1			
ALAG1 (h)	0.229	Fixed	-
Inter-individual variability(%CV)			
CL/F	45.9	3.23	-
V2/F	59.7	4.33	-
Q/F	54.7	5.15	-
V3/F	37.4	6.16	
Ka	120	Fixed	
Inter-occasion variability (%CV)			
CL/F	14.8	0.0218	
Residual variability			
Proportional (%CV)	19.9	0.402	
Additive (ng/mL)	1.41	1.86	

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL/F = apparent clearance, V2/F = apparent central volume of distribution; Q=inter-compartment clearance; Ka = first order absorption rate constant; V3/F = apparent peripheral volume of distribution; ALAG1 = duration of zero order absorption; h = hour; WGT = body weight; CI = confidence interval; %CV = Square root of variance *100.

Overall PK parameters were estimated with a good precision (RSE <10%).

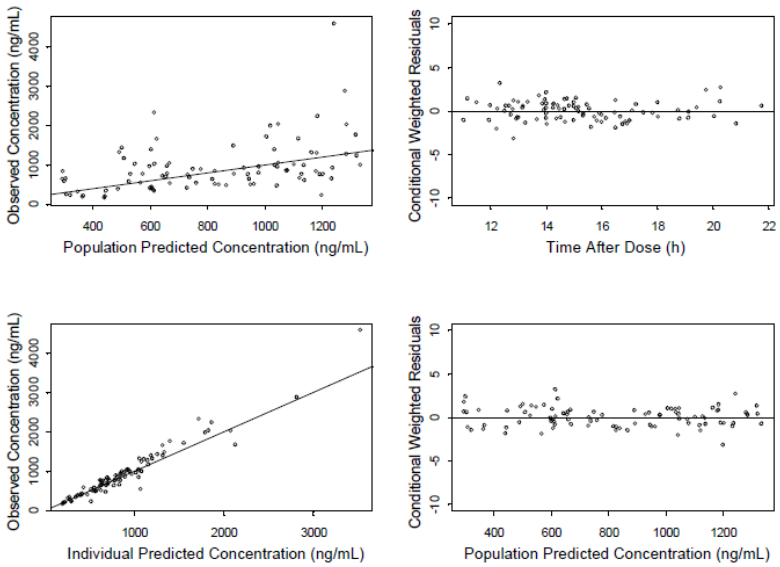
The final population PK model for perampanel contained the statistically significant effects of body weight on V2/F, Q/F and V3/F with fixed allometric scaling for all subjects and on CL/F for subjects aged < 18 years of age only, sex and the concomitant medications of AEDs carbamazepine, oxcarbazepine/phenytoin, and topiramate/phenobarbital (significant AEDs), on perampanel CL/F. Carbamazepine resulted in a 3.04-fold increase in CL/F whereas co-administration of oxcarbazepine or phenytoin resulted in 1.97-fold increases in CL/F. Co-administration of topiramate or phenobarbital increases perampanel CL/F by 1.22-fold. CL/F was 18.5% lower in females compared to males. These results are consistent with those from previous analyses. In the final PK model, the basal estimate for CL/F was slightly lower in subjects < 18 years old compared to adults (0.613 vs 0.646 L/h).

Model Evaluation

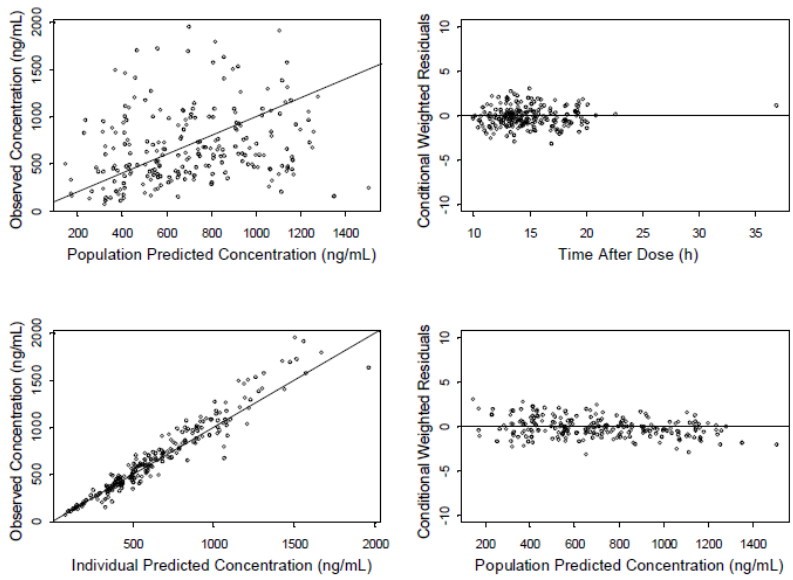
Goodness-of-fit plots for the final PK model for perampanel are presented hereafter (without inducers) for study 311.

GOF for Study 311 (without inducers)

Age 4 to < 7 Years without Inducers



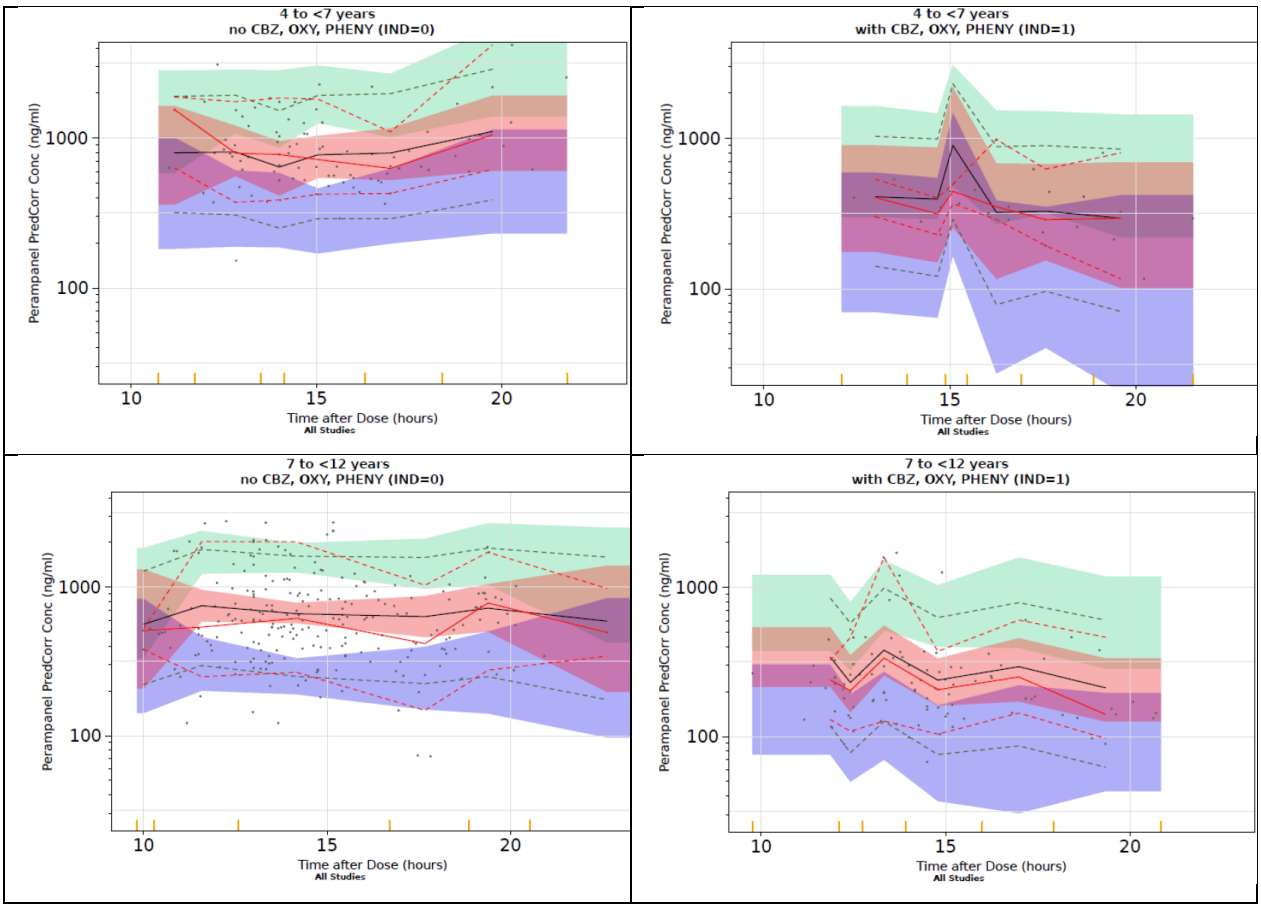
Age 7 to < 12 Years without Inducers



Visual Predictive check (VPC)

pcVPC were presented by studies in the following figure. According to the MAH, the majority of the observed concentrations are within the 90% prediction intervals for all data.

pcVPC for Study 311



Simulation to assess PK extrapolation to PEDIATRIC subjects aged 4 to < 12 years and Dosing recommendations

To further assess the effect of body weight on the exposure to perampanel during the maintenance period (i.e., at steady state) PK simulations in subjects aged < 18 years were performed, using parameter estimates from the final PK model (N=100), for subjects at body weights of < 20 kg, 20 to < 30 kg, 30 to < 40 kg, 40 to < 60 kg and 60 kg, based on median weights within these ranges from the actual population PK analysis dataset.

The median bodyweights used for the simulations for the following body weight categories < 20 kg, 20 to < 30 kg, 30 to < 40 kg, 40 to < 60 kg and ≥ 60 kg were 18.5, 24.4, 36.2, 53.0 and 74.4 kg, respectively.

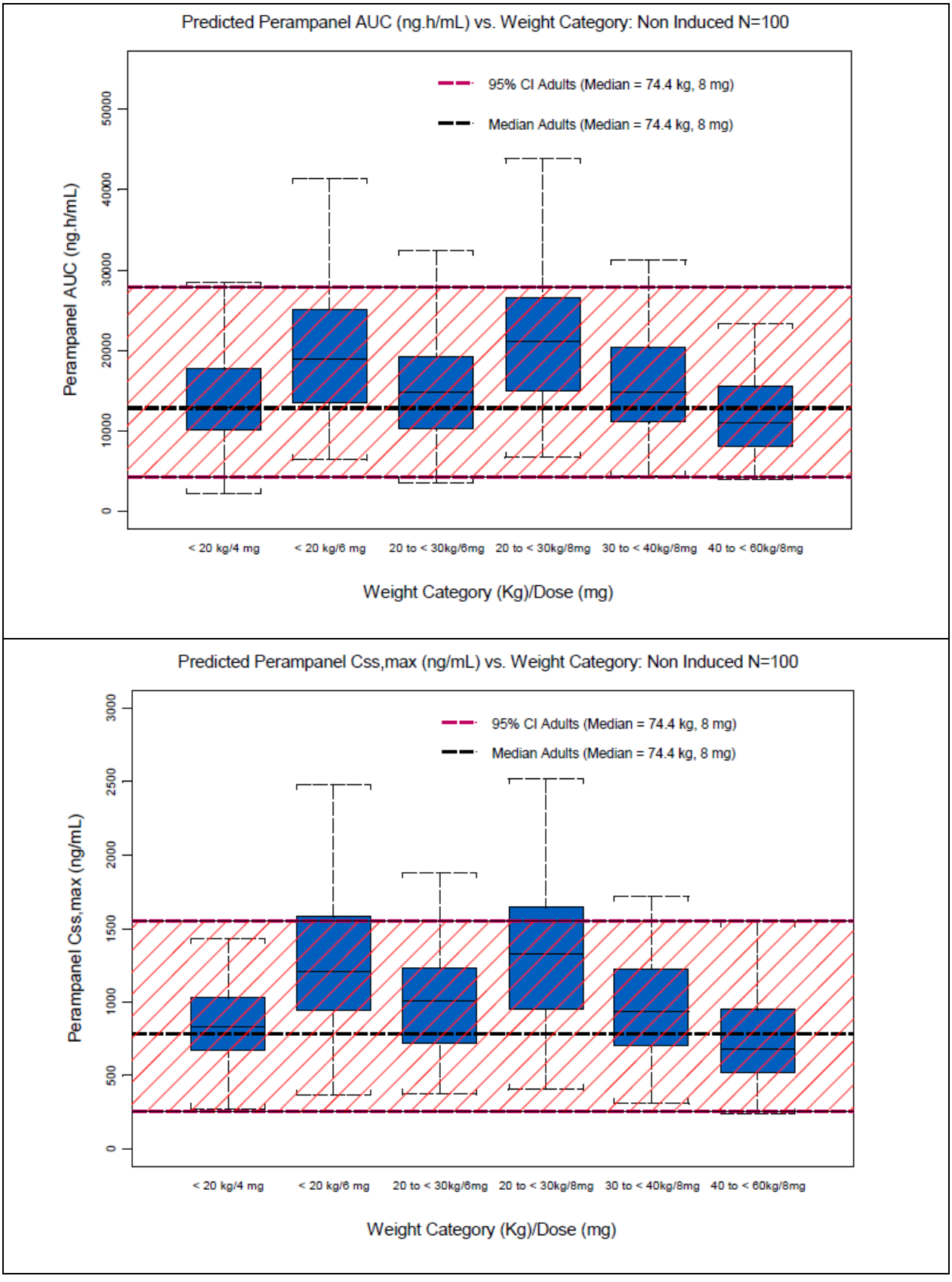
Simulations were performed based on dosing during maintenance dosing of 4 mg and 6 mg perampanel once daily to subjects < 20 kg body weight, 6 mg and 8 mg perampanel once daily to subjects 20 to < 30 kg bodyweight and 8 mg perampanel once daily to all other subjects. Simulations were performed by using parameter estimates from the final PK model.

Based on the simulations for body weight group, descriptive statistics of model derived AUCss, Css,max and Css,min for each body weight/dose category were determined and are presented in the following table. In addition, box and whisker plots for model derived AUCss, Css,max and Css,min for each body weight/dose category are presented in the figure below.

Perampanel predicted PK exposure parameters during maintenance period following once daily dosing of tablets to adults and oral suspension to pediatric subjects without concomitant inducers

Weight Category	Dose	Mean	SD	Min	Max	%CV	P5	P50	P95
AUC (ng*hr/mL)									
< 20 kg	4 mg	14143	5599	2240	29300	27060	39.6	7006	12900
< 20 kg	6 mg	20584	9465	6370	56000	49630	46.0	8226	18850
20 to < 30kg	6 mg	16173	8161	3610	60800	57190	50.5	6979	14800
20 to < 30kg	8 mg	22920	11708	6700	72700	66000	51.1	7957	21150
30 to < 40kg	8 mg	16214	7154	4480	43700	39220	44.1	6458	14850
40 to < 60kg	8 mg	12356	6190	3980	36300	32320	50.1	4931	10950
≥ 60 kg	8 mg	14257	6468	3930	37500	33570	45.4	4899	12750
Css,max (ng/mL)									
< 20 kg	4 mg	879	320	277	1940	1663	36.4	400	832
< 20 kg	6 mg	1282	506	369	3020	2651	39.5	558	1205
20 to < 30kg	6 mg	1053	494	376	3710	3334	46.9	436	1005
20 to < 30kg	8 mg	1409	654	407	3890	3483	46.4	542	1325
30 to < 40kg	8 mg	999	412	310	2490	2180	41.2	397	939
40 to < 60kg	8 mg	751	347	243	1930	1687	46.2	317	683
≥ 60 kg	8 mg	858	378	256	2110	1854	44.1	310	786
Css,min (ng/mL)									
< 20 kg	4 mg	374	168	26	894	868	44.9	154	349
< 20 kg	6 mg	554	294	148	1520	1372	53.1	180	502
20 to < 30kg	6 mg	442	253	39	1690	1651	57.1	114	412
20 to < 30kg	8 mg	617	353	118	1990	1872	57.2	192	540
30 to < 40kg	8 mg	421	200	90	1100	1010	47.5	147	372
40 to < 60kg	8 mg	331	191	65	1140	1075	57.8	109	294
≥ 60 kg	8 mg	385	194	89	1130	1041	50.4	144	355

Predicted perampanel AUCss (up) and Css, max (down) vs weight category



Compared to adults of body weight and Css, max (down) vs weight categoryuring maintenance, the simulations demonstrated comparable exposure based on AUCss, Cmax,ss and Cmin,ss will be achieved with a target dose of 4 mg once daily administered to paediatric subjects of bodyweight < 20 kg, with a target dose of 6 mg/once daily administered to paediatric subjects of bodyweight 20 to < 30 kg and with a target dose of 8 mg/day for paediatric subjects with body weight of 30 to < 60 kg.

2.3.3. Discussion on clinical pharmacology

The pharmacokinetic of perampanel has been well characterized in adult patients

The proposed extension of the indication in the pediatric population (2 to < 12 years) have been addressed according to the paediatric investigation part of perampanel clinical development. In support of an extrapolation of adult and adolescent efficacy to patients aged 2 to < 12 years, the MAH conducted an exploratory Phase 2 study (Study 232) in patients aged 2 to <12 years with POS or PGTC, and a pivotal Phase 3 study (Study 311) in patients aged 4 to < 12 years with POS or PGTC.

Both Study 232 and Study 311 used validated micromethods to measure perampanel concentration, however two bioanalytical methods were developed. A DBS method for Study 232 was used where perampanel concentration was quantified in human blood samples, then concentration in human plasma was derived using a blood plasma ratio factor of 0.88 which appear far from that determined by a dedicated in vitro study method (initial MAA) of 0.55. In addition to this discrepancy, the DBS method claimed to be reproducible, seems not. Therefore the validity of the PK data from study 232 was questioned, two concerns was raised from which no clear evidence was provided by the applicant to definitively consider these PK data as reliable as claimed. A conventional bioanalytical method was applied for Study 311 and this method show satisfactory results and is considered validated.

Initially a population PK model using PK data from 20 Phase 1 studies in adults, 6 Phase 2/3 in adult and adolescent patients, and the two studies in the paediatric population (Study 232 and Study 311) was developed (Report CPMS-E2007-015R-v2). Overall, the developed PK model seemed to fit for purpose, however several uncertainties remained with regards to the covariate screening procedure, the weight effect on clearance and its predictive performance particularly. These issues appeared critical since an adequate PopPK model is needed to support extrapolation From that PK model, a simulation study was performed using individual derived exposure parameters of perampanel. To allow a comparison between groups of different age strata the MAH have proposed a metric, the dose normalized AUCss at 8 mg. From that analysis a clear over-exposure was predicted in the age group 4 to <7 years vs above 18 years as shown below suggesting that a weight effect on clearance should be accounted for.

As second Population PK model was therefore requested where PK data from Study 232 were asked to be discarded, and weight effect on clearance should be accounted for only in the pediatric population <18 years (Report CPMS-E2007-015R-v3). The main result from that analysis was the clear weight effect on perampanel clearance from which a dosing schedule in the paediatric population aged 4 to <12 years based on body weight group (< 20 kg, 20-30 kg and > 30 kg) was proposed and accepted.

Only 4 patients aged 2 < 4 years with 4 PK observations were included in Study 232. These patients received perampanel dose up to 2.5 mg which are considered far from the target dose of 8 mg. The paucity of the PK data and PD data (efficacy/safety) in this age group associated to the uncertainties associated to the quantification method are not in favor to use a full or a partial extrapolation approach at this stage.

2.3.4. Conclusions on clinical pharmacology

Following a wealth population PK analysis, the MAH proposal to use a dosing schedule in the paediatric

population aged 4 to <12 years based on body weight group (< 20 kg, 20-30 kg and > 30 kg) is acceptable.

2.4. Clinical efficacy

2.4.1. Main studies

Study E2007-G000-232

Methods

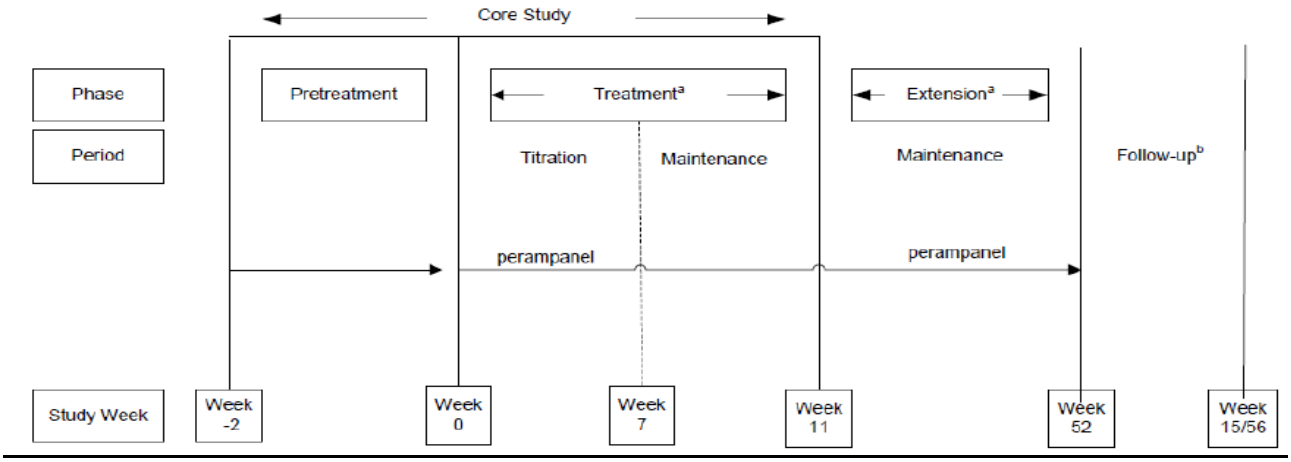
This study is a multicenter, multiple ascending dose, open-label study with an extension phase conducted to evaluate PK and to generate preliminary safety, tolerability, and efficacy data for perampanel oral suspension when given as an adjunctive therapy in pediatric patients from 2 to <12 years of age with a diagnosis of epilepsy with any type of seizure according to the International League Against Epilepsy's (ILAE) Classification of Epileptic Seizures., including patients with PGTC of IGE (n=3).

Patients were enrolled into 2 cohorts depending upon age at the time of consent/assent:

- Cohort 1 consisted of patients 7 to <12 years of age,
- Cohort 2 consisted of patients 2 to <7 years of age.

The Core Study consisted of 2 phases:

- Pretreatment Phase: The Pretreatment Phase lasted up to 2 weeks in duration, during which patients were assessed for their eligibility to participate in the study.
- Treatment Phase: The Treatment Phase consisted of 3 periods: Titration (7 weeks), Maintenance (4 weeks), and Follow-up (4 weeks; for those patients not rolling over to the Extension Phase of the study, for those patients who early terminate from the study, and for all patients completing the Extension Phase).



- *Titration*

During the 7-week Titration Period, patients received perampanel oral suspension once daily. Patients started at a set daily dose of 0.015 mg/kg and had doses up-titrated at 1-week intervals (6 titration steps) to a maximum daily dose of 0.18 mg/kg or until the maximum tolerated dose based on tolerability was reached. The maximum total daily dose a patient will be allowed is 12 mg.

Doses are based on mg/kg of body weight and calculated from adult doses assuming an adult body weight of 70 kg
Starting dose (Week 0) -Visit 2 - 0.015 mg/kg ~ (1 mg/70 kg)
Titration #1 (Week 1) -Visit 3- 0.03 mg/kg ~ (2 mg/70 kg)
Titration #2 (Week 2) - (no visit) - 0.06 mg/kg ~ (4 mg/70 kg)

Titration #3 (Week 3) - Visit 4 - 0.09 mg/kg ~ (6 mg/70 kg)
Titration #4 (Week 4) - (no visit) - 0.12 mg/kg ~ (8 mg/70 kg)
Titration #5 (Week 5) - Visit 5- 0.15 mg/kg ~ (10 mg/70 kg)
Titration #6 (Week 6) - (no visit) - 0.18 mg/kg ~ (12 mg/70 kg)

At the completion of the Titration Period, patients began the Maintenance Period of the Treatment Phase.

- *Maintenance/Follow-Up*

During the 4-week Maintenance Period, patients continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period.
Patients continued taking this dose level QD for the duration of the Maintenance Period of the Treatment Phase.
Patients who did not roll over into the Extension Phase or those who discontinued from the study were required to complete the Follow-up Period 4 weeks after the last dose of treatment, as part of the Treatment Phase of the Core Study. During this period, patients did not receive study drug.

- Extension Phase

All patients who completed all scheduled visits up to and including the final visit of the Treatment Phase (Visit 8) were eligible to participate in the Extension Phase of the study.

The Extension Phase consisted of 2 periods: Maintenance (41 weeks) and Follow-up (4 weeks).

Patients continued taking perampanel oral suspension once daily at the dose level achieved at the end of the Treatment Phase. The maximum daily dose level patients could receive was 0.18 mg/kg; the maximum total daily dose a patient was allowed was 12 mg. For patients who rolled over into the Extension Phase, the last visit of the Maintenance Period in the Treatment Phase of the Core Study was the first visit of the Extension Phase.

During the Extension Phase, changes of concomitant AEDs (addition, deletion, or adjustment in dose) were allowed. However, if changes did occur, patients were to be carefully monitored, especially when switching between an inducer AED (ie, EIAED) and a non-inducer AED (ie, non-EIAED).

Study participants

The key inclusion criteria were male or female, from 2 to <12 years of age, had a diagnosis of epilepsy with any type of seizure according to the ILAE Classification of Epileptic Seizures. Diagnosis should have been established at least 6 months prior to Visit 1, by clinical history and an EEG that was consistent with epilepsy; normal interictal EEGs were allowed provided that the patient met the other diagnosis criterion (ie, clinical history), had not a progressive cause of epilepsy and had 1 or more seizure(s) during the 4 weeks prior to Visit 1
Regarding treatment, they had been on their current concomitant AED regimen for 2 months or more with a stable dose for at least 4 weeks prior to Visit 1 and no more than half of patients in each age cohort were allowed to be treated with stable doses of 1 perampanel -inducing AED (ie, carbamazepine, oxcarbazepine, and phenytoin).
Choice of patient population / Sample size
It was planned to enroll approximately 48 male and female patients from 2 to <12 years of age who had a diagnosis of epilepsy with any type of seizure according to the International League Against Epilepsy's (ILAE) Classification of Epileptic Seizures. Patients who did not meet all the inclusion criteria or who met any of the exclusion criteria were not eligible to receive study drug.

Treatments

Perampanel was administered orally and once daily. Dosing occurred at bedtime.
Dosing and administration of perampanel in Study 232 was based on the efficacy and safety data obtained for perampanel doses up to 12 mg/day studied in patients (12 years and above) with refractory POS in 3 randomized, double-blind, placebo-controlled, parallel-group Phase 3 studies: Study 304 and Study 305 (8 and 12 mg/day perampanel) and Study 306 (2, 4, and 8 mg/day perampanel).

Objectives

Primary objective: To evaluate the pharmacokinetics of perampanel in pediatric patients (age 2-11 years) with refractory epilepsy as adjunctive therapy.

Secondary objectives: To evaluate the safety and tolerability of perampanel as well as its efficacy given as an adjunctive therapy in pediatric patients (age 2-11)

Outcomes/endpoints

Primary endpoint: PK
The population PK/PD approach will be used to explore the exposure-response relationship for efficacy and most frequent AE(s).

Main secondary endpoints: safety and efficacy

- Safety assessments: AEs, SAEs, clinical laboratory values, vital with time(s) of assessment signs, ECGs, physical and neurological examinations, and photosensitivity questionnaire. Growth will be assessed by measurement of height and weight, and by thyroid and insulin-like growth factor-1 (IGF-1) testing. A suicidality scale questionnaire (Columbia-Suicide Severity Rating Scale [C-SSRS]) will also be administered for patients aged 6 years and older at the time of consent/assent.

- Exploratory Efficacy Variables: Percentage change in seizure frequency compared to the baseline and the proportion of responders, seizure-free status, and clinical global impression of change.

Sample size

Randomisation

Not applicable (Open-label study)

Blinding (masking)

Statistical methods

For the Core Study, summary statistics were displayed for all efficacy parameters.
The FAS (full analysis set) was the group of patients who received study drug, had any seizure frequency data during the 2-week Pretreatment Phase plus the 4 weeks prior to the Pretreatment Phase, and during the Treatment Phase.
For the Extension Phase, all efficacy analyses were performed on the FAS, defined as all patients who took at least 1 dose of perampanel during the Extension Phase, and had any seizure frequency data during the 2-week Pretreatment Phase plus the 4 weeks prior to Pretreatment Phase of the Core Study and had any seizure frequency data during the Extension Phase.

For this study, the efficacy seizure endpoints were the percent change in 28-day seizure frequency during treatment compared to baseline, responder rate during the Maintenance Period, and seizure-free status during the Maintenance Period.

The baseline 28-day seizure frequency for the primary analyses used seizure data from the 2-week Pretreatment Phase.

The responder rate during the Maintenance Period used the last observation carried forward-type imputation.

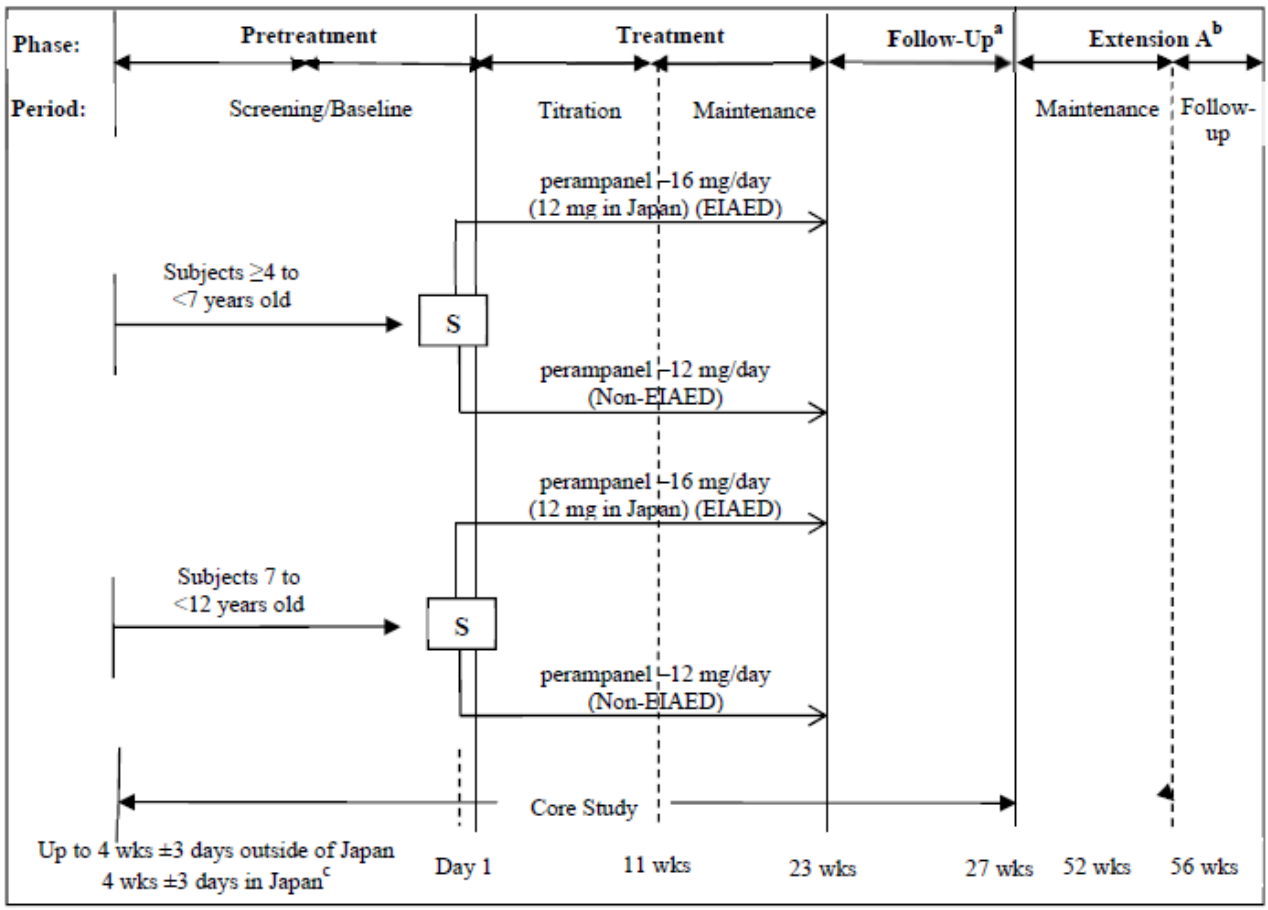
The seizure-free status during the Maintenance Period was only calculated for patients who completed the Maintenance Period (ie, those who completed the Core Study).

CGIC scores at end of treatment (EOT) were summarized. The EOT value was the last non-missing value while on-treatment.

Study E2007-G000-311

Methods

This study is an ongoing multicenter, open-label single-arm study in children (ages ≥4 to <12 years) with inadequately controlled POS or PGTCS receiving 1 to 3 other AEDs.



The study consists of a Core Study and Extension Phase.

- *Pre-treatment phase*

The Pretreatment Phase consisted of a Screening/Baseline Period that lasted up to 4 weeks ±3 days outside of Japan. Patients in Japan were required to complete 4 full weeks ±3 days of the Screening/Baseline Period. Patients were stratified by age range (≥4 to <7 years, 7 to <12 years) with at least 30% of patients planned to be enrolled in the ≥4 to <7 year age group for each seizure type (ie, at least 36 with POS and at least 12 with PGTCS).

- *Treatment phase*

The duration of the Treatment Phase was up to 27 weeks and included 3 periods: Titration (up to 11 weeks), Maintenance (up to 12 weeks), and Follow-up (up to 4 weeks; only for those patients who did not roll over into the Extension Phase).

  - *Titration*

During the Titration Period, patients were stratified by the presence or absence of concomitant EIAEDs. The perampanel dose was titrated up to 16 mg per day whether an EIAED is administered.

The Titration Period had a duration of up to 11 weeks, during which multiple dose adjustments were allowed in order to identify each patient's optimum dose. All visits were done within ±3 days of the schedule.

According to the investigator's clinical judgment, patients who experienced intolerability at any dose remained at the same dose or had their dose decreased 1 dose level down to the previously tolerated dose. Multiple dose adjustments were allowed during the Titration Period. Upon completion of the Titration Period, patients entered the Maintenance Period.

- *Maintenance*

During the Maintenance Period, patients continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period. Multiple dose adjustments were allowed if a patient experienced intolerable AE(s) or a higher dose was deemed to be beneficial.
During the Titration and Maintenance Periods, all dose adjustments were done via one dose level up or down. Patients who could not tolerate a minimum of a 2-mg dose must have discontinued from the study.

- *Follow-up/Extension phase*

All patients who completed all scheduled visits up to and including Visit 9 of the Core Study were eligible to participate in Extension phase.
Extension phase consisted of a Maintenance Period (up to 29 weeks) and a Follow-up Period (up to 4 weeks).
During the Maintenance Period of Extension phase, patients continued with their optimal perampanel dose (ie, the dose level the patients maintained at the completion of the Core Study).
Addition, deletion, and dose changes to concomitant AEDs were allowed during the Maintenance Period of Extension phase. Conversion-to-monotherapy on perampanel was also permitted at the discretion of the investigator, if it was considered appropriate to maintain seizures control.

Study participants

The key inclusion criteria were male or female, from 4 to <12 years of age, with a diagnosis of epilepsy with POS with or without SG seizures or PGTCS according to the ILAE Classification of Epileptic Seizures (1981). Diagnosis should have been established at least 6 months prior to Visit 1 by clinical history and an EEG that was consistent with the diagnosis; normal interictal EEGs were allowed provided that the patient met the other diagnosis criterion (ie, clinical history). They had a minimum weight of 16 kg (35 lb). A progressive cause of epilepsy was ruled out. During the 12 weeks ±3 days prior to Visit 2, patients must have had ≥1 POS or 1 PGTC seizure. Only simple POS with motor signs, complex POS, and complex POS with secondary generalization were counted toward this inclusion for POS.

Regarding the treatment, they had been on stable doses of 1 to a maximum of 3 approved AEDs. Doses must have been stable for at least 4 weeks before Visit 1; in the case where a new AED regimen was initiated for a patient, the dose must have been stable for at least 8 weeks prior to Visit 1. Only 1 EIAED (defined as carbamazepine, phenytoin, oxcarbazepine, or eslicarbazepine) out of the maximum of 3 AEDs was allowed (a vagal nerve stimulator was counted as 1 of the 3 allowed AEDs).

Treatments

Perampanel was administered orally and once daily. Dosing occurred at bedtime.
Patients will be stratified by concomitant use of enzyme inducing antiepileptic drugs EIAEDs:
1) The starting dose for patients not on concomitant EIAEDs is 2 mg/day with a titration one week later to 4 mg/day, followed by biweekly titration steps to 6 mg/day, 8 mg/day 10 mg/day and 12 mg/day, or until MTD is reached.
2) The starting dose for patients on concomitant EIAEDs is 4 mg/day followed by weekly titration to 6 mg/day and 8 mg/day, followed by biweekly titration to 10 mg/day, 12 mg/day, 14 mg/day and 16 mg/day or until MTD is reached.

Objectives

Primary Objective
To evaluate the safety and tolerability of perampanel oral suspension when administered as an adjunctive therapy in children (age 4 to <12 years) with inadequately controlled partial-onset seizures (POS) or primary generalized tonic-clonic (PGTC) seizures.
Secondary Objectives

- 1. To characterize the pharmacokinetics (PK) of perampanel and the relationship between perampanel plasma concentrations, efficacy, and safety using population PK/pharmacodynamics (PD) modeling
- 2. To evaluate the effects of perampanel on cognition, behavior, visuomotor skills, and growth and development in children during short-term (23 weeks) and long-term (up to 52 weeks) treatment
- 3. To evaluate the frequency of EEG abnormalities during awake and sleep state during 52 weeks of treatment
- 4. To evaluate suicidal ideation and suicidal behavior in children 6 years to <12 years as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS) during 52 weeks of treatment
- 5. To evaluate the efficacy of perampanel as measured by the median percent change per 28 days in seizure frequency, by the proportion of responders (≥25%, ≥50%, and ≥75%), and by the proportion of patients who were seizure-free for POS, PGTC, and Generalized Tonic-Clonic seizures
- 6. To assess the effects of perampanel on the Clinical Global Impression (CGI), as measured by CGI of Change (CGIC)

Outcomes/endpoints

Efficacy
Seizure diaries were used to collect daily seizure counts. All seizure types were counted.
PK
Plasma concentrations of perampanel were determined via collection of blood samples during the Maintenance Phase using a sparse sampling technique at specified visits for subsequent population PK analysis.(See PK part of this report)
Safety
The safety and tolerability includes incidence of treatment emergent adverse events (TEAEs) and SAEs, laboratory parameters, vital signs and ECG parameters of perampanel oral suspension in children (age 4 to <7 years and ≥7 years to <12 years) with POS or PGTC.
Safety was assessed by monitoring and recording all AEs and serious adverse events (SAEs).
Additional assessments included regular monitoring of hematology, blood chemistry, and urine values, regular measurements of vital signs, ECGs, and physical and neurological examinations.
Growth and development were assessed by weight, height, thyroid function tests, and insulin-like growth factor-1 (IGF-1).
For cognitive testing AldenKamp-Baker neuropsychological assessment schedule [ABNAS], behavioral questionnaires (Child Behavior Checklist [CBCL]), and visuomotor skills testing using the Lafayette Grooved
Pegboard Test (LGPT) were performed.
An assessment of suicidal ideation and behavior using the C-SSRS was performed throughout the study for patients aged 6 years and older at the time of consent/assent. Suicidal ideation and behavior was monitored in patients less than 6 years at the time of consent/assent based upon clinical impression.

An EEG was performed over a minimum of 1-hour up to a 2-hour period in an awake and sleep state at specified visits.
The CGI (CGI Severity at Baseline Visit and CGI Change [CGIC] at subsequent visits) was assessed.

Sample size

Randomisation

Not applicable (Open-label study)

Blinding (masking)

Statistical methods

The percent change in seizure frequency per 28 days with respect to baseline assessment was summarized using descriptive statistics (n, mean, median, minimum and maximum):

- by age cohorts : 4 to <7 years, ≥7 to <12 years),
- by disease cohorts : POS, PGTCS, SGTC seizures (a subset of the POS cohort, patients who had complex partial seizures with SGTC seizures at baseline),
- by the presence or absence of concomitant EIAED.

Seizure types within each disease cohort are defined as follows:

• POS cohort:
- Total seizures, defined as the sum of all seizures, including POS, generalized and other seizures.
- Total POS defined as the sum of all POS, including simple partial seizures without motor signs, simple partial seizures with motor signs, complex partial seizures, and complex partial seizures with SG;
- Total complex partial seizures.

• The SGTC subset of the POS cohort: Complex partial seizures with secondary generalization.

• PGTC cohort:
- Total seizures, defined as the sum of all seizures, including PGTCS, absence seizures, myoclonic seizures, and other seizures;
- Tonic-clonic seizures
- Absence seizures
- Myoclonic seizures

Patients who completed the core study and had no seizures during the maintenance period were considered seizure-free.

The proportion of patients who were seizure-free and the proportion of responders based on decrease from baseline in 28-day seizure frequency of ≥50% were summarized using frequency count (number and percentage) by age cohorts (4 to <7 years, ≥7 to <12 years), by disease cohorts (POS, PGTCS, and SGTC seizures), and by the presence or absence of concomitant EIAED in the FAS.

The CGIC was summarized using frequency count (number and percentage) by age cohorts (4 to <7 years, ≥7 to <12 years), by disease cohorts (POS, PGTCS, and SGTC seizures), and by the presence or absence of concomitant EIAED in the FAS.

Results of studies 311 and 232

Participant flow

Participant flow/recruitment study population for study 311

Core study

Efficacy analyses in Core Study 311 were conducted using the full analysis set (FAS).

In Core Study 311, a total of 180 patients were included in the FAS (149 patients in the POS cohort, including 54 patients in the secondarily generalized tonic-clonic (SGTC), and 31 patients in the PGTC cohort, including 24 patients in the PGTCS of IGE subset of the PGTC cohort.

Of the 180 patients, 46 patients (40 patients with POS and 6 patients with PGTCS) were in the 4 to <7 year age group and 134 patients (109 patients with POS and 25 patients with PGTCS) were in the ≥7 to <12 year age group.

Study 311	**POS** **n = 149**	**PGTCS (of which PGTCS of IGE = 22)** **n = 31**
4-7 years, n = 46	**40**	**6 (3 IGE patients actually)**
7-12 years, n = 134	**109**	**25 (19 IGE patients actually)**

Participant flow/recruitment study population for study 232

Core study

For the Core Study, it was planned to enroll approximately 48 male and female patients from 2 to <12 years of age who had a diagnosis of epilepsy.

Approximately 60 patients were screened with an aim to enroll at least 48 evaluable patients into 2 age-matched cohorts with approximately 24 patients each (patients from ≥7 to <12 years of age and patients from ≥2 to <7 years of age).

Patients were enrolled at 15 centers in North America and were assigned to a single treatment group: perampanel oral suspension.

A total of 50 patients were treated with perampanel: 22 patients 2-7 years, and 28 patients 7-12 years). There were 3 patients in this study with PGTC of IGE (1 in Cohort 2 and 2 in Cohort 1).

Study 232	**POS n = 41**	**PGTCS (of which PGTCS of IGE = 3) n = 9**
2-7 years (cohort 2), n = 22	**16**	**6 (1 IGE patient actually)**
7-12 years (cohort 1), n = 28	**25**	**3 (2 IGE patients actually)**

Participant flow/recruitment study population for patients with PGTCS of IGE across study 311 and study 232

The number of patients diagnosed with PGTCS and PGTCS of IGE in both studies are provided by age cohort:

Table 2.5-1 Number of Subjects With PGTCS and PGTCS of IGE by Study and Age Cohort

Age Cohort	Study 311		Study 232		Total	
	PGTCS, n	PGTCS of IGE, n	PGTCS, n	PGTCS of IGE, n	PGTCS, n	PGTCS of IGE, n
≥2 to <4	0	0	0	0	0	0
≥4 to <7	6	5	6	1	12	6
≥7 to <12	25	19	3	2	28	21
Total	31	24	9	3	40	27

IGE = idiopathic generalized epilepsy, PGTCS = primary generalized tonic-clonic seizures.
Source: Core Study 311 Table 14.1.1.5.1, SCS Table 14.1.1.5.2, Core Study 232 Listing 16.2.4.2.1.

Recruitment

Conduct of the study

Baseline data

Patient Demographics:

In Study 232, the age group of enrolled patients is ≥2 to <12 years, with a median age of 7.5 years.
In Study 311, the age group of enrolled patients is ≥4 to <12 years, with a median age of 8.0 years.
The patients ratio distribution between male and female is 68.0% for study 232 (2/3 of male patients) compared to 51.1% for study 311.
Weight, height, and body mass index (BMI) were similar across patients in both studies.

Disease cohorts and Prior treatments:

The number of AEDs taken at baseline by disease cohort for Core Study 232 and Core Study 311 is summarized in Table 2.7.3-21.

Overall, a generally similar percentage of patients between Core Study 232 and Core Study 311 were taking a total of 1 AED (24.0% vs 19.4%, respectively), 2 AEDs (52.0% vs 55.6%, respectively), and 3 AEDs (24.0% vs 25.0%, respectively) at baseline.
The percentages of patients in Core Study 232 and Core Study 311 taking EIAEDs were 36.0% and 27.2%, respectively, and the percentages of patients in Core Study 232 and Core Study 311 for those not taking EIAEDs were 64.0% vs 72.8%, respectively.

Table 2.7.3-21 Number of Antiepileptic Drugs at Baseline by Disease Cohort in Core Study 232 and Core Study 311 - Safety Analysis Set

Type of Medication Number of Medications	Disease Cohort					
	Study 232 Any Seizure Type (N=50) n (%)	Study 311				
		POS (N=149) n (%)	SGTC[a] subset of POS (N=54) n (%)	PGTC (N=31) n (%)	PGTC of IGE[a] subset of PGTC (N=24) n (%)	Total[b] (N=180) n (%)
Inducer[c]	18 (36.0)	47 (31.5)	12 (22.2)	2 (6.5)	1 (4.2)	49 (27.2)
1 AED	2 (4.0)	13 (27.7)	4 (33.3)	2 (100.0)	1 (100.0)	15 (30.6)
2 AEDs	12 (24.0)	27 (57.4)	7 (58.3)	0	0	27 (55.1)
3 AEDs	4 (8.0)	7 (14.9)	1 (8.3)	0	0	7 (14.3)
Noninducer[c]	32 (64.0)	102 (68.5)	42 (77.8)	29 (93.5)	23 (95.8)	131 (72.8)
1 AED	10 (20.0)	14 (13.7)	7 (16.7)	6 (20.7)	4 (17.4)	20 (15.3)
2 AEDs	14 (28.0)	56 (54.9)	22 (52.4)	17 (58.6)	15 (65.2)	73 (55.7)
3 AEDs	8 (16.0)	32 (31.4)	13 (31.0)	6 (20.7)	4 (17.4)	38 (29.0)
Total	50 (100)	149 (100.0)	54 (100.0)	31 (100.0)	24 (100.0)	180 (100.0)
1 AED	12 (24.0)	27 (18.1)	11 (20.4)	8 (25.8)	5 (20.8)	35 (19.4)
2 AEDs	26 (52.0)	83 (55.7)	29 (53.7)	17 (54.8)	15 (62.5)	100 (55.6)
3 AEDs	12 (24.0)	39 (26.2)	14 (25.9)	6 (19.4)	4 (16.7)	45 (25.0)

Percentages are based on the total number of subjects in relevant treatment group. Subjects reporting the same medication more than once are counted only once.
Prior to Study 311 Amendment 01, Version 5.0 (20 Apr 2017), subjects were allowed a maximum of 2 AEDs at Baseline.
AED=antiepileptic drug, IGE=idiopathic generalized epilepsy, N=total number of subjects in the sample group, n=number of subjects used in the analysis, PGTC=primary generalized tonic-clonic, POS=partial-onset seizures, SGTC=secondarily generalized tonic-clonic.
a: Subjects are assigned as POS or PGTC by the investigator. SGTC is the subset of POS subjects who recorded secondarily generalized seizures during the baseline period. PGTC of IGE is the subset of PGTC subjects with idiopathic generalized epilepsy.
b: Total=POS + PGTC. SGTC is a subset of POS. PGTC of IGE is a subset of PGTC.
c: An inducer subject took at least 1 inducing AED at baseline. Inducer AEDs include carbamazepine, oxcarbazepine, eslicarbazepine (Study 311 only), and phenytoin. All other AEDs are noninducer AEDs.
Source: Core Study 232 CSR Table 14.1.4.3.2, Core Study 311 CSR Table 14.1.4.3.2.1, Module 2.7.4 Table 14.1.4.3.2.1

Patient Disposition and primary reason for discontinuation

This table presents the patient disposition and primary reason for discontinuation from both studies.

Table 2.7.3–23 Subject Disposition and Primary Reasons for Discontinuation from Study 232 and Study 311 (Core Study) – All Treated Subjects

Parameter	Perampanel					
	Study 232 Any Seizure Type	Study 311				
		POS	SGTC[a] subset of POS	PGTC	PGTC of IGE[a] subset of PGTC	Total[b]
Treated, n (%)	50 (100)	149 (100.0)	54 (100.0)	31 (100.0)	24 (100.0)	180 (100.0)
Completed Core Study, n (%)	42 (84.0)	122 (81.9)	48 (88.9)	24 (77.4)	18 (75.0)	146 (81.1)
Discontinued Core Study, n (%)	8 (16.0)	27 (18.1)	6 (11.1)	7 (22.6)	6 (25.0)	34 (18.9)
Primary reason for discontinuation[c], n (%)						
Adverse event	2 (4.0)	11 (7.4)	2 (3.7)	3 (9.7)	2 (8.3)	14 (7.8)
Lost to follow-up	1 (2.0)	0	0	0	0	0
Subject choice	1 (2.0)	6 (4.0)	1 (1.9)	1 (3.2)	1 (4.2)	7 (3.9)
Inadequate therapeutic effect	1 (2.0)	6 (4.0)	0	2 (6.5)	2 (8.3)	8 (4.4)
Withdrawal of consent	1 (2.0)	1 (0.7)	1 (1.9)	1 (3.2)	1 (4.2)	2 (1.1)
Other	2 (4.0)	3 (2.0)	2 (3.7)	0	0	3 (1.7)

Percentages are based on the number of enrolled and treated subjects.
CRF=case report form, IGE=idiopathic generalized epilepsy, N=total number of subjects in the sample group, n=number of subjects used in the analysis, PGTC=primary generalized tonic-clonic, POS=partial-onset seizures, SGTC=secondarily generalized tonic-clonic.
a: Subjects are assigned as POS or PGTC by the investigator. SGTC is the subset of POS subjects who record Secondarily Generalized Seizures during the baseline period. PGTC of IGE is the subset of PGTC subjects with idiopathic generalized epilepsy.
b: Total=POS + PGTC. SGTC is a subset of POS. PGTC of IGE is a subset of PGTC.
c: As reported on the Subject Disposition CRF.
Source: Core Study 232 CSR Table 14.1.1.3, Core Study 311 CSR Table 14.1.1.5.1, Module 2.7.4 Table 14.1.1.5.1.

Numbers analysed

Outcomes and estimation

Efficacy results for Study E2007-G000-311

In Study 311, the majority of patients (overall, 52.2%) had a mean daily dose of > 4 to 8 mg/day. The same trend was observed across disease cohorts (POS, the SGTC subset of the POS cohort, and PGTC; however, in the PGTC of IGE subset of PGTC cohort, the majority of patients (58.3%) received a mean daily dose of >8 to 12 mg/day).

In patients without concomitant EIAEDs, the majority of patients had a mean daily perampanel dose of >4 to 8 mg/day (56.1%). None received doses beyond 12 mg/day.
In patients receiving concomitant EIAEDs, the majority of patients had a mean daily perampanel dose of >4 to 8 mg/day (41.7%) and >8 to 12 mg/day (31.3%). Ten (20.8%) patients received perampanel doses of >12 to 16 mg/day.
The following tables summarized the main descriptive efficacy results for this study.

Table 2.7.3-4 Seizure Frequency per 28 Days and Percent Change During Treatment Summary for Age Cohort by Each Disease Cohort - Full Analysis Set

Disease Cohort Analysis Seizures	4 to <7 Years (N=46)		7 to <12 Years (N=134)		Total (N=180)	
Analysis Window Statistic	Actual	Percent Change	Actual	Percent Change	Actual	Percent Change
POS						
Total POS seizures						
Pretreatment phase						
n	40	-	108	-	148	-
Mean (SD)	90.5 (178.40)	-	102.0 (177.10)	-	98.9 (176.92)	-
Median	18.7	-	27.0	-	25.2	-
Min, max	0.5, 932.6	-	0.5, 1028.5	-	0.5, 1028.5	-
Treatment phase						
n	40	40	108	108	148	148
Mean (SD)	54.0 (105.87)	-31.9 (47.98)	61.9 (100.01)	-14.0 (107.36)	59.8 (101.32)	-18.8 (95.21)
Median	13.2	-42.7	14.9	-40.1	14.7	-40.1
Min, max	0.0, 434.1	-100.0, 79.1	0.0, 635.5	-100.0, 549.0	0.0, 635.5	-100.0, 549.0
95% CI for median	-	(-56.3, -26.3)	-	(-53.3, -30.8)	-	(-53.0, -31.4)
PGTC						
PGTC seizures						
Pretreatment phase						
n	3	-	19	-	22	-
Mean (SD)	1.8 (1.94)	-	9.4 (13.94)	-	8.3 (13.19)	-
Median	1.1	-	3.1	-	3.1	-
Min, max	0.3, 4.0	-	0.9, 50.2	-	0.3, 50.2	-
Treatment phase						
n	3	3	19	19	22	22
Mean (SD)	5.3 (7.74)	353.7 (748.46)	8.9 (15.03)	198.0 (1038.90)	8.4 (14.17)	219.2 (990.69)
Median	1.7	-56.5	0.9	-81.9	1.3	-69.2
Min, max	0.0, 14.2	-100.0, 1217.6	0.0, 47.4	-100.0, 4470.6	0.0, 47.4	-100.0, 4470.6
95% CI for median	-	(-100.0, 1217.6)	-	(-100.0, -17.7)	-	(-100.0, -17.7)
SGTC						
SG seizures						
Pre-Treatment Phase						
n	17	-	37	-	54	-
Mean (SD)	64.2 (96.39)	-	55.1 (102.03)	-	58.0 (99.47)	-
Median	10.8	-	10.4	-	10.6	-
Min, max	1.0, 333.9	-	1.0, 483.3	-	1.0, 483.3	-
Treatment phase						
n	17	17	37	37	54	54
Mean (SD)	35.0 (70.14)	-53.5 (31.36)	26.3 (48.39)	-51.1 (45.27)	29.0 (55.61)	-51.8 (41.11)
Median	5.3	-56.3	4.6	-60.6	4.95	-58.7
Min, max	0.2, 286.8	-91.6, 31.5	0.0, 211.3	-100.0, 118.0	0.0, 286.8	-100.0, 118.0
95% CI for median	-	(-78.12, -39.13)	-	(-75.89, -42.54)	-	(-70.17, -48.85)

Table 2.7.3-5 Seizure Frequency per 28 Days and Percent Change During Treatment Summary for Age Cohort by Each Disease Cohort - Core Full Analysis Set – PGTC Cohort

Disease Cohort Analysis Seizures	4 to <7 Years (N=6)		7 to <12 Years (N=25)		Total PGTC (N=31)	
Analysis Window Statistic	Actual	Percent Change	Actual	Percent Change	Actual	Percent Change
IGE subjects						
PGTC seizures						
Pretreatment phase						
n	2	-	17	-	19	-
Mean (SD)	2.5 (2.07)	-	9.7 (14.72)	-	8.9 (14.07)	-
Median	2.5	-	3.1	-	3.1	-
Min, max	1.1, 4.0	-	0.9, 50.2	-	0.9, 50.2	-
Treatment phase						
n	2	2	17	17	19	19
Mean (SD)	8.0 (8.80)	580.5 (900.92)	9.7 (15.73)	226.6 (1098.02)	9.5 (14.99)	263.8 (1062.66)
Median	8.0	580.5	0.9	-81.9	1.7	-56.5
Min, max	1.7, 14.2	-56.5, 1217.6	0.0, 47.4	-100.0, 4470.6	0.0, 47.4	-100.0, 4470.6
95% CI for median	-	(-56.5, 1217.6)	-	(-100.0, -24.7)	-	(-100.0, -17.7)
Non-IGE subjects						
PGTC seizures						
Pretreatment phase						
n	1	-	2	-	3	-
Mean (SD)	0.3 (NC)	-	6.5 (3.54)	-	4.5 (4.35)	-
Median	0.3	-	6.5	-	4.0	-
Min, max	0.3, 0.3	-	4.0, 9.0	-	0.3, 9.0	-
Treatment phase						
n	1	1	2	2	3	3
Mean (SD)	0.0 (NC)	-100.0 (NC)	2.3 (2.75)	-45.0 (72.25)	1.5 (2.36)	-63.4 (60.14)
Median	0.00	-100.0	2.3	-45.0	0.4	-96.1
Min, max	0.0, 0.0	-100.0, -100.0	0.4, 4.2	-96.1, 6.1	0.0, 4.2	-100.0, 6.1
95% CI for median	-	(NC, NC)	-	(-96.1, 6.1)	-	(-100.0, 6.1)
Total PGTC subjects						
PGTC seizures						
Pretreatment phase						
n	3	-	19	-	22	-
Mean (SD)	1.8 (1.94)	-	9.4 (13.94)	-	8.3 (13.19)	-
Median	1.1	-	3.1	-	3.1	-
Min, max	0.3, 4.0	-	0.9, 50.2	-	0.3, 50.2	-
Treatment phase						
n	3	3	19	19	22	22
Mean (SD)	5.3 (7.74)	353.7 (748.46)	8.9 (15.03)	198.00 (1038.90)	8.4 (14.17)	219.2 (990.69)
Median	1.7	-56.5	0.9	-81.9	1.3	-69.2
Min, max	0.0, 14.2	-100.0, 1217.6	0.0, 47.4	-100.0, 4470.6	0.0, 47.4	-100.0, 4470.6
95% CI for median	--	(-100.0, 1217.6)	-	(-100.0, -17.7)	-	(-100.0, -17.7)

Only subjects who had at least 1 seizure during the baseline period are included in the analysis.
CI=confidence interval, IGE=idiopathic generalized epilepsy, max=maximum, Min=minimum, N=total number of subjects in the sample group, n=number of subjects in the specified group, PGTC=primary generalized tonic-clonic.
Source: Module 2.7.3 Table 14.2.1.1.1.

Table 2.7.3-7 Responder Rate During Maintenance-LOCF for Age Cohort by Each Disease Cohort – Full Analysis Set

Disease Cohort Analysis Seizures Responder Frequency	4 to <7 Years (N=46)	7 to <12 Years (N=134)	Total (N=180)
POS			
Total POS seizures			
Equal or greater than 50%			
Yes, n (%)	18 (45.0)	51 (47.2)	69 (46.6)
No, n (%)	22 (55.0)	57 (52.8)	79 (53.4)
Total	40 (100.0)	108 (100.0)	148 (100.0)
Seizure-free			
Yes, n (%)	3 (7.5)	14 (13.0)	17 (11.5)
No, n (%)	37 (92.5)	94 (87.0)	131 (88.5)
Total	40 (100.0)	108 (100.0)	148 (100.0)
PGTC			
PGTC seizures			
Equal or greater than 50%			
Yes, n (%)	2 (66.7)	12 (63.2)	14 (63.6)
No, n (%)	1 (33.3)	7 (36.8)	8 (36.4)
Total	3 (100.0)	19 (100.0)	22 (100.0)
Seizure-free			
Yes, n (%)	2 (66.7)	10 (52.6)	12 (54.5)
No, n (%)	1 (33.3)	9 (47.4)	10 (45.5)
Total	3 (100.0)	19 (100.0)	22 (100.0)
SGTC			
SG seizures			
Equal or greater than 50%			
Yes, n (%)	12 (70.6)	23 (62.2)	35 (64.8)
No, n (%)	5 (29.4)	14 (37.8)	19 (35.2)
Total	17 (100.0)	37 (100.0)	54 (100.0)
Seizure-free			
Yes, n (%)	3 (17.6)	7 (18.9)	10 (18.5)
No, n (%)	14 (82.4)	30 (81.1)	44 (81.5)
Total	17 (100.0)	37 (100.0)	54 (100.0)

Efficacy results for Study E2007-G000-232

The following table summarizes the main descriptive efficacy results for this study.

Efficacy was measured by evaluating seizure frequency, responder rate, seizure-free rate and CGIC.
A total of 50 patients were treated with perampanel in Study 232 (22 patients in Cohort 2 and 28 patients in Cohort 1), and all 50 patients were included in the FAS.
There were 3 patients in this study with PGTC of IGE (1 in Cohort 2 and 2 in Cohort 1).

Table 2.7.3–20 Key Efficacy Results from Study 232 (Core Study) – Full Analysis Set

	Cohort 2 ≥2 to <7 Years N=22	Cohort 1 ≥7 to <12 Years N=28	Total N=50
Percent change in seizure frequency from Baseline to end of the Treatment Phase			
Overall seizures			
n	22	26	48
Mean (SD)	-36.9 (54.13)	130.5 (342.45)	53.7 (266.07)
Median	-43.6	-33.9	-36.0
Overall partial seizures			
n	17	23	40
Mean (SD)	-47.8 (63.02)	62.0 (378.24)	15.4 (292.16)
Median	-82.5	-46.8	-55.8
Overall generalized seizures			
n	13	9	22
Mean (SD)	-42.6 (73.91)	382.7 (425.67)	131.4 (343.46)
Median	-53.1	305.4	-35.8
Unclassified seizures			
n	3	2	5
Mean (SD)	14.5 (176.10)	-67.3 (46.25)	-18.2 (134.35)
Median	-73.7	-67.3	-73.7
Responder rate during the Maintenance-LOCF Period			
Overall seizures			
Total number (%) of subjects	22 (100)	26 (100)	48 (100)
Number (%) of responders[a]	16 (72.7)	14 (53.8)	30 (62.5)
Overall partial seizures			
Total number (%) of subjects	17 (100)	23 (100)	40 (100)
Number (%) of responders[a]	14 (82.4)	14 (60.9)	28 (70.0)
Overall generalized seizures			
Total number (%) of subjects	13 (100)	9 (100)	22 (100)
Number (%) of responders[a]	10 (76.9)	3 (33.3)	13 (59.1)
Unclassified seizures			
Total number (%) of subjects	3 (100)	2 (100)	5 (100)
Number (%) of responders[a]	2 (66.7)	2 (100)	4 (80.0)
Seizure-free status during the Maintenance Period			
Overall seizures			
Total number (%) of subjects	20 (100)	22 (100)	42 (100)
Number (%) of seizure-free subjects	3 (15.0)	6 (27.3)	9 (21.4)
Overall partial seizures			
Total number (%) of subjects	20 (100)	22 (100)	42 (100)
Number (%) of seizure-free subjects	10 (50.0)	10 (45.5)	20 (47.6)
Overall generalized seizures			
Total number (%) of subjects	20 (100)	22 (100)	42 (100)
Number (%) of seizure-free subjects	11 (55.0)	17 (77.3)	28 (66.7)
Unclassified seizures			
Total number (%) of subjects	20 (100)	22 (100)	42 (100)
Number (%) of seizure-free subjects	20 (100)	21 (95.5)	41 (97.6)

Results from the extension study

Study 311

Core Study 311 is completed and data from Extension Phase Study 311 are interim, with a data cutoff date of 20 Jul 2018.

The efficacy results during the extension phase were provided for five 13-weeks periods until the last period at 53-65 weeks of the extension phase. The median percent change in seizure frequency, the

responder rate and the seizure-free status were assessed for each 13-weeks period, for each disease cohort and for each age range.

Study 232

In the Study 232 Extension Phase, efficacy was measured using the same endpoints as in the Core Study.

Of the 42 patients who completed the Core Study, a total of 41 patients continued into the Extension Phase (22 patients in Cohort 1 and 19 patients in Cohort 2).

The 3 patients with PGTC of IGE completed the Core Study and entered the Extension Phase, but did not complete it due to patient choice (1 patient) and unable to adhere to study protocol (2 patients).

Ancillary analyses

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial E2007-G000-311

Title: phase 3 clinical study to evaluate safety, tolerability, pharmacokinetics, and PK/PD relationship of perampanel suspension when administered as an adjunctive therapy in paediatric patients (4-12 years)			
Study identifier	E2007-G000-311		
Design	Open-label, multicentre, uncontrolled, single-arm study with an extension phase to evaluate safety, tolerability, pharmacokinetics, and PK/PD relationship of perampanel suspension when administered as an adjunctive therapy in paediatric patients (from 4 to less than 12 years of age) with inadequately controlled partial onset seizures or Primary Generalized Tonic-Clonic Seizures.		
	Duration of main phase:		Treatment: up to 27 weeks (up to 11-week Titration; 12-week Maintenance; 4-week FU for patients not continuing into Extension Phase)
	Duration of Run-in phase:		4 weeks ± 3 days
	Duration of Extension phase:		33 weeks (29-week Maintenance+ 4-week Follow-up).
Hypothesis	Exploratory: descriptive statistics for efficacy and safety		
Treatments groups	perampanel		Oral administration Patients will be stratified by concomitant use of enzyme inducing antiepileptic drugs (EIAEDs): 1. The starting dose for patients not on concomitant EIAEDs is 2 mg/day with a titration one week later to 4 mg/day, followed by bi-weekly titration steps to 6 mg/day, 8 mg/day 10 mg/day and 12 mg/day, or until MTD is reached. 2. The starting dose for patients on concomitant EIAEDs is 4 mg/day followed by weekly titration to 6 mg/day and 8 mg/day, followed by bi-weekly titration to 10 mg/day, 12 mg/day, 14 mg/day and 16 mg/day or until MTD is reached.
	No placebo		
Endpoints and definitions	Primary endpoint		Safety and tolerability of perampanel oral suspension (administered at least for up to 52 weeks) summarized by age cohorts (4 to < 7 years, ≥7 years to <12 years).

	1. Secondary endpoint		To characterize the PK of perampanel and the relationship between perampanel plasma concentrations, efficacy, and safety using population PK/PD modelling (see study 12)
	2. Secondary endpoint		The population PK and PK/PD approach to be used to explore the exposure-response relationship for efficacy and most frequent AE(s).
	3. Secondary endpoint		To evaluate physical (including height, weight, thyroid hormones and IGF1) and cognitive development, behaviour using scales validated for paediatric patients: A-B Neuropsychological Assessment Schedule (ABNAS) if validated for use in paediatric patients, behavioural questionnaires (CBCL), and visuomotor skills testing using the Lafayette Grooved Pegboard Test (LGPT)
	4. Secondary endpoint		To evaluate EEGs (minimum 1hr- maximum 2hrs) recorded awake and asleep at Baseline, Month 3, and Month 12. Comparison of post-baseline EEGs to the pre-treatment one to assess eventual worsening and the presence of abnormalities not present at baseline.
	5. Secondary endpoint		To evaluate the activity of perampanel as captured on seizure diaries and measured by the median percent change per 28 days in seizure frequency and the proportion of responders (~50% reduction in seizures)
	6. Secondary endpoint		Median percent change in seizure frequency and proportion of responders (50% responders defined as ~50% decrease in seizure frequency) during the Treatment Phase compared to baseline seizure frequency
Database lock	Extension study ongoing		

Results and Analysis

Analysis description	**Descriptive statistics for efficacy**			
Analysis population and time point description	At least 160 patients with POS or PGTCS at 80 sites in the US, EU, and Asia Pacific were planned to be enrolled			
Descriptive statistics and estimate variability	perampanel	4 to <7 years cohort	7 to <12 years cohort	total
	Number of patients	40	108	148
	Percent change in seizure frequency per 28 days (POS)	-42.7	-40.1	-40.1
	95% CI for median	[-56.3;-26.3]	[-53.3;-30.8]	[-53.0;-31.4]
	>50% responder rate (POS)	45.0%	47.2%	46.6%
	Seizure free status (POS)	7.5%	13.0%	11.5%
Descriptive statistics and estimate variability	perampanel	4 to <7 years cohort	7 to <12 years cohort	total
	Number of patients	**3**	**19**	**22**

	Percent change in seizure frequency per 28 days (PGTCS)	-56.5	-81.9	- 69.2
	95% CI for median	[-100.0;1217.6]	[-100.0;-17.7]	[-100.0;-17.7]
	>50% responder rate (PGTCS)	66.7%	63.2%	63.6%
	Seizure free status (PGTCS)	66.7%	52.6%	54.5%

Analysis performed across trials (meta-analysis)

In addition to studies 232 and 311, the Applicant submitted a meta-analysis of the literature to substantiate the possibility of extrapolating efficacy from adults to paediatric patients with PGTCS.

Objective of this meta-analysis:
A meta-analysis of published studies was performed to determine whether the efficacy of AEDs in adolescents and adults with primary generalized tonic-clonic seizures (PGTCS) could be used to predict the efficacy of some AEDs in the pediatric population (4 – 11 years of age) with PGTCS.

Results from this meta-analysis provided by the MAH:
Efficacy measures were consistent between adults and children with PGTCS among the 7 adjunctive drug therapy trials for lamotrigine (LTG), topiramate (TPM), and perampanel. The median percent change in reduction of PGTCS frequency between drug and placebo was consistently in favor of the drug treatment group across trials and similar between the children and adult subgroups. Furthermore, the estimated risk ratios in the 50% or greater responder rate between drug and placebo groups were comparable between the children and adult subgroups consistently favored the drug group across trials.

2.4.2. Discussion on clinical efficacy

For the current submission, the MAH proposes to extend the approved Fycompa indications to children aged 2 years and older through extrapolation of adult and adolescent efficacy data to the paediatric population.
The extrapolation of perampanel efficacy in adults to the paediatric population is mainly supported by clinical data from two clinical studies:

- Study 311: a phase 3 open-label, uncontrolled trial, performed to assess the exposure-efficacy relationship of perampanel as adjunctive therapy in 180 paediatric patients (aged 4 to 11 years old) with inadequately controlled POS or PGTC seizures. Patients were titrated over 11 weeks to a target dose of 8 mg/day or the maximum tolerated dose (not to exceed 12 mg/day) for patients not taking EIAED (carbamazepine, oxcarbazepine, eslicarbazepine and phenytoin) or 12 mg/day or the maximum tolerated dose (not to exceed 16 mg/day) for patients taking an EIAED.
- Study 232: a phase 2 pilot, open-label, uncontrolled, ascending-dose trial, performed to evaluate the PK and preliminary safety, tolerability, and efficacy of perampanel oral suspension when given as an adjunctive therapy in paediatric patients (≥2 to <12 years) with epilepsy.

In the main study 311, in the POS cohort (n=148), the median change in seizure frequency per 28 days was -40.1%, the 50% or greater responder rate was 46.6%, and seizure-free rate was 11.5%. In the SGTCS cohort (n=54, subset of the POS cohort), the median change in seizure frequency per 28 days was -58.7%, the 50% or greater responder rate was 64.8%, and seizure-free rate was 18.5%.
In the PGTCS cohort (n=22), the median change in seizure frequency per 28 days was -69.2%, the 50% or greater responder rate was 63.6%, and seizure-free rate was 54.5%. Similar results were obtained in a subset of patients with PGTCSs in IGE (56.5%, 63.2%, and 52.6%, respectively). Considering the small number of patients, these results should however be considered cautiously.
For both studies 311 and 232, for up to nearly 1 year, efficacy was observed during the extension phase: the rate of median change in seizure frequency per 28 days, the 50% or greater responder rate and

seizure-free rate were overall consistent with those observed during the maintenance phase of the core studies. However, these results should be considered cautiously as the number of patients decreased gradually until the end of the extension phases.
Some factors like the number of baseline AED and the administration of EIAED were assessed and although the efficacy showed a reduction with the number of baseline associated AEDs as well as with the concomitant administration of inducer drugs, the observed efficacy results are consistent with those observed during the core studies. However, these results should also be considered cautiously because of the open-label trial design.
In line with the guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/98 Rev.2/Corr) and the statement '*Focal epilepsies especially cryptogenic and symptomatic, and idiopathic generalized epilepsies, with absences, myoclonic and/or generalized convulsive seizures, where the efficacy of AEDs seems to be comparable in childhood and adulthood. Focal epilepsies in children older than 4 years old have a similar clinical expression to focal epilepsies in adolescents and adults. In refractory focal epilepsies, the results of efficacy trials performed in adults could to some extent be extrapolated to children provided the dose is established'*, it is agreed that the efficacy in POS for children from 4-year-old could be extrapolated from the results in adults, provided the dosing regimen is established and justified.
Initially, there were uncertainties on the dosing scheme for patients. These were subsequently resolved and the dose in the various age groups determined as a weight-based dose for three weight categories: <20kg, 20 to < 30 kg and > 30 kg (see Discussion on clinical pharmacology above).
Although the efficacy data show a positive effect on the median seizure frequency reduction, on the responder rate and on the seizure-free status in the POS cohort, in the SGTCS subset of the POS cohort and in the PGTCS cohort for both age groups (2 to <7 years and 7 to <12 years), these efficacy results from both single-arm open labelled studies remain only of supportive nature. Further data were therefore provided and discussed.
The CHMP considered that for the treatment of POS and SGTCS, the clinical efficacy observed through descriptive data from study 311 was overall reassuring. The efficacy results could be considered clinically meaningful for both age cohorts (4 to <7 years and 7 to<12 years). The efficacy between adults and children > 4 years of age in the treatment of POS and SGTCS seems comparable and acceptable from a clinical point of view. In line with the guideline, the effect of perampanel on POS, with or without SGTCS, could be extrapolated from adults to children > 4 years of age, provided the dose is established. The CHMP agreed that the number of subjects was large enough to consider that these observed clinical results were sufficient for an established dosing regimen, based on PK/PD extrapolation from adults to the target population, to be accepted.
Regarding patients with PGTCS, although the clinical efficacy observed through descriptive data from study 311 is overall in favour of perampanel, the CHMP agreed that the small number of paediatric subjects less than 7 years of age (only 4 patients <7 years) made the clinical relevance disputable and did not allow to yield any conclusion in the PGTCS indication for this paediatric population under 7 years of age.
This is in line with the Scientific Advice "*the similarity of therapeutic response cannot be ensured, especially in the youngest children, as the brain is maturing until 7 years of age with different hyper or hypoexcitability thresholds depending on the area considered*". It was also noted that the PDCO recommended that, from studies 9 (311) and 7 (232), at least 40 patients to be evaluable for primary endpoint with PGTCS, including at least 12 patients (30%) in the age group of 4 to <7 years, and 28 patients in the 7 to < 12 years of age (PIP EMEA-000467-PIP01-08). Therefore, the number of patients was not enough in PGTCS and in PGTCS of IGE for the 4-7 age range.
Regarding patients aged 2 to <4 years old, the pilot study 232 included 5 patients aged 2 to <4 years old (one patient discontinued early and 4 patients completed study) and the main clinical phase 3 study 311, containing the majority of supportive efficacy data, only included children from 4 years old. No information regarding the efficacy of perampanel in patients aged 2 to 4 years of age was available from the main study and the CHMP therefore agreed that the data were too limited to extend the indication in patients below 4 years of age.

2.4.3. Conclusions on the clinical efficacy

Following the review of the available data, the CHMP concluded that the extension of indication of perampanel for the treatment of partial onset seizure (POS), with or without secondary generalized tonic-clonic seizures (SGTCS) was considered acceptable in children (from 4 to < 12 years of age) with the weight-based established dosing regimen.

The extension of indication for the treatment of primary generalised tonic-clonic (PGTC) seizures in patients from 7 years of age and older with idiopathic generalized epilepsy (IGE) was also considered acceptable in children (from 7 to < 12 years of age) with the weight-based established dosing regimen. For primary PGTCS in IGE, the data in the paediatric population less than 7 years of age are too limited to allow for a solid estimate of the actual efficacy.
In paediatric patients aged 2 to <4 years of age, no indication is approvable since the extrapolation, based on data from PK/PD was not considered acceptable in this age group and the efficacy data were too limited.

2.5. Clinical safety

Introduction

The safety profile of perampanel in pediatric patients with POS and PGTCS is based on data from the 2 open-label studies 311 and 232.

Post-marketing use

All safety data received by the MAH are from worldwide sources. Using the available wholesale data on the number of tablets sold and 8 mg as the WHO Defined Daily Dose for FYCOMPA, it is estimated that there have been approximately 45 million patient-days of exposure from product launch through 22 Jul 2018.
The post-marketing safety profile of FYCOMPA has been consistent with the safety profile observed during the original clinical studies. The most frequently reported spontaneous AEs in patients receiving FYCOMPA are dizziness, somnolence, and aggression followed by irritability and seizure. A literature review has not identified any new safety concerns.
Since initial marketing approval, there have been 2 additions to the safety profile. Suicidal ideation and suicide attempt were added as uncommon events to Section 4.8, Undesirable effects and Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) was added in Section 4.4 Special warnings and precautions for use and in Section 4.8 Undesirable effects in Post-marketing use.
There were no significant changes in the frequency and severity of previously identified adverse reactions or important risks.

Patient exposure

Table 2.7.4-8 Combined Extent of Exposure From Both Core and Extension Study 232 and Study 311

Extent of Exposure	Study 232			Study 311			Combined No. of Subjects With at Least 6 Months of Exposure
	Age Cohort			Age Cohort			
	≥2 to <7 Years (N=19) n (%)	≥7 to <12 Years (N=22) n (%)	Total (N=41) n (%)	4 to <7 Years (N=46) n (%)	≥7 to <12 Years (N=134) n (%)	Total (N=180) n (%)	
>26 weeks	NA	NA	NA	34 (73.9)	97 (72.4)	131 (72.8)	166[a]
>28 weeks	15 (78.9)	20 (90.9)	35 (85.4)	29 (63.0)	86 (64.2)	115 (63.9)	

N = total number of subjects in the sample group, n = number of subjects used in the analysis, NA = not available.

a: Sum of total number of subjects in ">28 weeks" row in Study 232 and ">26 weeks" row in Study 311.

Source: Study 232 Extension Phase Table 14.3.1.1.1, Study 311 Extension Phase Table 14.3.1.1.2.

Extension phase
Patients eligible to participate in Extension phase of Study 311 were those who completed the Core Study.
A total of 146 patients completed the Core Study; 136 patients enrolled into Extension phase.

As of the cutoff date of 20 Jul 2018, 132 patients have been treated. Of these, 83 patients are ongoing, 40 patients have completed, and 9 patients have discontinued: 4 patients discontinued due to an AE, 2 patients withdrew by choice, and 3 patients discontinued due to inadequate therapeutic effect.

Extension phase

A total of 42 patients completed the Core Study; 41 patients entered the Extension Phase and 27 patients completed the Study 232 Extension Phase.

Table 2.7.4-9 Cumulative Extent of Exposure by Disease Cohort - Core Study 311: Safety Analysis Set

Extent of Exposure	Disease Cohort			
	POS (N=149)	PGTC (N=31)	SGTC (Subset of POS) (N=54)	Total (N=180)
Any exposure[a], n (%)	149 (100.0)	31 (100.0)	54 (100.0)	180 (100.0)
>1 day	149 (100.0)	31 (100.0)	54 (100.0)	180 (100.0)
>1 week	148 (99.3)	31 (100.0)	53 (98.1)	179 (99.4)
>2 weeks	146 (98.0)	31 (100.0)	53 (98.1)	177 (98.3)
>3 weeks	145 (97.3)	31 (100.0)	52 (96.3)	176 (97.8)
>4 weeks	142 (95.3)	30 (96.8)	52 (96.3)	172 (95.6)
>8 weeks	134 (89.9)	29 (93.5)	50 (92.6)	163 (90.6)
>10 weeks	133 (89.3)	28 (90.3)	50 (92.6)	161 (89.4)
>12 weeks	131 (87.9)	27 (87.1)	50 (92.6)	158 (87.8)
>14 weeks	130 (87.2)	26 (83.9)	49 (90.7)	156 (86.7)
>16 weeks	129 (86.6)	26 (83.9)	49 (90.7)	155 (86.1)
>18 weeks	129 (86.6)	26 (83.9)	49 (90.7)	155 (86.1)
>20 weeks	121 (81.2)	23 (74.2)	49 (90.7)	144 (80.0)
>22 weeks	106 (71.1)	18 (58.1)	44 (81.5)	124 (68.9)
>24 weeks	10 (6.7)	3 (9.7)	7 (13.0)	13 (7.2)
>26 weeks	3 (2.0)	1 (3.2)	2 (3.7)	4 (2.2)
Duration of exposure[b] (weeks)				
n	149	31	54	180
Mean (SD)	20.6 (5.89)	20.2 (5.76)	21.6 (5.25)	20.5 (5.86)
Median	23.0	22.4	23.0	22.9
Min, Max	0, 27	3, 26	0, 27	0, 27
Number of subject-weeks[c]	3071.6	626.3	1168.7	3697.9

For remind, of the 180 patients, 46 patients (40 patients with POS and 6 patients with PGTCS) were in the 4 to <7 year age group and 134 patients (109 patients with POS and 25 patients with PGTCS) were in the ≥7 to <12 year age group.

Study 311	**POS n = 149**	**PGTCS (of which PGTCS of IGE = 22) n = 31**
4-7 years, n = 46	**40**	**6 (3 IGE patients actually)**
7-12 years, n = 134	**109**	**25 (19 IGE patients actually)**

Table 2.7.4-11 Extent of Exposure - Core Study 232: Safety Analysis Set

Extent of Exposure	Perampanel		
	Cohort 2 ≥2 to <7 Years (N=22)	Cohort 1 ≥7 to <12 Years (N=28)	Total (N=50)
Duration of exposure[a] (weeks)			
n	22	28	50
Mean (SD)	10.8 (1.34)	9.3 (3.73)	10.0 (2.99)
Median	11.1	11.0	11.0
Min, Max	5.9, 12.0	0.3, 12.0	0.3, 12.0
Number of subject-weeks[b]	236.86	261.14	498.00
Maximum dose received (mg/kg)			
n	22	28	50
Mean (SD)	0.149 (0.0409)	0.121 (0.0654)	0.133 (0.0573)
Median	0.16	0.16	0.16
Min, Max	0.05, 0.19	0.01, 0.18	0.01, 0.19
Maximum dose received (mg/kg), n (%)			
≤0.03	0	4 (14.3)	4 (8.0)
>0.03 to 0.06	2 (9.1)	5 (17.9)	7 (14.0)
>0.06 to 0.12	4 (18.2)	4 (14.3)	8 (16.0)
>0.12 to 0.15	3 (13.6)	1 (3.6)	4 (8.0)
>0.15	13 (59.1)	14 (50.0)	27 (54.0)
Maintenance Period			
Mean daily dose (mg/kg)			
n	20	22	42
Mean (SD)	0.144 (0.0405)	0.140 (0.0537)	0.142 (0.0473)
Median	0.16	0.18	0.17
Min, Max	0.06, 0.18	0.02, 0.18	0.02, 0.18
Mean daily dose (mg/kg) Category, n (%)			
≤0.03	0	1 (3.6)	1 (2.0)
>0.03 to 0.06	2 (9.1)	3 (10.7)	5 (10.0)
>0.06 to 0.12	5 (22.7)	3 (10.7)	8 (16.0)
>0.12 to 0.15	3 (13.6)	3 (10.7)	6 (12.0)
>0.15	10 (45.5)	12 (42.9)	22 (44.0)

A total of 50 patients were treated with perampanel: 22 patients 2-7 years, and 28 patients 7-12 years). There were 3 patients in this study with PGTC of IGE (1 in Cohort 2 and 2 in Cohort 1).

Study 232	**POS n = 41**	**PGTCS (of which PGTCS of IGE = 3) n = 9**
2-7 years (cohort 2), n = 22	**16**	**6 (1 IGE patient actually)**
7-12 years (cohort 1), n = 28	**25**	**3 (2 IGE patients actually)**

Adverse events

Safety was assessed by monitoring and recording all AEs and serious adverse events (SAEs).
Additional assessments included regular monitoring of hematology, blood chemistry, and urine values, regular measurements of vital signs, ECGs, and physical and neurological examinations.
Growth and development were assessed by weight, height, thyroid function tests, and insulin-like growth factor-1 (IGF-1).
Cognitive testing (Aldenkamp-Baker neuropsychological assessment schedule [ABNAS]), behavioral questionnaires (Child Behavior Checklist [CBCL]), and visuomotor skills testing using the Lafayette Grooved
Pegboard Test (LGPT) were performed.
An assessment of suicidal ideation and behavior using the C-SSRS was performed throughout the study for patients aged 6 years and older at the time of consent/assent. Suicidal ideation and behavior was monitored in patients less than 6 years at the time of consent/assent based upon clinical impression.
An EEG was performed over a minimum of 1-hour up to a 2-hour period in an awake and sleep state at specified visits (baseline, month 3 and month 12).

Treatment-emergent adverse events

Treatment emergent adverse events are presented and discussed for Study 311 (Core and Extension) and Study 232 (Core and Extension).

Of note, a TEAE is defined as an AE that emerges from the date of first dose of study drug to 28 days after last end date of dose in prescribed dose entry, having been absent at pretreatment (Baseline) or reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Patients with 2 or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).

Table 2.7.4-21 Overview of Treatment-Emergent Adverse Events by Disease Cohort - Core Study 311: Safety Analysis Set

Category	Disease Cohort			
	POS (N=149) n (%)	PGTC (N=31) n (%)	SGTC (Subset of POS) (N=54) n (%)	Total (N=180) n (%)
TEAEs	134 (89.9)	26 (83.9)	53 (98.1)	160 (88.9)
Treatment-related TEAEs	95 (63.8)	25 (80.6)	36 (66.7)	120 (66.7)
Severe TEAEs	10 (6.7)	4 (12.9)	4 (7.4)	14 (7.8)
Serious TEAEs	23 (15.4)	4 (12.9)	13 (24.1)	27 (15.0)
Deaths	1 (0.7)	0	0	1 (0.6)
Other SAEs	22 (14.8)	4 (12.9)	13 (24.1)	26 (14.4)
Life threatening	0	0	0	0
Requires inpatient hospitalization or prolongation of existing hospitalization	21 (14.1)	4 (12.9)	13 (24.1)	25 (13.9)
Persistent or significant disability or incapacity	1 (0.7)	0	0	1 (0.6)
Congenital anomaly/birth defect	0	0	0	0
Important medical events	1 (0.7)	0	0	1 (0.6)
TEAEs leading to study drug dose adjustment	69 (46.3)	15 (48.4)	24 (44.4)	84 (46.7)
TEAEs leading to study drug withdrawal	14 (9.4)	3 (9.7)	2 (3.7)	17 (9.4)
TEAEs leading to study drug dose increase	0	1 (3.2)	0	1 (0.6)
TEAEs leading to study drug dose reduction	60 (40.3)	13 (41.9)	22 (40.7)	73 (40.6)
TEAEs leading to study drug dose interruption	0	0	0	0

Table 2.7.4-22 Overview of Treatment-Emergent Adverse Events in Core Study 311 and Extension Phase by Disease Cohort: Core Safety Analysis Set

Category	Disease Cohort			
	POS (N=149) n (%)	PGTC (N=31) n (%)	SGTC (Subset of POS) (N=54) n (%)	Total (N=180) n (%)
TEAEs	136 (91.3)	26 (83.9)	53 (98.1)	162 (90.0)
Treatment-related TEAEs	97 (65.1)	25 (80.6)	36 (66.7)	122 (67.8)
Severe TEAEs	12 (8.1)	5 (16.1)	4 (7.4)	17 (9.4)
Serious TEAEs	27 (18.1)	5 (16.1)	14 (25.9)	32 (17.8)
Deaths	1 (0.7)	0	0	1 (0.6)
Other SAEs	26 (17.4)	5 (16.1)	14 (25.9)	31 (17.2)
Life threatening	0	0	0	0
Requires inpatient hospitalization or prolongation of existing hospitalization	25 (16.8)	5 (16.1)	14 (25.9)	30 (16.7)
Persistent or significant disability or incapacity	1 (0.7)	0	0	1 (0.6)
Congenital anomaly/birth defect	0	0	0	0
Important medical events	1 (0.7)	0	0	1 (0.6)
TEAEs leading to study drug dose adjustment	72 (48.3)	17 (54.8)	24 (44.4)	89 (49.4)
TEAEs leading to study drug withdrawal	16 (10.7)	5 (16.1)	2 (3.7)	21 (11.7)
TEAEs leading to study drug dose increase	0	1 (3.2)	0	1 (0.6)
TEAEs leading to study drug dose reduction	62 (41.6)	13 (41.9)	22 (40.7)	75 (41.7)
TEAEs leading to study drug dose interruption	0	0	0	0

MedDRA Version 21.0.

Subjects were classified as POS or PGTC seizures by the investigator. SGTC is the subset of POS subjects who record secondarily generalized seizures during the Baseline period.

For each row category, a subject with two or more adverse events in that category is counted only once.

MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects in the sample group, n = number of subjects with an event, PGTC = primary generalized tonic-clonic, POS = partial-onset seizures, SAE = serious adverse event, SGTC = secondarily generalized tonic-clonic, TEAE = treatment-emergent adverse event.

Source: Study 311 Extension Phase Table 14.3.1.2.1.1.

Table 2.7.4-24 Overview of Treatment-Emergent Adverse Events in the Core Study 232 - Safety Analysis Set

Category	Perampanel		
	Cohort 2 ≥2 to <7 Years (N=22) n (%)	Cohort 1 ≥7 to <12 Years (N=28) n (%)	Total (N=50) n (%)
All TEAEs	22 (100)	27 (96.4)	49 (98.0)
Treatment-related TEAEs[a]	19 (86.4)	22 (78.6)	41 (82.0)
Severe TEAEs	3 (13.6)	3 (10.7)	6 (12.0)
Treatment-emergent SAEs	3 (13.6)	5 (17.9)	8 (16.0)
Deaths[b]	0	0	0
Other SAEs[c]	3 (13.6)	5 (17.9)	8 (16.0)
Life threatening	0	0	0
Required inpatient hospitalization or prolongation of existing hospitalization	3 (13.6)	4 (14.3)	7 (14.0)
Persistent or significant disability or incapacity	0	0	0
Congenital anomaly/birth defect	0	0	0
Important medical events	0	2 (7.1)	2 (4.0)
TEAEs leading to study drug dose adjustment	9 (40.9)	8 (28.6)	17 (34.0)
TEAEs leading to study drug withdrawal	1 (4.5)	2 (7.1)	3 (6.0)
TEAEs leading to study drug dose increases	1 (4.5)	0	1 (2.0)
TEAEs leading to study drug dose reduction	8 (36.4)	6 (21.4)	14 (28.0)
TEAEs leading to study drug dose interruption	1 (4.5)	0	1 (2.0)

Table 2.7.4-25 Overview of Treatment-Emergent Adverse Events in Study 232 Extension - Safety Analysis Set

Category	Perampanel		
	Cohort 2 ≥2 to <7 Years (N=19) n (%)	Cohort 1 ≥7 to <12 Years (N=22) n (%)	Total (N=41) n (%)
TEAEs	19 (100)	22 (100)	41 (100)
Treatment-related TEAEs[a]	16 (84.2)	21 (95.5)	37 (90.2)
Severe TEAEs	6 (31.6)	5 (22.7)	11 (26.8)
Treatment-emergent SAEs	6 (31.6)	7 (31.8)	13 (31.7)
Deaths	0	0	0
Other SAEs	6 (31.6)	7 (31.8)	13 (31.7)
Life threatening	0	0	0
Required inpatient hospitalization or prolongation of existing hospitalization	6 (31.6)	7 (31.8)	13 (31.7)
Persistent or significant disability or incapacity	0	0	0
Congenital anomaly/birth defect	0	0	0
Important medical events	0	1 (4.5)	1 (2.4)
TEAEs leading to study drug dose adjustment	10 (52.6)	7 (31.8)	17 (41.5)

Category	Perampanel		
	Cohort 2 ≥2 to <7 Years (N=19) n (%)	Cohort 1 ≥7 to <12 Years (N=22) n (%)	Total (N=41) n (%)
TEAEs leading to study drug withdrawal	3 (15.8)	2 (9.1)	5 (12.2)
TEAEs leading to study drug dose increase	1 (5.3)	0	1 (2.4)
TEAEs leading to study drug dose reduction	8 (42.1)	6 (27.3)	14 (34.1)
TEAEs leading to study drug dose interruption	2 (10.5)	0	2 (4.9)

Common adverse events in study 311

Table 2.7.4-26 Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects Overall - Core Study 311: Safety Analysis Set

MedDRA System Organ Class Preferred Term	Disease Cohort			
	POS (N=149) n (%)	PGTC (N=31) n (%)	SGTC (Subset of POS) (N=54) n (%)	Total (N=180) n (%)
Subjects with any TEAE	134 (89.9)	26 (83.9)	53 (98.1)	160 (88.9)
Gastrointestinal disorders	40 (26.8)	11 (35.5)	19 (35.2)	51 (28.3)
Diarrhoea	8 (5.4)	3 (9.7)	3 (5.6)	11 (6.1)
Vomiting	16 (10.7)	4 (12.9)	7 (13.0)	20 (11.1)
General disorders and administration site conditions	34 (22.8)	6 (19.4)	10 (18.5)	40 (22.2)
Fatigue	8 (5.4)	1 (3.2)	2 (3.7)	9 (5.0)
Pyrexia	20 (13.4)	3 (9.7)	7 (13.0)	23 (12.8)
Infections and infestations	81 (54.4)	11 (35.5)	35 (64.8)	92 (51.1)
Gastroenteritis	11 (7.4)	2 (6.5)	6 (11.1)	13 (7.2)
Influenza	15 (10.1)	0	8 (14.8)	15 (8.3)
Nasopharyngitis	32 (21.5)	3 (9.7)	16 (29.6)	35 (19.4)
Upper respiratory tract infection	10 (6.7)	1 (3.2)	2 (3.7)	11 (6.1)
Nervous system disorders	80 (53.7)	21 (67.7)	29 (53.7)	101 (56.1)
Dizziness	18 (12.1)	5 (16.1)	7 (13.0)	23 (12.8)
Headache	9 (6.0)	4 (12.9)	1 (1.9)	13 (7.2)
Somnolence	42 (28.2)	5 (16.1)	17 (31.5)	47 (26.1)
Psychiatric disorders	55 (36.9)	11 (35.5)	17 (31.5)	66 (36.7)
Aggression	15 (10.1)	1 (3.2)	2 (3.7)	16 (8.9)
Irritability	18 (12.1)	5 (16.1)	8 (14.8)	23 (12.8)

Common adverse events in study 232

Table 2.7.4-29 Treatment-Emergent Adverse Events Occurring in at Least 10% of Subjects in Either Cohort in the Core Study 232, by SOC and PT - Safety Analysis Set

MedDRA SOC PT	Perampanel		
	Cohort 2 ≥2 to <7 Years (N=22) n (%)	Cohort 1 ≥7 to <12 Years (N=28) n (%)	Total (N=50) n (%)
Subjects with any TEAE	22 (100)	27 (96.4)	49 (98.0)
Gastrointestinal disorders	6 (27.3)	11 (39.3)	17 (34.0)
Vomiting	3 (13.6)	5 (17.9)	8 (16.0)
Abdominal pain upper	0	4 (14.3)	4 (8.0)
General disorders and administration site conditions	13 (59.1)	12 (42.9)	25 (50.0)
Pyrexia	8 (36.4)	4 (14.3)	12 (24.0)
Fatigue	1 (4.5)	8 (28.6)	9 (18.0)
Irritability	3 (13.6)	5 (17.9)	8 (16.0)
Infections and infestations	9 (40.9)	8 (28.6)	17 (34.0)
Upper respiratory tract infection	3 (13.6)	2 (7.1)	5 (10.0)
Investigations	4 (18.2)	7 (25.0)	11 (22.0)
Weight increased	1 (4.5)	3 (10.7)	4 (8.0)
Metabolism and nutrition disorders	4 (18.2)	6 (21.4)	10 (20.0)
Increased appetite	0	3 (10.7)	3 (6.0)
Nervous system disorders	15 (68.2)	14 (50.0)	29 (58.0)
Somnolence	4 (18.2)	3 (10.7)	7 (14.0)
Dizziness	3 (13.6)	2 (7.1)	5 (10.0)
Psychiatric disorders	9 (40.9)	12 (42.9)	21 (42.0)
Aggression	3 (13.6)	1 (3.6)	4 (8.0)
Respiratory, thoracic and mediastinal disorders	8 (36.4)	3 (10.7)	11 (22.0)
Cough	3 (13.6)	1 (3.6)	4 (8.0)

Adverse Events of Special Interest

The occurrence of TEAEs of special interest was assessed in detail: TEAEs Related to Abuse Potential, TEAEs Related to Alertness and Cognition, TEAEs Related to Hostility/Aggression, TEAEs Related to Psychosis and Psychotic Disorders, TEAEs Related to Status Epilepticus/Convulsions, TEAEs Related to Laboratory Abnormalities, Cardiac and ECG TEAEs, TEAEs Related to Rash, TEAEs related to Falls and TEAEs Related to Suicidal Ideation and Behavior.

TEAEs Related to Abuse Potential: 3 accidental overdose; no patient reported an abuse potential related SAE.patients
TEAEs Related to Alertness and Cognition: the most commonly reported TEAEs related to alertness and cognition were **somnolence** and **aggression**. Some patients discontinued, some TEAE led to a reduction in study drug dose, and some other reported a SAE.

TEAEs Related to Hostility/Aggression:
The most common events for most subgroups were **irritability** and **aggression**.
There were also cases of agitation, psychomotor hyperactivity, laceration and anger.
Although the sample size across subgroups was too small for definitive conclusions, differences in incidences of TEAEs were observed. The incidence of TEAEs for patients taking 1 baseline AED was higher (45.7%) than that for patients taking 2 or 3 baseline AEDs (26.0% and 28.9%).
A higher incidence of TEAEs was observed in the non-EIAED subgroup compared to the EIAEDs subgroup (33.6% versus 22.4%).
The incidence of TEAEs was overall similar in patients taking AEDs with sodium channel MOA versus mixed action MOA (25.0% and 20.0%).

TEAEs Related to Psychosis and Psychotic Disorders (in 12 patients for both studies)
The most common TEAE in this category related to psychosis/psychotic disorders was 5 **bradyphrenia**. There was also 3 **abnormal behaviors**. One **visual hallucination** was considered serious, related to study drug and led to study discontinuation.

Table 2.7.4-46 Treatment-Emergent Adverse Events by Narrow and Broad MedDRA SMQ Terms Related to Psychosis/Psychotic Disorders by Disease Cohort: Decreasing Frequency - Core Study 311 - Safety Analysis Set

Preferred Term	Disease Cohort			
	POS (N=149) n (%)	PGTC (N=31) n (%)	SGTC (Subset of POS) (N=54) n (%)	Total[a] (N=180) n (%)
Subjects with any TEAE	6 (4.0)	1 (3.2)	0	7 (3.9)
Bradyphrenia	5 (3.4)	0	0	5 (2.8)
Abnormal behaviour	0	1 (3.2)	0	1 (0.6)
Affect lability	1 (0.7)	0	0	1 (0.6)

Table 2.7.4-47 Treatment-Emergent Adverse Events by Narrow and Broad MedDRA SMQ Terms Related to Psychosis and Psychotic Disorder in Extension Study 232 - Safety Analysis Set

MedDRA SOC PT	Perampanel		
	Cohort 2 ≥2 to <7 Years (N=19) n (%)	Cohort 1 ≥7 to <12 Years (N=22) n (%)	Total (N=41) n (%)
Subjects with any TEAE	4 (21.1)	1 (4.5)	5 (12.2)
Nervous System Disorders	1 (5.3)	0	1 (2.4)
Speech Disorder	1 (5.3)	0	1 (2.4)
Psychiatric Disorders	3 (15.8)	1 (4.5)	4 (9.8)
Abnormal Behaviour	1 (5.3)	1 (4.5)	2 (4.9)
Echolalia	1 (5.3)	0	1 (2.4)
Hallucination[a]	1 (5.3)	0	1 (2.4)

TEAEs Related to Status Epilepticus/Convulsions:
In study 311, overall, 20 (11.1%) patients experienced TEAEs by MedDRA SMQ convulsions, 14 (9.4%) patients in the POS cohort including 7 (13.0%) patients in the SGTC subset, and 6 (19.4%) patients in the PGTC cohort.

The most common TEAEs in this category were **seizure**, **epilepsy, focal dyscognitive seizures**, **generalised tonic-clonic seizure**, **petit mal epilepsy**, and **seizure cluster**.
The other TEAEs related to **status epilepticus/convulsions** were atonic seizures, postictal state, and status epilepticus (each reported by 1 [0.6%] patient).

Three patients discontinued the study due to seizure. Two patients (one in the POS and one in the PGTCS of IGE subset, both in ≥7 to <12 years, and without concomitant EIAEDs) reported a status epilepticus/convulsions-related AE with a PT of seizure, and 1 patient (in the POS, 4 to <7 years, without concomitant EIAEDs) reported a status epilepticus/convulsions-related AE with a PT of focal dyscognitive seizure leading to drug withdrawal. The patients with a SAE of generalised tonic-clonic seizure discontinued the study.
In Study 232, 1 patient in Cohort 2 had an event of grand mal convulsion. This event was mild in severity and possibly related to study drug; the event led to withdrawal from the study and resolved.

TEAEs Related to Laboratory Abnormalities

In study 311**, no patient experienced TEAEs related to drug-related hepatic disorders**. No patients discontinued the study or the study drug, or reported a SAE related to this category of TEAE.

In study 232, events reported in more than 1 patient included **blood uric acid decreased** and **thrombocytopenia** in 3 patients each, and **metabolic acidosis, neutropenia,** and **thyroxine decreased** in 2 patients each.
The events of blood alkaline phosphatase increased, total bile acids increased, and urine bilirubin increased that occurred in 1 patient resulted in discontinuation. These 3 events were non serious, mild in intensity, possibly related to study drug, and did not resolve at the time of discontinuation.

All events were non serious except for an event of hypoglycemia, reported in the Follow-up Period in one patient (Cohort 1), which was a SAE. The event was moderate in severity and considered to be possibly related to study drug; treatment was given, and the event resolved.

Cardiac and ECG TEAEs

In study 311, cardiac and ECG TEAEs were reported in 2 patients in the POS cohort. The PTs of lower respiratory tract congestion and viral myocarditis were reported. Patient **1501108, a 4 year-old male died on Day 68 during the Core Study having contracted severe viral myocarditis the same day**. The event was assessed by the investigator as unrelated to study drug.
A 4-year-old female patient had lower respiratory tract congestion (reported term, discrete brachial congestion) during the Core Study. The event was not considered serious, and was assessed by the investigator as unrelated to study drug.

One patient had a TEAE of **mental status changes**, which was included in the sub-SMQ of cardiomyopathy. The event was reported as a severe SAE that was not related to study drug; study drug was interrupted and the SAE resolved.
In study 232, the most common TEAE related to cardiac and ECG results was mental status changes (in 2 patients in Cohort 2), which was the only event that was reported in more than 1 patient overall.

TEAEs Related to Rash

In study 311, 26 patients experienced TEAEs related to **rash**, 22 patients in the POS cohort including 7 in the SGTC subset and 4 patients in the PGTC cohort. The most common TEAEs related to rash were rash, eczema, and urticaria.
No patients reported a SAE related to rash.
One patient in the SGTC subset of the POS cohort discontinued the study due to drug eruption.
In the extension phase, 7 additional patients in the POS cohort including 3 patients in the SGTC subset reported a TEAE related to rash.

In Study 232, one patients had a TEAE of rash papular, which was not a SAE and did not led to treatment discontinuation.
In the extension phase of study 232, TEAE related to rash were reported in 3 patients in Cohort 2 and 1 patients in Cohort 1. None of these events were serious or resulted in study drug dose modification and none of the patient reported a positive skin reaction on the Photosensitivity Questionnaire.

NB: Photosensitivity Questionnaire, performed as part of safety evaluation in Study 232, showed that the majority of patients had no notable reaction, and none of the patients reported relevant SAEs or TEAEs that resulted in discontinuation of study drug. No safety concerns related to photosensitivity reactions were identified in Study 232.

TEAEs related to fall

In study 311, a total of 5 falls occurred, 2 in the POS disease cohort including 1 in the SGTC subset of the POS cohort, and 3 in the PGTC cohort. Of the falls in the PGTC cohort, 2 were reported in the PGTCS of IGE subset.
The 5 falls occurred during the Titration Phase. No patient discontinued the study or the study drug, or reported a SAE related to falls. There were no additional falls during the Extension Phase

In Study 232, 2 patients in Cohort 2 and 1 patient in Cohort 1 experienced falls. All the events were non serious and resolved; no action was taken with study drug.

TEAEs Related to Suicidal Ideation and Behavior

In study 311, there were 23 TEAEs related to **suicidal ideation and behavior** reported by 20 patients. All the identified TEAEs were mild or moderate. **One patient** with a PT of altered mood was **discontinued** from study. **No patient reported a suicidality-related SAE**.

There was 1 patient (10 years old) in the PGTCS of IGE subset of the PGTC cohort, taking a 10 mg dose of perampanel, who reported 2 TEAEs related to suicidality (PT of suicidal ideation; suicidal thinking for this patient was also identified through Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire). These TEAEs were mild in severity, transient, and considered related to the study drug by the investigator.
There were 4 additional TEAEs reported by 4 patients during the Extension Phase: psychomotor hyperactivity (2 reports), initial insomnia, and memory impairment; all events were mild or moderate.

In Study 232, 1 patient in Cohort 1 had a TEAE related to suicidal ideation and behavior; the event was not a SAE, did not result in treatment discontinuation or dose adjustment, was rated mild and not related to treatment by the investigator, and resolved without sequelae.

One patient in Cohort 2 and one patient in Cohort 1 had TEAEs related to suicidal ideation and behavior in the Extension Phase.

Table 2.7.4-1 Listing of Adverse Events Related to Suicidal Ideation and Behavior in Study 232 - Safety Analysis Set

Subject Age (y), Sex, Race	Study Phase/ Period of AE onset	Dose at or Prior to AE Onset[a]	Duration of Treatment[b] (Days)	Preferred Term	Study Day AE Started/ Stopped	Severity/ Relationship to Study Drug	Study Drug Action Taken/ Other Action Taken	Outcome
8, F, W	Extension/ Maintenance	0.023 mg/kg	119	Suicidal ideation	111/111	Severe/ Possibly Related	Drug withdrawn/ Withdrawn from study	Recovered/ Resolved
6, F, W	Extension/ Maintenance	0.197 mg/kg	364	Suicidal ideation	226/227	Mild/ Possibly Related	Drug interrupted/ None	Recovered/ Resolved
10, F, W	Core Study/ Titration	0.014 mg/kg	365	Suicidal ideation	3/3	Mild/ Not Related	Dose not changed/ None	Recovered/ Resolved

AESI in the specific age group 2 to 4 years of age from study 232:

Regarding the AESI in the specific age group 2 to 4 years of age, there were 5 patients aged 2 to <4 years old in Study 232.
One patient was treated for a duration of 55 days before discontinuing early from the core study.
The other 4 patients completed the Core study and entered the Extension Phase.
Overall, their duration of treatment ranged from 27 to 52 weeks.
None of these patients were in the PGTCS of IGE subset.

The AESI were irritability, lethargy, oppositional defiant disorder and aggression.
Hereafter the listing of SAEs and AESIs in these subjects:

Table 2.7.4-2 Listing of SAEs and AESIs in Subjects ≥2 Years to <4 Years Old in Study 232

Subject Age (y), Sex, Race	Study Period of AE Onset	Dose at or Prior to AE Onset	Duration of Treatment[a] (days)	MedDRA Preferred Term	Study Day AE Started/ Stopped	Seriousness Criteria	AESI	Severity/Relationship to Study Drug	Study Drug Action Taken/ Other Action Taken	Outcome
2, M, W[b]	Core Study/ Titration	0.16 mg/kg	55	Respiratory syncytial virus bronchiolitis	44/48	Hosp	No	Moderate/NR	Dose not changed/ Treatment given	Recovered/ Resolved
2, M, B	Extension/ OL Maintenance	0.195 mg/kg	364	Otitis media	267/267	Hosp	No	Severe/NR	Dose not changed/ Treatment given	Recovered/ Resolved
3, M, W	Core Study/ Titration	0.145 mg/kg	189	Irritability	40/47	No	Yes	Moderate/Poss	Dose reduced/ None	Recovered/ Resolved
	Core Study/ Titration	0.145 mg/kg	189	Lethargy	42/47	No	Yes	Moderate/Poss	Dose reduced/ None	Recovered/ Resolved
	Extension/ OL Maintenance	0.161 mg/kg	189	Constipation	103/110	Hosp	No	Severe/Poss	Dose not changed/ None	Recovered/ Resolved
	Extension/ OL Maintenance	0.177 mg/kg	189	Gingival recession	176/-	No	No	Moderate/Poss	Drug withdrawn/ Withdrawn from study	Not recovered/ Not resolved
	Extension/ OL Maintenance	0.177 mg/kg	189	Oral mucosal discolouration	176/-	No	No	Moderate/Poss	Drug withdrawn/ Withdrawn from study	Not recovered/ Not resolved
3, M, W	Core Study/ Titration	0.052 mg/kg	360	Irritability	17/-	No	Yes	Mild/NR	Dose not changed/ None	Recovering/ Resolving
3, M, W	Core Study/ Titration	0.121 mg/kg	281	Oppositional defiant disorder	44/-	No	Yes	Mild/Poss	Dose not changed/ None	Not recovered/ Not resolved
	Extension/ OL Maintenance	0.094 mg/kg	281	Aggression	233/-	No	Yes	Moderate/Prob	Drug withdrawn/ Withdrawn from study	Recovering/ Resolving

Discontinuations

The below tables summarize the TEAEs that resulted in discontinuation of study drug by disease cohort in study 311.

Table 2.7.4-49 Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term by Disease Cohort - Safety Analysis Set

MedDRA System Organ Class Preferred Term	Disease Cohort			
	POS (N=149) n (%)	PGTC (N=31) n (%)	SGTC (Subset of POS) (N=54) n (%)	Total[a] (N=180) n (%)
Subjects with any TEAE	14 (9.4)	3 (9.7)	2 (3.7)	17 (9.4)
General disorders and administration site conditions	1 (0.7)	0	0	1 (0.6)
Gait disturbance	1 (0.7)	0	0	1 (0.6)
Infections and infestations	1 (0.7)	0	0	1 (0.6)
Viral myocarditis	1 (0.7)	0	0	1 (0.6)
Injury, poisoning and procedural complications	0	1 (3.2)	0	1 (0.6)
Contusion	0	1 (3.2)	0	1 (0.6)
Nervous system disorders	5 (3.4)	2 (6.5)	0	7 (3.9)
Balance disorder	1 (0.7)	1 (3.2)	0	2 (1.1)
Cognitive disorder	1 (0.7)	0	0	1 (0.6)
Dizziness	1 (0.7)	0	0	1 (0.6)
Dysarthria	1 (0.7)	0	0	1 (0.6)
Focal dyscognitive seizures	1 (0.7)	0	0	1 (0.6)
Rasmussen encephalitis	1 (0.7)	0	0	1 (0.6)
Seizure	1 (0.7)	1 (3.2)	0	2 (1.1)
Psychiatric disorders	8 (5.4)	2 (6.5)	1 (1.9)	10 (5.6)
Abnormal behaviour	0	1 (3.2)	0	1 (0.6)
Aggression	3 (2.0)	0	0	3 (1.7)
Anger	1 (0.7)	0	0	1 (0.6)
Anxiety	1 (0.7)	0	0	1 (0.6)
Bradyphrenia	1 (0.7)	0	0	1 (0.6)
Disruptive mood dysregulation disorder	1 (0.7)	0	0	1 (0.6)
Irritability	2 (1.3)	1 (3.2)	1 (1.9)	3 (1.7)
Mood altered	1 (0.7)	0	0	1 (0.6)
Skin and subcutaneous tissue disorders	1 (0.7)	0	1 (1.9)	1 (0.6)
Drug eruption	1 (0.7)	0	1 (1.9)	1 (0.6)

Subject with 2 or more AEs in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).

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Table 2.7.4-50 Treatment-Emergent Adverse Events in Core Study and Extension Phase Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term by Disease Cohort Core Safety Analysis Set - PGTC Cohort

MedDRA System Organ Class Preferred Term	Disease Cohort		
	PGTCS of IGE (N=24) n (%)	Non-IGE (N=7) n (%)	Total PGTC (N=31) n (%)
Subjects with any TEAE	4 (16.7)	1 (14.3)	5 (16.1)
General disorders and administration site conditions	1 (4.2)	0	1 (3.2)
Fatigue	1 (4.2)	0	1 (3.2)
Injury, poisoning and procedural complications	1 (4.2)	0	1 (3.2)
Contusion	1 (4.2)	0	1 (3.2)
Nervous system disorders	3 (12.5)	0	3 (9.7)
Balance disorder	1 (4.2)	0	1 (3.2)
Generalised tonic-clonic seizure	1 (4.2)	0	1 (3.2)
Seizure	1 (4.2)	0	1 (3.2)
Psychiatric disorders	1 (4.2)	1 (14.3)	2 (6.5)
Abnormal behaviour	1 (4.2)	0	1 (3.2)
Irritability	0	1 (14.3)	1 (3.2)

Overall, such TEAEs were overall reported in 17/180 (9.4%) patients*:* 14/149 (9.4%) patients in the POS cohort, including 2/54 (3.7%) patients in the SGTC subset and 3/31 (9.7%) patients in the PGTC cohort.

The only TEAEs that resulted in discontinuation of more than 1 patient were **balance disorder** (2 patients; 1 patient in each cohort), **seizure** (2 patients; 1 patient in each cohort), **aggression** (3 patients in the POS cohort), and **irritability** (3 patients; 2 in the POS cohort including 1 patient in the SGTC subset, and 1 in the PGTC cohort).

TEAEs leading to discontinuation were reported by 4 additional patients during the Extension Phase, 2 patients in the POS cohort and 2 patients in the PGTC cohort.
Additional events included **fatigue, ataxia, generalised tonic-clonic seizure, and visual hallucination** reported by 1 patient each.

Overall, a total of 21 (11.7%) patients discontinued study drug due to TEAEs: 16 (10.7%) patients in the POS cohort including 2 (3.7%) patients in the SGTC subset, and 5 (16.1%) patients in the PGTC cohort.

In the PGTC cohort, 4 (16.7%) patients in the PGTCS of IGE subset and 1 (14.3%) patient in the non-IGE subset had TEAEs that resulted in discontinuation of study drug. All TEAEs in this category were reported by single patients.

In study 232, Overall, TEAEs leading to treatment discontinuation were reported in 3 (6.0%) patients (1 patient and 2 patients, respectively, in Cohort 2 and Cohort 1). None of the AEs leading to discontinuation were reported in more than 1 patient.

In the extension study 232, Treatment-emergent AEs that resulted in discontinuation occurred in 3 (15.8%) patients in Cohort 2 and 2 (9.1%) patients in Cohort 1. The only TEAE (PT) that resulted in discontinuation of more than 1 patient was aggression (1 patient in each cohort).

Adverse Drug Reactions

Adverse drug reactions (ADRs) are defined as TEAEs for which there is some basis to believe a causal relationship exists between the occurrence of the TEAE and the use of perampanel.

In the POS submission, identification of potential ADRs was based on an assessment of the full safety database for perampanel, including clinical studies in epilepsy and other indications. The methods used are described in detail in the summary of clinical safety.

The following ADRs resulted from this evaluation: dizziness, somnolence, fatigue, irritability, fall, nausea, ataxia, weight increased, vertigo, balance disorder, gait disturbance, anxiety, vision blurred, dysarthria, back pain, decreased appetite, aggression, diplopia, anger, increased appetite and confusional state.

For the PGTC seizure submission, the ADR analysis, which included the PGTC seizure data alone and the PGTC seizure data pooled with the data from the POS double-blind studies, did not indicate any new ADRs from those previously identified in the POS submission.

For this submission, TEAEs are consistent with TEAEs observed on perampanel treatment in adults and adolescents.
This review does not indicate any **new** ADRs for perampanel in this pediatric population.

Serious adverse event/deaths/other significant events

One (0.7%) death was reported in the POS cohort. The subject was a 4 year old male in the POS cohort with concomitant EIAEDs, with a cause of death (by PT) of viral myocarditis determined by autopsy. The TEAE was not considered related to the drug according to the investigator.

Table 2.7.4-3 Listing of All Deaths in Core Study and Extension Phase 311 - All Enrolled Subjects

Subject Age (y), Sex Race	Disease Cohort, With/ Without EIAEDs	Date of Death/ Study Day of Death[a]	Last Dose Prior to Death (mg)	Cause of Death (Investigator Term/Preferred Term)	AE Start Date/Study Day	AE Possibly Caused by Study Drug	Duration of Treatment[b] (Days)	Day of Death in Relation to Last Dose[c]	TEAE?
4, M	POS, w	2017-12-12/68	8	Viral Myocarditis/ Viral Myocarditis	2017-12-12/68	No	67	1	Y

Table 2.7.4-33 Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term - Core Study 311: Safety Analysis Set

MedDRA System Organ Class Preferred Term	Disease Cohort			
	POS (N=149) n (%)	PGTC (N=31) n (%)	SGTC (Subset of POS) (N=54) n (%)	Total (N=180) n (%)
Subjects with any TESAE	23 (15.4)	4 (12.9)	13 (24.1)	27 (15.0)
Gastrointestinal disorders	2 (1.3)	0	2 (3.7)	2 (1.1)
Dental caries	1 (0.7)	0	1 (1.9)	1 (0.6)
Gastritis erosive	1 (0.7)	0	1 (1.9)	1 (0.6)
General disorders and administration site conditions	2 (1.3)	0	1 (1.9)	2 (1.1)
Gait disturbance	1 (0.7)	0	0	1 (0.6)
Hyperthermia	1 (0.7)	0	1 (1.9)	1 (0.6)
Infections and infestations	10 (6.7)	2 (6.5)	7 (13.0)	12 (6.7)
Bronchitis	3 (2.0)	0	3 (5.6)	3 (1.7)
Encephalitis	1 (0.7)	0	1 (1.9)	1 (0.6)
Gastroenteritis	2 (1.3)	0	2 (3.7)	2 (1.1)
Influenza	2 (1.3)	0	2 (3.7)	2 (1.1)
Pneumonia	3 (2.0)	0	1 (1.9)	3 (1.7)
Rhinovirus infection	0	1 (3.2)	0	1 (0.6)
Urinary tract infection pseudomonal	1 (0.7)	0	1 (1.9)	1 (0.6)
Viral infection	0	1 (3.2)	0	1 (0.6)
Viral myocarditis	1 (0.7)	0	0	1 (0.6)
Musculoskeletal and connective tissue disorders	1 (0.7)	0	0	1 (0.6)
Epiphysiolysis	1 (0.7)	0	0	1 (0.6)
Nervous system disorders	9 (6.0)	4 (12.9)	5 (9.3)	13 (7.2)
Ataxia	1 (0.7)	0	1 (1.9)	1 (0.6)
Dysarthria	1 (0.7)	0	0	1 (0.6)
Epilepsy	2 (1.3)	1 (3.2)	2 (3.7)	3 (1.7)
Focal dyscognitive seizures	1 (0.7)	0	0	1 (0.6)
Generalised tonic-clonic seizure	1 (0.7)	1 (3.2)	1 (1.9)	2 (1.1)

Table 2.7.4-33 Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term - Core Study 311: Safety Analysis Set

MedDRA System Organ Class Preferred Term	Disease Cohort POS (N=149) n (%)	PGTC (N=31) n (%)	SGTC (Subset of POS) (N=54) n (%)	Total (N=180) n (%)
Petit mal epilepsy	1 (0.7)	0	0	1 (0.6)
Rasmussen encephalitis	1 (0.7)	0	0	1 (0.6)
Seizure	2 (1.3)	1 (3.2)	1 (1.9)	3 (1.7)
Seizure cluster	1 (0.7)	1 (3.2)	1 (1.9)	2 (1.1)
Somnolence	1 (0.7)	1 (3.2)	0	2 (1.1)
Psychiatric disorders	2 (1.3)	0	0	2 (1.1)
Aggression	1 (0.7)	0	0	1 (0.6)
Disruptive mood dysregulation disorder	1 (0.7)	0	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders	4 (2.7)	0	2 (3.7)	4 (2.2)
Acute respiratory failure	2 (1.3)	0	1 (1.9)	2 (1.1)
Asthma	1 (0.7)	0	0	1 (0.6)
Atelectasis	1 (0.7)	0	1 (1.9)	1 (0.6)
Upper respiratory tract inflammation	1 (0.7)	0	0	1 (0.6)

Overall, the number of treatment-emergent SAEs was low across the disease cohorts.

Treatment-emergent SAEs were reported in a total of 27 (15.0%) subjects overall, with 23 (15.4%) subjects in the POS cohort including 13 (24.1%) subjects in the SGTC subset of the POS cohort, and 4 (12.9%) subjects in the PGTC cohort.

Thirteen (28.3%) subjects with treatment-emergent SAEs were in 4 to <7 years and 14 (10.4%) were in ≥7 to <12 years age cohort in the core study 311. A higher number of subjects had treatment emergent SAEs in the without concomitant EIAEDs cohort (22 [16.7%] subjects) compared to those taking concomitant EIAEDs (5 [10.4%] subjects).

All TESAEs were reported by 1 or 2 subjects across all cohorts, with the exception of bronchitis, pneumonia, epilepsy and seizure which occurred in 3 (1.7%) subjects.

An additional 5 subjects reported SAEs during the Extension Phase, 4 subjects in the POS cohort including 1 subject in the SGTC subset, and 1 subject in the PGTC cohort. As of the data cut-off date of 20 Jul 2018, a total of 32 (17.8%) subjects experienced SAEs. This represents cumulative data and includes SAEs from both Core Study and Extension Phase.

In the PGTC cohort, 3 subjects in the PGTCS of IGE subset and 2 subjects in the non-IGE subset experienced SAEs. All SAEs were reported by single subjects.

Laboratory findings and Other Safety Evaluations

Laboratory parameters

There were no clinically important changes in hematology and clinical chemistry mean laboratory results values from Baseline to Week 23 for any cohort. Specifically, no clinically relevant changes were observed

for glucose, triglycerides, and cholesterol. The laboratory results shift analyses revealed that shifts from normal to high or low were generally infrequent.

Twelve subjects had markedly abnormal laboratory hematology results, 2 with markedly abnormal low hemoglobin, and 10 with markedly abnormal low neutrophils.

Seven subjects had markedly abnormal laboratory clinical chemistry results. Five subjects had markedly abnormal high gamma glutamyl transferase (GGT), including 1 subject who also had markedly abnormal high alanine aminotransferase (ALT), 1 subject had markedly abnormal high potassium and 1 subject had markedly abnormal low sodium and calcium (Core Study 311 Table 32). No subjects had markedly abnormal laboratory urinalysis results.

There were no clinically important changes in mean urinalysis results values from baseline to Week 23 for any of the 3 disease cohorts. For urinalysis results, 6 (3.8%) subjects had shifts from normal values at Baseline to high values at EOT of the Core Study. The urinalysis results shift analysis revealed that the patterns of shifts were similar across the disease, age, and concomitant EIAEDs cohorts.

No laboratory abnormalities led to study discontinuation. No laboratory abnormalities were related to SAEs.

Growth and neurodevelopmental assessments

Aldenkamp–Baker Neuropsychological Assessment Schedule (ABNAS) scores for fatigue, slowing, memory, concentration, motor-coordination and language were assessed. Higher scores indicate a worsening of these cognitive parameters.

Child Behavior Checklist (CBCL) is a tool to assess behavioral and emotional problems in children as reported by the primary caregiver.

Lafayette Grooved Pegboard Test (LGPT) is a tool to estimate the visuomotor skills. It is a manipulative dexterity test that consists of a metal matrix of 25 holes with randomly positioned slots. The subject was required to insert 25 pegs for 8 years or older or 10 pegs for under 8 years old for each hand. The task was timed up to a maximum of 300 seconds, and a shorter time to completion indicated increased dexterity.

There were no clinically significant results at the end of treatment in comparison to baseline as regards the three scores.

Subjects showed height and weight gain proportionate with the expected growth of subjects in this pediatric population. No meaningful embarrassing effects were observed in height and weight data.

Mean thyroid and insulin-like growth factor-2 and mean change from Baseline are recorded.
Mean insulin-like growth factor-2 was lower at baseline and at end of treatment in Cohort 2 (2 to <7 years) than in Cohort 1 (7 to <12 years).

Electroencephalogram
EEG analysis included 145 subjects with Asleep EEGs, and 154 subjects with Awake EEGs during the Core Study (baseline and Visit 9 [end of Core Study Treatment visit] or Early Discontinuation Visit).
EEG data collected during the Extension Phase (ie, Visit 12 or Early Discontinuation Extension Phase) will be analyzed and presented in a separate report when the Extension is completed.

Overall, observed primary EEG endpoints (POS and PGTCS) were low at all visits, with only 2 cases of POS being observed, and no cases of PGTCS were observed during the baseline or Visit 9 EEG assessments. Therefore, the primary EEG endpoints of changes in the frequency of POS or PGTCS from baseline to Visit 9 were not determinable.

Results of secondary EEG endpoints of changes from baseline to Visit 9 in the frequency of absence seizures, atypical absence seizures, myoclonic seizures, seizure not able to be classified, secondarily generalized clonic seizures, and epileptiform activity are summarized as follows:

- Overall, observed seizures were low for most secondary endpoints, with no cases of myoclonic seizures or SGTC seizures reported at any visit.
- Six subjects were reported to have absence seizures in either the awake or sleep state. Three subjects were reported to have atypical absence seizures in either the awake or sleep state.

- Thirteen subjects were reported to have not able to be classified seizures in either the awake or sleep state.
- No statistically significant changes from baseline to Visit 9 were observed in the mean number of absence seizures, unclassifiable seizures, or epileptiform activities (prevalence sharp waves, prevalence spike-slow waves, and rhythmic runs of spike-waves complexes ≥1 second).

Overall, there were no statistically significant changes in any of the EEG parameters measured following 23 weeks of perampanel treatment, compared to baseline. Similarly, no significant changes from baseline in any of the EEG parameters were observed between the ≥4 to <7 years and ≥7 to <12 years age subgroups and in the inducer and non-inducer subgroups. Therefore, EEG data collected so far do not suggest any safety concerns related to EEG abnormalities

2.5.1. Discussion on clinical safety

Overall, 160 (88.9%) patients experienced TEAEs. TEAEs occurred in 134 (89.9%) patients in the POS cohort including 53 (98.1%) patients in the SGTC subset of the POS cohort, and 26 (83.9%) subjects in the PGTC cohort.
Overall, 14 (7.8%) patients had severe TEAEs.
Treatment-related TEAEs were reported in 120 (66.7%) subjects overall, 95 (63.8%) subjects in the POS cohort including 36 (66.7%) patients in the SGTC subset and 25 (80.6%) patients in the PGTC cohort.
One (0.7%) patient in the POS cohort (a 4-year-old white male) died on Day 68 during the Core Study due to viral myocarditis; the death was not considered related to study drug.
There were 17 (9.4%) patients who had TEAEs leading to study drug withdrawal. Nearly half of the patients (46.7%) with TEAEs leading to study drug adjustment reduced their study drug dose (40.6%). Only 1 patient (0.6%) had drug dose increased.

There were no clinically significant results at the end of treatment in comparison to baseline as regards the scores of cognitive testing (ABNAS), child behavioral questionnaires (CBCL), and visuomotor skills testing (LGPT).

Patients showed height and weight gain proportionate with the expected growth of patients in this pediatric population. No meaningful embarrassing effects were observed in height and weight data.

Mean thyroid and insulin-like growth factor-2 and mean change from Baseline are recorded.
Mean insulin-like growth factor-2 was lower at baseline and at end of treatment in Cohort 2 (2 to <7 years) than in Cohort 1 (7 to <12 years).

It is noted that, in PGTCS, the safety profile of perampanel in children aged 2 years and <7 years could not be assessed properly due to the scarcity of the number of patients studied.

No new adverse event was reported in the submitted studies. However, according to the guideline regarding the assessment of safety, a minimum of 100 children treated by the study drug should be followed for at least one year. Moreover short term and long-term studies should be designed to detect possible impact on brain development, learning, intelligence, growth, endocrine functions and puberty. In this application, only study 311 (open label, single arm, 136 children over 52 weeks in its extension phase) made it possible to meet these specifications. Study 232 (open label 41 children over 52 weeks in its extension phase) completed these data. The other studies included children 12 years and over.

Although the level of recruitment in paediatric studies is a known issue, the data safety collection is a major point, in particular regarding the long-term aspects (neurodevelopment, motor development, cognition, behaviour, growth, endocrine functions and puberty). There were some uncertainties regarding the safety profile of perampanel that needed further clarifications and the effect of perampanel on neuropsychological aspects in a developing brain and on growth was considered as a concern which has to be specifically assessed in the paediatric population on a longer term manner (up to 1 year).

Consequently, according to the Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders, the MAH provided additional data and a thorough analysis of the impact of

perampanel on brain development, learning, intelligence, growth, endocrine functions and puberty for the paediatric population. Adverse events reported in clinical studies and post-marketing data related to developmental disorders reported few numbers of cases in children less than 12 years but these effects were not identified until now for perampanel. This is a safety concern and it will be specifically monitored in the future PSUR (attention deficit/hyperactivity disorder, learning disability, cognitive disorder, disturbance in attention, precocious puberty).

Adverse events reported in children less than 12 years in clinical studies and post-marketing data related to behavioral disorders are consistent with the known safety profile of perampanel, highlighting a large number of aggression and drowsiness effects in children.

The literature review did not bring new information on the safety profile of perampanel in children < 12 years.

The assessment of cognitive functions, behavior, visuomotor skill development, growth and endocrine functions did not seem to show clinically significant impact of perampanel. Puberty/sexual maturation and skeletal development neither, however this was assessed on a too small number of children to draw any robust conclusion. The MAH is therefore requested to continue to monitor these effects in the ongoing paediatric study (Studies 236) and in the future PSUR.

The relevant statements have been added in the SmPC regarding the higher incidence of some AE and some precautions were amended or added.

2.5.2. Conclusions on clinical safety

Based on the available safety data, the CHMP concludes that the safety profile in the extended paediatric population is acceptable and in line with the known safety profile of perampanel.

The highlighted safety concerns will continue to be monitored via the subsequent PSURs.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC advice on the submitted Risk Management Plan: the PRAC considered that the RMP version 4.5 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.5 with the following content:

Safety concerns

Summary of Safety Concerns

Important identified risks	• Aggression • Interaction with levonorgestrel-containing contraceptives, and unintended pregnancy exposures • Suicidality
Important potential risks	• Hepatic disorders (excluding hepatic disorders induced by SCARs)
Missing information	• Impact on cognition and growth in the paediatric population • Use in human pregnancy and lactation

SCARs = severe cutaneous adverse reactions

Pharmacovigilance plan

The following routine pharmacovigilance activities beyond adverse reactions reporting and signal detection should be performed.

Specific Adverse Reaction Follow-Up Questionnaires for Aggression and Suicidality and Exposure During Pregnancy

Follow-Up Questionnaire	Safety Concern(s)	Purpose
Questionnaire for reports of Aggression	Aggression	Follow-up questionnaire for serious reports of aggression to obtain complete information
Questionnaire for reports of suicidal behaviour, ideation, attempt or self-injurious behaviour	Suicidality	Follow-up questionnaire for serious reports of suicidality to obtain complete information
Questionnaire for reports of exposure during pregnancy	Use in pregnancy and lactation	Follow-up questionnaire to obtain complete information on pregnancy outcomes

Other Forms of Routine Pharmacovigilance Activities for Pregnancy

Description of Activity	Safety Concern(s)	Objectives	Milestones
• Contribution to EURAP registry • Contribution to the UK Epilepsy and Pregnancy Registry	Use in human pregnancy and lactation	To collect data on pregnancy exposure and outcomes with the use of Fycompa	Review pregnancy information provided by EURAP

EURAP=European and International Registry of Anti-Epileptic Drugs in Pregnancy.

Overall, data presented by the MAH responded to the concerns raised on the potential effect of perampanel in patients under 12 years of age regarding impact on brain development, learning, intelligence, and growth and endocrine function, with the exception of puberty / sexual maturation and skeletal development which could not be evaluated in a sufficient number of these children.

Adverse events in patients under 12 years of age (reported from clinical studies, post marketing and literature data) related to behavioural disorders are consistent with the known safety profile of perampanel, highlighting a large number of aggression and drowsiness effects in these patients. However, in few (clinical and post-marketing) cases, involving patients under 12 years of age, data about adverse events linked to developmental disorders were reported. Therefore, cases of attention deficit/hyperactivity disorder, learning disability, cognitive disorder, disturbance in attention, precocious puberty should be closely monitored in future PSURs.

The MAH acknowledged that data regarding sexual development in subjects under 12 years of age have not been collected. However, it considered that perampanel did not have a clinically meaningful effect on puberty or sexual development in this population as Tanner staging assessments were conducted for up to 2 years in Study 235 or up to 4 years in Study 307 in subjects aged 12 to <18 years and. The MAH also believed that whilst the onset of puberty and sexual development is occurring at younger ages, especially in females, assessment in the adolescent population is acceptable for assessing any possible effects of perampanel on puberty and sexual development. However, the PRAC and CHMP are of the view that these criteria should however be thoroughly followed in patients under 12 years of age, particularly in females, in the ongoing studies (236 and 238) for a sufficient timeframe, and in enough patients, to allow relevant conclusions. Also, studies 236 and 238 should provide additional data of the long-term effect of perampanel regarding ABNAS, CBCL and LGPT scores focusing on cognition, behavior, and dexterity.

No additional pharmacovigilance activities are deemed necessary.

Risk minimisation measures

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Aggression	Routine risk minimisation measures: • SmPC Section 4.4, where recommendations for perampanel dose reduction or discontinuation are provided • SmPC Section 4.8 • PL Section 2 • PL Section 4	Routine PV activities including targeted follow-up
Interaction with Levonorgestrel-Containing Contraceptives, and Unintended Pregnancy Exposures	Routine risk minimisation measures:	Routine PV activities

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.6 • PL Section 2	
Suicidality	Routine risk minimisation measures: • SmPC Section 4.4, where advice for monitoring signs of suicidality is provided • SmPC Section 4.8 • PL Section 4	Routine PV activities including targeted follow-up
Important Potential Risks		
Hepatic Disorders (excluding hepatic disorders induced by SCARs)	Routine risk minimisation measures: • SmPC Section 4.4 • PL Section 2	Routine PV activities
Missing Information		
Impact on cognition and growth in the paediatric population	Routine risk minimisation measures: SmPC Section 4.8 and Section 5.1	Routine PV activities
Use in Human Pregnancy and Lactation	Routine risk minimisation measures: • SmPC Section 4.6 • PL Section 2	Routine PV activities including follow-up questionnaire to obtain complete information on pregnancy outcomes

PL=Package Leaflet, PV=pharmacovigilance, SCARs = severe cutaneous adverse reactions, SmPC=Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this new extension of indication, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Please refer the attachment 1 for further information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package

leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the revised text is presented in the same layout as the existing PL, which has successfully passed both full and "bridged" user testing and is intended for an age group where the caregiver would be responsible for administering the product to the patients.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Epilepsy affect individuals of all ages and are among the most common neurologic disorders. The annual cumulative incidence of epilepsy has been reported to be 67.77 per 100,000 persons and the point prevalence of active epilepsy of 6.38 per 1,000 persons (Fiest, et al., 2017). Although 8 to 10% of the population will experience a seizure during their lifetime, only 2 to 3% will go on to develop epilepsy. (Gavvala and Schuele, 2016).

According to the current International Classification of Epileptic Seizures, the classification of epileptic seizures depends upon the age of onset and clinical symptoms and signs. Both etiology (idiopathic, symptomatic and cryptogenic) and localization (partial vs generalized) are considered crucial prerequisites for an adequate evaluation and treatment of epileptic disorders.

Recently proposed terminology by the International League Against Epilepsy (ILAE) has redefined POS as "focal seizures" with a variety of seizure subtypes: focal aware seizures, focal impaired awareness seizures, focal motor seizures, focal non-motor seizures, and focal to bilateral tonic–clonic seizures (Fisher, 2017). The term POS will be used throughout this report.

Half of the epilepsies begin before the age of 18 and one fourth of these are intractable, having severe social and cognitive consequences. The majority of paediatric epilepsies consist of age-dependent epilepsy syndromes whose manifestations are affected by ongoing brain maturation. Uncontrolled seizures are not only associated with noteworthy lifestyle limitations and social handicaps (e.g., loss of driving privileges, social isolation, difficulty maintaining employment), but can result in significant adverse consequences, including severe trauma, depression, anxiety, and sudden death (Baranowski, 2018; Sadr, 2018).

Partial-onset (focal) seizures (POS) account for the majority of diagnosed cases of epilepsy (Hauser WA et al., 1996, Kotsopoulos IA et al., 2005). Childhood is the peak age of onset for seizures, particularly partial-onset seizures (POS) and Idiopathic Generalized Epilepsies (IGE).

As opposed to POS, PGTCS have apparent clinical or EEG onset in both hemispheres of the brain, with no clear focus or foci. PGTCS are associated with idiopathic generalized epilepsy and several generalized epilepsy syndromes. Onset of PGTCS typically starts in older children, adolescents, and young adults, but does present in children as young as 2 years. One critical EEG hallmark of a susceptibility to generalized seizures, including PGTCS, are well-formed generalized spike-wave discharges. These are occasionally seen, but are not well developed, widely distributed and highly stereotyped until 2 to 3 years of age.

Occurrence of generalized tonic-clonic seizures (GTCS) is one of the most important risk factors of seizure-related complications and comorbidities in patients with epilepsy. Their prevention is therefore an important aspect of therapeutic management both in idiopathic generalized epilepsies and in focal epilepsies. Because of the complications related to GTCS, including increased risk of SUDEP, their prevention is an important aspect of therapeutic management both in idiopathic generalized epilepsies and in partial epilepsies.

3.1.2. Available therapies and unmet medical need

Antiepileptic drugs (AEDs) are the main treatment option. Over the past 20 years, several AEDs have been developed with the objective of improving efficacy, tolerability, and ease of use when compared with classic currently-used AEDs such as carbamazepine, phenytoin, valproic acid, phenobarbital, and benzodiazepines.

Approximately 60 % of newly diagnosed patients are seizure-free with monotherapy and an additional 10-20% with polytherapy. It follows that about 30% of patients are not satisfactorily controlled. In addition, many patients suffer from significant adverse effects.

It has been shown that the efficacy of antiepileptic drugs (AEDs) varies across epilepsy syndromes, with some AEDs efficacious against focal seizures with secondary GTCS (sGTCS) but aggravating primary GTCS (pGTCS). In patients with SGTCS, all AEDs approved in the treatment of focal epilepsies might be used.

The AED efficacious against focal seizures are mostly granted in adults and adolescents. Only some of the AED are indicated as adjunctive therapy in children 2 years of age and older (clonazepam, clobazam, lamotrigine, topiramate, levetiracetam) or in children 4 years of age and older (lacosamide). It is to be noted that the enzyme-inducing AED like carbamazepine, phenytoin and phenobarbital may aggravate primary GTCS.
In patients with PGTCS, evidence-based data support the preferential use of valproic acid, lamotrigine, levetiracetam and topiramate.

Therefore, there is an unmet medical need for a safe and effective treatment option for children from 2 to 12 years of age in the POS as well as in the PGTCS treatment. This need is increased with the restrictions in the use of valproate (VPA), especially in girls, as the treatment of choice for PGTCS of IGE.

3.1.3. Main clinical studies

For the current submission, the MAH proposes to widen the approved indications to children aged 2 years and older through extrapolation of adult and adolescent efficacy and pediatric pharmacokinetic (PK) data derived from the open-label Phase 3 study E2007-G000-311 (Study 311) in patients aged 4 to <12 years with inadequately controlled POS or PGTC seizures and from the Phase 2 study E2007-G000-232 (Study 232), which analyzed PK data from patients with epilepsy aged 2 to <12 years.

3.2. Favourable effects

The clinical efficacy observed through descriptive data from study 311 seems overall at a rate comparable to that seen in adults and adolescents >12 years of age for the treatment of partial onset seizure (POS) and secondary generalized tonic-clonic seizures (SGTCS). The efficacy results could be considered clinically meaningful for this cohort in both age cohorts (4 to <7 years and 7 to<12 years).

<u>For the POS cohort,</u>

The *median percent change in seizure frequency per 28 days* as compared to baseline for total POS seizures was -40.1% (total, n = 148), -42.7% (age 4 to <7 years, n = 108) and -40.1% (age 7 to <12 years, n = 40). The results are considered clinically meaningful for the POS cohort as the number of patients was rather large; as an indirect comparison, this median percent change in adults and adolescents >12 years of age was -35% for 8 mg as well as for 12 mg daily.

There were 69 (46.6%) subjects with a *responder rate of 50% or greater* of whom 18 (45.0%) subjects aged 4 to <7 years, and 51 (47.2%) subjects aged 7 to <12 years.

As an indirect comparison, in adults and adolescents >12 years of age, the responder rate in the POS cohort is around 35% when the 3 phase III studies are considered.

The overall *seizure free status* was achieved in 17 (11.5%) subjects. Seizure free status was achieved by 3 (7.5%) subjects aged 4 to <7 years and 14 (13.0%) subjects aged 7 to <12 years.

For the SGTC subset of the POS cohort, the same trend as for the POS is observed.

Overall, the clinical effect as regards to the POS or SGTCS seems comparable to that observed in adults. When considering the guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/98 Rev.2/Corr), the effect of perampanel on partial seizures, with or without secondary generalization, is extrapolated from adults to children > 4 years of age, after an agreement regarding the weight-based dose has been established.

3.3. Uncertainties and limitations about favourable effects

For the POS cohort and SGTC subset of the POS cohort,

The observed favourable effects are weakened by methodological limitations (open-labelled, no placebo group) which *per se* do not allow to draw any robust conclusion. Therefore, the clinical efficacy results remain only descriptive hence no formal statistics were performed.

For the PGTC cohort,

The *median percent change in seizure frequency per 28 days* as compared to baseline for the PGTC cohort was overall -69.2% (total; n=22), -56.5% (age 4 to <7 years; n=3) and -81.9% (age 7 to <12 years; n=19). There were 14 (63.6%) subjects with a *responder rate of 50% or greater* of whom 2 (66.7%) subjects aged 4 to <7 years, and 12 (63.2%) subjects aged 7 to <12 years. These results should however be considered very cautiously because of the small number of patients, all the more in the 4 to 7 age cohort (n = 3 patients, 2 IGE and 1 non-IGE) for which no conclusion could be drawn.

The overall *seizure free status* was achieved in 12 (54.5%) subjects. Seizure free status was achieved by 2 (66.70%) subjects aged 4 to <7 years and 10 (52.6%) subjects aged 7 to <12 years.

Although the clinical efficacy through descriptive data from study 311 is overall observed among idiopathic generalized epilepsy (IGE) or non-IGE subjects in both age cohorts (4 to <7 years and 7 to<12 years), the clinical relevance in the PGTC cohort is disputable and does not allow to yield any conclusion in the 4 to <7 years group considering the small number of subjects.

PK/PD assessment:
As a result of the assessment of the submitted studies, the true PK/PD relationship in children was not established, since PK/PD data from both adult/adolescent and the paediatric population were pooled. In addition the MAH initially claimed that a weight-based dose regimen in the paediatric population (4 to < 12years) was still not required because the weight had no effect on clearance. This was not endorsed. In fact, results from one simulation study clearly showed that with a fixed dose regimen, exposure tended to increase more than adult exposure, because age (and weight) decrease suggested that a weight-based dosing regimen should be studied.
The uncertainties regarding the dose in the various age groups were further solved through the determination of a weight-based dose for three weight categories : <20kg, 20 to < 30 kg and > 30 kg.

According to the scientific advice 2017, the following concerns were issued.

- Regarding safety, this aspect should specifically be assessed in children as it cannot be extrapolated from the safety observed in adults; as PGTCS appears within more complex syndromes associating different seizure types, the effect of perampanel on these other seizure types should be assessed within the safety assessment, at least to rule out a detrimental effect (or quantify it to integrate it into the overall benefit/risk assessment). The effect of perampanel on neuropsychological aspects in a developing brain and on growth should also be specifically assessed in the paediatric population.

The clinical efficacy data from the study 232 in patients aged 2 to 12 years were overall similar to those collected in study 311. However, the number of patients was very small and therefore the results of this study only brought few information regarding the safety profile. In addition, from a pharmacokinetic aspect, PK data from Study 232 were interpreted with caution before the critical issues with the developed bioanalytical method were solved.

3.4. Unfavourable effects

No new adverse event was reported in the submitted studies. However, there were some uncertainties regarding the submitted safety data and also the lack of long-term data which are of major importance, especially in the paediatric population.

Indeed, according to the guideline, regarding the assessment of safety, a minimum of 100 children treated by the study drug should be followed for at least one year. Moreover short term and long-term studies should be designed to detect possible impact on brain development, learning, intelligence, growth, endocrine functions and puberty.
Firstly, the submitted studies were not designed to collect enough long-term safety information; secondly, there were some uncertainties that needed clarifications regarding the safety profile of

perampanel. Although the level of recruitment in paediatric studies is a known issue, the data safety collection was a major point, in particular regarding the long-term aspects (neurodevelopment, motor development, cognition, behaviour, growth, endocrine functions and puberty). These aspects were lacking and the MAH was requested to further provide data related to puberty / sexual maturation and skeletal development, which could not be evaluated in a sufficient number of children. The applicant was therefore requested to continue to monitor the effects in the ongoing paediatric study (Studies 236) and in the future PSUR.

3.5. Uncertainties and limitations about unfavourable effects

In PGTCS, the safety profile of perampanel in children aged 2 years and <7 years could not be assessed properly due to the low number of patients studied.

The data presented by the MAH responded to the concerns about the potential effect of perampanel in children under 12 years of age regarding impact on brain development, learning, intelligence, and growth and endocrine function, with the exception of puberty / sexual maturation and skeletal development, which could not be evaluated in a sufficient number of children. Consequently, the MAH was requested to continue to monitor the puberty / sexual maturation and skeletal development in the ongoing paediatric study (Studies 236) and in the future PSUR.

The relevant statements have been added in the SmPC regarding the higher incidence of some AE and some precautions were amended or added.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

For the treatment of partial onset seizure (POS) and secondary generalized tonic-clonic seizures (SGTCS), the clinical efficacy observed through descriptive data from study 311 is overall reassuring.
The efficacy results could be considered clinically meaningful for both age cohorts (4 to <7 years and 7 to<12 years).

When considering the guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/98 Rev.2/Corr), the effect of perampanel on partial seizures, with or without secondary generalization, could be extrapolated from adults to children > 4 years of age, provided the dose is established. Based on that statement, the efficacy between adults and children > 4 years of age in the treatment of POS and SGTCS seems comparable and acceptable from a clinical point of view.
It could be considered that the number of subjects is large enough to consider that these observed clinical results are sufficient for an established weight-based dose based on PK/PD extrapolation from adults to the target population. However, the favourable effect for this cohort is weakened by methodological limitations (open-labelled, no placebo group) which *per se* do not allow to draw any robust conclusion. Therefore, the clinical efficacy results remain only descriptive and no formal statistics were performed.

For the treatment of primary generalized tonic-clonic seizures (PGTCS), although the clinical efficacy observed through descriptive data from study 311 is overall in favour of perampanel, the clinical relevance in the PGTC cohort is disputable, all the more in the paediatrics <7 years of age and does not allow to yield any conclusion on the efficacy of perampanel in PGTCS considering the small number of subjects. The occurrence of other types of seizures such as absences and myoclonic seizures, were not completely described and reassuring and a warning is added in section 4.4 of the SmPC accordingly.

For the non-IGE subjects (n=3 overall in study 311), the very small number of patients do not allow to draw any conclusion.

The safety profile of perampanel in children aged 2 years and <4 years cannot be considered as sufficiently established, due to the very low number of patients, and the fact that extrapolation from 2 years was not considered acceptable.

According to the draft guideline of clinical investigation of medicinal products in the treatment of epilepsy disorders, it is stated: "Generally, from the safety point of view, preferably 100 children should be treated by the study drug and followed for at least one year. Moreover, short term and long-term studies should be designed to detect possible impact in the neurodevelopment, motor development, cognition, behaviour, growth, endocrine functions and puberty... Some of these studies may require continuation in the post marketing period [see Guideline on clinical investigation of medicinal products in children (CPMP/EWP/462/95)]. Prospective disease-based registries (per paediatric epilepsy syndromes or symptoms) may be helpful and are encouraged".
After assessment of the submitted data, some safety aspects were considered reassuring while other need further safety data. Consequently, the MAH was requested to continue to monitor the puberty / sexual maturation and skeletal development in the ongoing paediatric study (Studies 236) and in the future PSUR.

To conclude, based on the submitted clinical data, the extension of indication of perampanel for the treatment of partial onset seizure (POS), with or without secondary generalized tonic-clonic seizures (SGTCS) in children from 4 years old and older was endorsed and depends on the weight-based dosing regimen.
The extension of indication of perampanel for primary generalized tonic-clonic seizures (PGTCS) in idiopathic generalized epilepsy (IGE) in children from 7 years of age and older is also endorsed and also depends on the same weight-based dosing regimen as for POS.

3.6.2. Balance of benefits and risks

Perampanel tablets (2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg) are approved in the European Union (EU) for the adjunctive treatment of partial-onset seizures (POS) with or without SG seizures in adult and adolescent patients with epilepsy aged 12 years and older (23 Jul 2012); and as adjunctive therapy for the treatment of PGTCS in adult and adolescent patients aged 12 years and older with IGE (22 Jun 2015).
A 0.5 mg/mL oral suspension was also approved in the EU for the same indications (19 Sep 2016).

In the United States of America (USA), perampanel tablets (2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg) and perampanel oral suspension 0.5 mg/mL are approved for monotherapy of POS with or without SG seizures in adult and adolescent patients, and as adjunctive therapy in the treatment of PGTCS in patients with epilepsy 12 years of age and older. In September 2018, the US Food and Drug Administration (FDA) approved extension of the indication of perampanel for monotherapy and adjunctive use in pediatric patients 4 years and older for the treatment of POS with or without SG seizures. The approval includes both tablet and oral suspension formulations.

For the current submission, the MAH proposed to widen the approved indications to children aged 2 years and older through extrapolation of adult and adolescent efficacy and pediatric pharmacokinetic (PK) data derived from the open-label Phase 3 study 311 in subjects aged 4 to <12 years with inadequately controlled POS or PGTC seizures and from the Phase 2 study 232, which analyzed PK data from subjects aged 2 to <12 years with a diagnosis of epilepsy with any type of seizure according to the International League Against Epilepsy's (ILAE) Classification of Epileptic Seizures.

In paediatric patients aged 2 to <4 years of age, no indication is approvable since the extrapolation from PK/PD is not acceptable in this age group. Moreover, the efficacy data are too sparse and the safety data are lacking.

Based on the assessment of the available clinical data, the extension of indication of perampanel for the treatment of partial onset seizure (POS), with or without secondary generalized tonic-clonic seizures

(SGTCS) is acceptable in children (from 4 to < 12 years of age) as the administered dose is adjusted according to a body-weight basis as detailed in the proposed SmPC.
For primary generalized tonic-clonic seizures (PGTCS) in idiopathic generalized epilepsy (IGE) in paediatrics < 7 years of age, the studied group is too small to estimate the actual efficacy. Moreover, the safety profile in this small group could not be extrapolated in this condition. The extension of indication of perampanel for the treatment of primary generalized tonic-clonic seizures (PGTCS) in idiopathic generalized epilepsy (IGE) is acceptable in children (from 7 to < 12 years of age) as the administered dose is also adjusted according to a body-weight basis as detailed in the proposed SmPC (same dose of for POS).

Some safety aspects were considered reassuring while other need further safety data. Consequently, the MAH was requested to continue to monitor the puberty / sexual maturation and skeletal development in the ongoing paediatric study (Studies 236) and in the future PSUR (attention deficit/hyperactivity disorder, learning disability, cognitive disorder, disturbance in attention, precocious puberty). Relevant statements have been added in the SmPC regarding the higher incidence of some AE and some precautions were amended or added.

3.7. Conclusions

The overall B/R of Fycompa in paediatric patients from 4 to 11 years of age for the adjunctive treatment of partial-onset seizures with or without secondary generalisation and from 7 to 11 years of age for the adjunctive treatment of primary generalised tonic-clonic seizures with idiopathic generalised epilepsy is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of Indication to include the paediatric patients from 4 to 11 years of age for the adjunctive treatment of partial-onset seizures with or without secondary generalisation and from 7 to 11 years of age for the adjunctive treatment of primary generalised tonic-clonic seizures with idiopathic generalised epilepsy for Fycompa.
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 4.5 has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0217/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Fycompa-H-C-002434-II-0047'