EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 May 2015
EMA/518002/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fycompa

International non-proprietary name: PERAMPANEL

Procedure No. EMEA/H/C/002434/II/0016

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Background information on the procedure 5
1.1. Type II variation 5
1.2. Steps taken for the assessment of the product 6

2. Scientific discussion 6
2.1. Introduction 6
2.2. Non-clinical aspects 7
2.2.1. Ecotoxicity/environmental risk assessment 7
2.2.2. Discussion on non-clinical aspects 8
2.2.3. Conclusion on the non-clinical aspects 9
2.3. Clinical aspects 9
2.3.1. Introduction 9
2.3.2. Clinical Pharmacology 10
2.3.3. Discussion on clinical pharmacology 21
2.3.4. Conclusions on clinical pharmacology 23
2.4. Clinical efficacy 24
2.4.1. Dose response study(ies) 24
2.4.2. Main study 24
2.4.3. Discussion on clinical efficacy 51
2.4.4. Conclusions on the clinical efficacy 54
2.5. Clinical safety 55
2.5.1. Discussion on clinical safety 62
2.5.2. Conclusions on clinical safety 63
2.5.3. PSUR cycle 63
2.6. Risk management plan 63
2.7. Update of the Product information 65
2.7.1. User consultation 67

3. Benefit-Risk Balance 67

4. Recommendations 70

5. EPAR changes 70

List of abbreviations

%RSE	Percent relative standard error of the estimate
ADR	Adverse Drug Reaction
AE	Adverse Event
AED	Anti-epileptic Drug
ALT	alanine aminotransferase
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AST	aspartate aminotransferase
Cav,ss	average steady state perampanel concentration estimated from population PK
CGI-C	Clinical Global Impression of Change scale
CHMP	Committee for Medicinal Products for Human Use
CL/F	apparent clearance
CNS	Central nervous system
CMH	Cochran-Mantel-Haenszel
CRCL	creatinine clearance
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of Variation
CYP	Cytochrome P450
E2007	Company code for perampanel sometimes used in studies
EAP	Expanded Access Program
EEG	Electroencephalogram
EMA	European Medicines Agency
ERA	Environmental risk assessment
EU	European Union
FAS	Full Analysis Set
IGE	Idiopathic generalised epilepsy
IIV	inter-individual variability
IOV	Inter-occasion variability
IVRS	Interactive Voice Response System
LC	liquid chromatography
LOCF	Last Observation Carried Forward

MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MS	Mass spectrometry
PD	Pharmacodynamics
PGTC	Primary Generalised Tonic-Clonic
PI	Product Information
PK	Pharmacokinetics
PL	Package Leaflet
POS	Partial Onset Seizures
PP	Per Protocol
QoL	Quality of Life
RMP	Risk Management Plan
SAE	Serious adverse event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
STP	Sewage treatment plant
TEAE	Treatment emergent adverse events
US	United States of America
V/F	apparent volume of distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eisai Europe Ltd. submitted to the European Medicines Agency on 20 August 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name**
Fycompa	perampanel

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 and IIIB

The MAH applied for an extension of the indication for adjunctive treatment of primary generalised tonic-clonic seizures in patients with epilepsy aged 12 years and older. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC. The Package Leaflet was proposed to be updated accordingly. In addition, the MAH took the opportunity to propose minor editorial changes to the Package Leaflet as well as an update to the contact details of the Maltese local representative.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0160/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0160/2014 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 did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings Co-Rapporteur: Pierre Demolis

Timetable	Actual dates
Submission date	20 August 2014
Start of procedure:	19 September 2014
CHMP Rapporteur Assessment Report	10 November 2014
CHMP CoRapporteur Assessment Report	12 November 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	4 December 2014
CHMP Rapporteur Updated Assessment Report	12 December 2014
Request for supplementary information (RSI)	18 December 2014
Joint PRAC / CHMP Rapporteurs' Assessment Report	19 February 2015
Joint PRAC / CHMP Rapporteurs' Updated Assessment Report	3 March 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	12 March 2015
Joint PRAC / CHMP Rapporteurs' Revised Assessment Report	23 March 2015
2nd Request for supplementary information (RSI)	26 March 2015
Joint PRAC and CHMP Rapporteur Assessment Report	28 April 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	7 May 2015
Updated Rapporteur's Assessment Report	19 May 2015
CHMP Opinion	21 May 2015

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-isoxazolepropionic 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. The precise mechanism by which perampanel exerts its antiepileptic effect has not yet been fully elucidated.

Fycompa is available as film-coated tablets in the strengths of 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg. 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.

Problem statement and rational for the proposed change

The Marketing Authorisation Holder (MAH) of Fycompa applied for an extension of the indication to adjunctive treatment of primary generalised tonic clonic (PGTC) seizures. Like other types of seizures, PGTC seizures are caused by the paroxysmal, uncontrolled discharge of central nervous system (CNS) neurons, leading to neurologic dysfunction. Unlike most other types of seizures, with PGTC seizures the cerebral hyperactivity extends to the entire brain.

Tonic-clonic seizures represent the most debilitating seizure type within the generalised epilepsies. PGTC seizures are associated with idiopathic generalised epilepsy (IGE) and several generalised epilepsy syndromes. Of the new anti-epileptic drugs (AEDs) developed over the past 20 years, at the time of this report only three (topiramate, levetiracetam, lamotrigine) were indicated for the treatment of PGTC seizures.

To support the application, the MAH submitted the results of one pivotal, randomised, double-blind, placebo-controlled Phase III study (Core Study 332). Patients in Core Study 332 were aged 12 years or older and received up to 8 mg/day of perampanel or placebo as adjunctive treatment for PGTC seizures. Population PK and a PK/PD analyses of the Core Study 332 data were also submitted. For the purpose of population PK modelling, the plasma concentration data from Study 332 were pooled with data from 3 other Phase III studies in subjects with POS.

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

An updated ERA was provided taking into account use of Fycompa in the proposed new indication of adjunctive treatment of PGTC seizures in patients with epilepsy aged 12 years and older.

The log octanol-water partition coefficient (Kow) value of perampanel was 2.86. Therefore, perampanel was not considered a Persistent, Bioaccumulative, and Toxic (PBT) substance.

Using a refined market penetration factor (Fpen) value of 0.00016 based on combined estimations from the sales forecast for adjunctive treatment of POS with or without secondarily generalized seizures and for adjunctive treatment of PGTC seizures in patients with epilepsy aged 12 years and older, the $PEC_{SURFACEWATER}$ for perampanel has been calculated to be 0.00096 µg/L. This is below the action limit (0.01µg/L) for Phase II analysis, and hence no further environmental assessment was required. However, with the initial marketing authorisation application, a Phase II analysis was provided and the CHMP recommended the conduct of the following additional studies: OECD 308 (aerobic system) study, and depending on results, perform an OECD 218 (sediment dwelling organism) study. The MAH took the opportunity of this application to provide the results of both studies.

Aerobic system (OECD 308)

The adsorption coefficient (Koc) of Fycompa was determined to be log Koc 2.71 and hence not expected to be retained in the sewage treatment plant (STP). Therefore risk to soil and groundwater compartment due to spreading to sludge on soul is considered to be low. A ready biodegradability test was performed and the active found not to be readily biodegradable. In the subsequent OECD 308 study, after 97 days of incubation, 91-93% of the active was recovered in 2 water-sediment systems, of which 7% was recovered in the water layer and 84% - 85% in the sediment extract. No degradation of Fycompa was detected in the sediment layers. In conclusion, the active ingredient perampanel was classified as

persistent and very persistent in the sediment according to OECD 308. Therefore OECD test 218 was conducted.

Sediment Dwelling (OECD 218)

Since the potential risk identified for Fycompa was its recovery at ~85% in the sediments of 2 water-sediment systems in the OECD 308 test, further testing in an OECD 218 sediment dwelling organism study was performed for the Phase II tier B assessment. Effects on the sediment dwelling organism *chironomus riparius* were negligible in this toxicity test. Specifically 120 larvae exposed to the top dose of the active (820 mg/kg) were not biologically affected from a toxicological perspective, following 28 days exposure to the test substance.

Table 1 – Summary of main ERA study results

Substance (INN/Invented Name): perampanel					
CAS-number: 380917-97-5					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.86			Potential PBT (N)
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)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =2.71			
Ready Biodegradability Test	OECD 301	no significant degradation of perampanel (1-2%)			NOT READILY BIODEGRADABLE
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ =7.9 $DT_{50,\ sediment}$ =ND $DT_{50,\ whole\ system}$ =879			persistent
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	>1200	µg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	220	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	60	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	$>1x10^6$	µg/L	
Phase IIb					
EFFECTS ON SEDIMENT DWELLING ORGANISM	OECD 218	NOEC Ec_{50}	820 >820	mg/kg	*risk to chironomus riparius was negligible*

2.2.2. Discussion on non-clinical aspects

The updated ERA presented by the MAH based on sales projections for the use of Fycompa in the existing as well as the proposed new indication showed that perampanel does not present a hazard to the environment. The updated data submitted in this application did not suggest a significant increase in environmental exposure further to the use of perampanel in the new indication. The MAH furthermore submitted the results of an OECD 308 and an OECD 218 study thereby complying with the CHMP recommendations at the time of the initial marketing authorisation. The studies showed that perampanel

was persistent in sediment, but that the effect on dwelling organisms was negligible. No new concerns arose from these two studies.

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

Good Clinical Practice (GCP)

The clinical trials were claimed by the MAH to have been performed in accordance with GCP.

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

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Population PK Study Reports									
Pooled Pop PK and PK/PD	CPMS-E2007-008R-v1	5.3.3.5	PopPK Objectives: • Describe the PK of perampanel in subjects with partial-onset seizures and PGTC seizures • Identify intrinsic and extrinsic factors that explain between subject variability in perampanel PK PK/PD Objectives: • Characterize the relationship of average seizure frequency over 28 days with perampanel concentration • Characterize the probability of response (responder or non-responder)	Randomized, double-blind, placebo-controlled, parallel-group	Perampanel tablets or matching placebo; oral. Study 332: 8 mg/day Study 304: 8 or 12 mg/day Study 305: 8 or 12 mg/day Study 306: 2, 4, or 8 mg/day	PopPK: Pooled data from Study 332 subjects (73 subjects providing 205 perampanel plasma concentrations) and Phase 3 Studies 304, 305 306 (770 subjects providing 4467 observations) PK/PD: 149 subjects from Study 332	PGTC and POS	Study 332: 17 weeks Studies 304/305/306: 19 weeks	Complete; Final Report
Study Reports of Controlled Clinical studies Pertinent to the Claimed Indication									
Phase 3 Efficacy	E2007-G000-332 (Core)	5.3.5.1	Primary: to demonstrate the efficacy of adjunctive perampanel therapy, compared to placebo, on PGTC seizures Secondary: • To evaluate the safety and tolerability of perampanel in subjects with inadequately controlled PGTC seizures • To evaluate the efficacy of adjunctive perampanel therapy, compared to placebo, on other subtypes of primary generalized seizure (myoclonic, absence, and all seizures)	Randomized, double-blind, placebo-controlled, parallel-group	Perampanel 2 mg tablets or matching placebo; oral.	N=164 Randomized (1 not treated, 81 perampanel, 82 placebo)	PGTC	17 weeks	Complete; Final CSR
Other Clinical Study Reports									
Phase 3 Safety	E2007-G000-332 (Extension)	5.3.5.4	To evaluate the long-term safety, tolerability, and efficacy of perampanel in subjects with PGTC seizures.	Open-label	Perampanel 2 mg or 4 mg tablets; oral. 2 mg to 12 mg per day, optimal dose determined per investigator's discretion	N=114	PGTC	Minimum 52 weeks, maximum 142 weeks	Ongoing; Interim Synoptic CSR
CSR=Clinical Study Report; CDR=Cognitive Drug Research; E2007=perampanel; PK=pharmacokinetic; PD=Pharmacodynamic; PGTC=primary generalized tonic-clonic; POS=partial-onset seizures; N/A = Not Applicable; Val=Validation									

2.3.2. Clinical Pharmacology

The clinical pharmacology program was designed to investigate the pharmacodynamic (PD) effects of perampanel related to the medicine's clinical efficacy and safety, and to establish the pharmacokinetic (PK) profile of perampanel, including its absorption, distribution, metabolism, and elimination characteristics.

The application partially relied on the perampanel clinical pharmacology program provided in support of the POS indication, which included 27 Phase I studies and 2 Phase II studies. One new phase III study in epilepsy patients with PGTC seizures including clinical pharmacology objectives was provided in support of this application (Core Study 332). A population PK and a PK/PD analysis of the Core Study 332 data was conducted (CPMS-E2007-008R-v1). For the population PK analysis, data of Core Study 332 were pooled with data from 3 other Phase III studies in epilepsy subjects with POS (Studies 304, 305, and 306), previously assessed during the review of the initial marketing authorisation application, The only dose of

perampanel evaluated in Core Study 332 was 8 mg/day, therefore a dose-response analysis was not performed.

Furthermore, since the approval of perampanel for refractory POS, additional in vitro studies were conducted as post-approval commitments to characterise the contributions of cytochrome P450 (CYP) enzymes and non-CYP enzymes to perampanel metabolism as well as to evaluate the effects of perampanel on CYP2B6 activity (DMPK2013-001). The MAH took the opportunity of this application to also provide the results of study DMPK2013-001.

2.3.2.1. Pharmacokinetics

Pharmacokinetic interaction studies

Study DMPK2013-001: Investigation of Potential Inhibition of E2007 on Human CYP2B6 in Human Liver Microsomes

This study was designed to investigate inhibition potency of E2007 (perampanel) on human cytochrome P450 (CYP) 2B6 using bupropion as CYP2B6 probe substrate and human liver microsomes. A reversible inhibition study was conducted. The CYP2B6-specific activity was evaluated by bupropion hydroxylation. The concentrations of the marker metabolite for CYP2B6 (hydroxybupropion) was determined using high performance liquid chromatography with tandem mass spectrometry (LC/MS/MS), which was validated by evaluating selectivity, accuracy of calibration curve, intra-assay variation, and stability in sample extracts. The suitability of the inhibition assay conducted in this study was evaluated by inhibition potency of positive control, ticlopidine at the concentration of 6.1 µmol/L.

Results

Validation Study of Quantitative Method

The quantification method including selectivity of the analytical condition for marker metabolite of reversible inhibition, lack of interference of the internal standard with the marker metabolite, accuracy of calibration standards, intra-assay variation for inhibition assay and stability of the marker metabolite in sample extracts was validated.

Reversible Inhibition Study

The inhibition percentage (%) on the formation of the marker metabolite of CYP2B6 by E2007 and positive control are shown in the following table.

Table 2 - Inhibition Percentage of E2007 and Ticlopidine on CYP2B6 Activity

Inhibitor	Conc. (µmol/L)	Inhibition (%)
E2007	0.1	2.8
	0.3	–2.5
	1	–0.2
	3	4.7
	10	3.1
	30	9.5
Ticlopidine	6.1	63.6

Inhibition (%) = $(C_{control} - C_{inhibitor}) / C_{control} \times 100$.
$C_{control}$: Mean concentration of the marker metabolite in the control sample.
$C_{inhibitor}$: Mean concentration of the marker metabolite in the inhibition sample.

2.3.2.2. PK/PD modelling

Population Analysis CPMS-E2007-008R-v1

The objectives of the population PK analysis were:

- Describe the PK of perampanel in subjects with partial-onset seizures and PGTC seizures
- Identify intrinsic and extrinsic factors that explain between subject variability in perampanel PK, such as demographics and co-administration of other AEDs.

The objectives of PK/PD analyses for efficacy (Study E2007-G000-332 only) were:

- Characterize the relationship of average PGTC seizure frequency over 28 days with perampanel concentration and intrinsic and extrinsic factors in subjects with PGTC seizures.
- Characterize the probability of response (responder or non-responder) at any time in subjects with PGTC seizures.

The objectives of the exploratory population PK/PD analysis for safety in subjects with PGTC (Study E2007-G000-332 only) were:

- Explore the relationship between perampanel exposure and most frequently occurring AEs.

Methods

See section 2.4.2. for a detailed description of study Core Study 332. Participation in the PK assessment was limited to study sites with appropriately trained staff and adequate equipment for procuring and processing the specimens. Plasma was used to determine the concentrations of perampanel by liquid chromatography with tandem mass spectrometry (LC-MS/MS) using previously validated methods.

The PK data underwent population PK and PK/PD modelling for the relationship between exposure and PGTC seizure frequency and the occurrence and severity of the most frequently occurring AEs during the Maintenance Period.

The studies whose data were included in the population PK analysis are summarized in the following Table. The PK/PD analyses were built on data from study E2007-G000-332 only.

Table 3 - Summary of Perampanel Studies Included in Population PK Analysis

Protocol Number	Study Design	Treatment Duration in Double-Blind Phase	Dose (mg/day)
E2007-G000-304	Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group in Subjects (≥12 years of age) with Refractory Partial Seizures	19 weeks	Placebo, 8 mg, 12 mg
E2007-G000-305	Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group in Subjects (≥12 years of age) with Refractory Partial Seizures	19 weeks	Placebo, 8 mg, 12 mg
E2007-G000-306	Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group in Subjects (≥12 years of age) with Refractory Partial Seizures	19 weeks	Placebo, 2 mg, 4 mg, 8 mg
E2007-G000-332	Double-blind, Randomized, Placebo-controlled, Multicenter, Parallel-group Study with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Adjunctive Perampanel in Primary Generalized Tonic-Clonic Seizures	17 weeks	Placebo, 2 mg, 4 mg, 6 mg, 8 mg,

Population analyses for PK, PK/PD for efficacy (log-transformed percentage change from Baseline in average seizure frequency over 28 days at Visit 6, 7, and 8) and logistic regression for responders were performed using non-linear mixed effect modelling in NONMEM v7.2. The final population PK model, and PK/PD models for PGTC seizure frequency and responder probability were evaluated for performance using graphical assessment, nonparametric bootstrapping and visual predictive checks. The resulting parameters from the final PK model were evaluated for fitness for calculation of individual derived values of perampanel steady-state exposure Cav,ss for use in evaluating the PK/PD relationship for efficacy and safety.

- **PK Model Development**

Base PK Model Development

Due to the sparse nature of the PK sampling scheme a one compartment model parameterised in terms of clearance (CL/F) and apparent volume of distribution (V/F) was the starting point for the PK structural base model. The inter-individual variability (IIV) (η, ETA) was assessed on CL/F using an exponential error structure, assuming normal distribution for these parameters. If deemed necessary, covariance between 2 inter-individual variability terms may have been assessed by application of the omega block. Inter-occasion variability (IOV) was assessed on both CL/F and V/F parameters. The residual variability was assessed by additive, proportional and combined additive/ proportional error structures. All permutations of interindividual and residual variability error structures were tested systematically.

Covariate PK Model Development

The effect of the following covariates was planned to be investigated on perampanel PK: demographics (gender, race, age, body weight, and seizure type), renal function (creatinine clearance; CRCL), liver function [alanine aminotransferase (ALT) and aspartate amino transferase (AST)] and concomitant carbamazepine, oxcarbazepine, phenytoin, valproic acid, lamotrigine, topiramate, levetiracetam, clobazam, phenobarbital, primidone, and zonisamide.

The association between subject covariates and PK parameters was evaluated in a stepwise fashion:

- Individual Bayes posthoc pharmacokinetic parameter estimates were generated from the base model. The difference of individual estimates from the corresponding population value (η) was plotted versus the covariates to identify potential relationships.
- η-shrinkage was calculated and reported for IIV parameters estimated by the model. A parameter with shrinkage greater than 30% was excluded from the covariate analysis.
- Covariates identified as being important were first assessed in the basic model by univariate addition and ranked in descending order according to the change in objective function value. All significant variables were then tested in a full model, and a subsequent backwards deletion was carried out at the 0.1% significance level where the relative influence of each covariate on the model was re-evaluated by deleting it from the full model on an individual basis.

The final model included the structural PK model, estimates of population mean and individual fixed effects parameters, and estimates of the random effects parameters. The estimation method used was FOCEI. The predictive performance of the final PK was assessed by applying a visual predictive check and validated using bootstrapping.

- **PK/PD Model Development**

Individual perampanel Cav,ss at each visit was derived from post-hoc estimate of individual CL/F and dose. For subjects on placebo, Cav,ss was set to zero. Twenty-eight day average PGTC seizure frequency

and response data at each visit during the Maintenance Period was used in the analysis, which was based on log-transformed percentage change from Baseline.

Demographics and concomitant AEDs were considered in the population PK/PD and logistic regression model selection process.

Methods for the covariate PK/PD analysis were identical to those used for the PK model development (see above). The final PK/PD model for 28-day average PGTC seizure frequency data was evaluated using the Bootstrap re-sampling technique and visual predictive check. The PK/PD model for response data was assessed by standard error estimates and nonparametric bootstrap analysis.

Perampanel /28-day Average PGTC Seizure Frequency Model Structure

The PK/PD relationship between exposure to perampanel and percentage change from Baseline in average seizure frequency over 28 days was modeled according to a model described by Girgis et al., 2010. Twenty-eight-day PGTC seizure frequency was considered as a continuous variable, after log-transformation.

Based on this, the exposure- efficacy relationship structural model for perampanel was the sum of a Baseline seizure frequency, the effect of perampanel exposure at steady state, the effect of time on seizure frequency and an interaction term between Baseline seizure frequency, the effect of perampanel exposure at steady state. Mixed effects modelling in NONMEM 7.2 was applied.

Perampanel /Response Model Structure

The probability of each subject, at any time, to be in one of the 2 responder classes was analysed by logistic regression. The logit model was of the form: sum of placebo effect, of perampanel exposure, effects of covariates and random effect to describe between interindividual variability.

The Laplacian method, which uses a second-order expansion around the empirical Bayes predictions of the inter-individual random effects, was implemented in NONMEM and was used to approximate the marginal likelihood.

- **Results**

PK Population and Dataset

For Study 332, 205 perampanel plasma concentrations from 73 subjects were available. POS Phase III Studies 304, 305 and 306 contributed 4467 observations from a total of 770 subjects. The final PK dataset included 4672 observations from a total of 843 subjects. For the pooled PK analysis data set a total of 7 observations were excluded, which were classified as below limit of quantification or outlying concentrations. Of the 843 subjects 614 were Caucasians and 229 of other ethnic background, including 4 subjects of Japanese origin. There were 403 males and 440 females. The population age and weight ranged from 12 to 74 years (median = 32 years) and 25 to 142 kg (median = 69 kg), respectively. A summary of the co-administered AEDs is given in the following table.

Table 4 - Summary of Selected Co-Administered AEDs Included in the Population PK Analysis of Perampanel – All Studies (N=843)

AED	Inducer	Number of Subjects	% of Subjects in the PK Population (N=843)
Carbamazepine	Yes	273	32.4
Levetiracetam	No	261	31.0
Lamotrigine	No	289	34.3
Oxcarbazepine	Yes	136	16.1
Topiramate	No	179	21.2
Valproate	No	272	32.3
Clobazam	No	82	9.73
Phenytoin*	Yes	73	8.66
Phenobarbital	No	40	4.74
Primidone	No	9	1.07
Zonisamide	No	66	7.83
Inducers		482	57.2

*Includes one subject receiving single dose rescue phenytoin

Population and Dataset for PK/PD Dataset for PGTC Seizure Frequency Analysis

A total of 151 subjects had 438 observation records including subjects on placebo treatment. Fifteen observations were excluded from the PK/PD analysis due to being outliers or the subjects not having perampanel exposure data available. The final analysis data set for Study 332, 28-day average PGTC seizure frequency and response PK/PD data had a total of 423 observations from 149 subjects.

Of these 149 subjects, 77 received placebo and 72 received active treatment. Overall, 78 were Caucasians and 71 non-Caucasians, including 10 Japanese and 35 Chinese subjects. There were 64 males and 85 females. The population age and weight ranged from 12 to 70 years (median = 25 years) and 36 to 154 kg (median = 67 kg), respectively. A summary of the 332 PK/PD population co-administered AEDs are given in the table below. The same analysis population was used in the responders/non-responders analysis.

A summary of the co-administered AEDs is given in the following table.

Table 5 - Summary of Selected Co-Administered AED Included in the Population PK/PD Analysis for PGTC Seizure Frequency - Study 332 Alone (N=149)

AED	Inducer	Number of Subjects	% of Subjects in the PK/PD Population
All Subjects (n=149)			
Carbamazepine	Yes	13	8.7
Levetiracetam	No	44	29.5
Lamotrigine	No	59	39.6
Oxcarbazepine	Yes	5	3.4
Topiramate	No	24	16.1
Valproate	No	50	33.6
Clobazam	No	7	4.7
Phenytoin*	Yes	10	6.7
Phenobarbital	No	5	3.4
Primidone	No	0	0.0
Zonisamide	No	18	12.1
Inducers		28	18.8
Placebo (n=77)			
Carbamazepine	Yes	9	11.7
Levetiracetam	No	18	23.4
Lamotrigine	No	29	37.7
Oxcarbazepine	Yes	3	3.9
Topiramate	No	7	9.1
Valproate	No	25	32.5
Clobazam	No	4	5.2
Phenytoin	Yes	6	7.8
Phenobarbital	No	2	2.6
Primidone	No	0	0.0
Zonisamide	No	13	16.9
Inducers		18	23.4
Perampanel (n=72)			
Carbamazepine	Yes	4	5.6
Levetiracetam	No	26	36.1
Lamotrigine	No	30	41.7
Oxcarbazepine	Yes	2	2.8
Topiramate	No	17	23.6
Valproate	No	25	34.7
Clobazam	No	3	4.2
Phenytoin*	Yes	4	5.6
Phenobarbital	No	3	4.2
Primidone	No	0	0.0
Zonisamide	No	5	6.9
Inducers		10	6.7

PK Analysis

For the final model, a one-compartment disposition model with linear elimination from the central compartment adequately described perampanel profiles from studies 304, 305, 306 and 332. This is the same model reported previously in patients with refractory POS. The IIV could be estimated for CL/F only, and IOV was also included on CL/F. V/F and IIV for this parameter were fixed to previously estimated values relating to the central volume of distribution for a two-compartment model determined for perampanel based on rich data sampling. The final population PK model for perampanel contained the statistically significant effects of body weight, gender and the concomitant medications of CYP3A4/5 inducing AEDs carbamazepine, oxcarbazepine, topiramate and phenytoin on perampanel CL/F. The final

model was repeated by omitting phenytoin co-administration in the subject who received a single dose rescue treatment, this resulted in negligible changes to model parameters.

The parameter estimates, precision of the estimate and 95 % confidence interval for the final PK model are presented in the following table.

Table 6 - Final Population PK Parameter Estimates of Perampanel – All Studies (N=843)

Parameter [Units]	Point Estimate	%RSE	95% CI
$CL/F = \Theta_{CL} * (WGT/69)^{\Theta WGT} * \Theta_{SEX}^{SEX} * \Theta_{CARB}^{CARB} * \Theta_{OXC}^{OXC} * \Theta_{TOP}^{TOP} * \Theta_{PHENY}^{PHENY}$			
Basal CL/F in L/h (Θ_{CL})	0.660	3.23	0.618 - 0.702
Weight effect on CL/F (Θ_{WGT})	-0.233	31.9	-0.379 - - 0.0872
Gender effect on CL/F (Θ_{SEX})	0.822	3.36	0.768 – 0.876
Carbamazepine effect on CL/F (Θ_{CARB})	2.75	3.55	2.56-2.94
Oxcarbazepine effect on CL/F (Θ_{OXC})	1.92	4.44	1.75-2.09
Topiramate effect on CL/F (Θ_{TOP})	1.23	3.69	1.14-1.32
Phenytoin effect on CL/F (Θ_{PHENY})	1.74	6.49	1.52-1.96
V/F in L (Θ_V)	31.3	Fixed	--
Inter-individual variability (%CV)			
CL/F	43.2	5.78	
V/F	30.6	Fixed	
Inter-occasion variability (%CV)			
CL/F	20.3	8.57	
Residual variability			
Proportional (%CV)	8.82	7.93	

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL/F = apparent clearance, V/F = apparent volume of distribution; CI = confidence interval, %CV = Square root of variance *100.

As seen from the 95% confidence intervals, all the parameters of the structural model were estimated with good precision (%RSE ≤6.49%), except for weight effect on CL/F (%RSE=31.9). IIV in CL/F was moderate at (43.2%) and estimated with good precision (%RSE ≤5.78). The estimate of IIV for V/F was fixed to a previous estimated value of 31.3%, obtained for the central volume of distribution. The residual variability in perampanel concentrations was low at 8.82 %.

In order to evaluate the predictive performance of the final PK model for perampanel, a visual predictive check (VPC) was performed. One thousand subjects receiving a steady state dose of 8mg perampanel were simulated using the final model. Using the simulated data the 90% prediction intervals were determined and plotted together with 8mg dose normalised observed perampanel concentrations. More than 90% of the data observations were within 90% prediction intervals for the model. Therefore, the perampanel concentration time course has been reasonably well defined in the final PK model with good predictive performance. Furthermore, a nonparametric bootstrap for the final PK model was conducted. The nonparametric bootstrap showed that the confidence intervals for all parameters were generally narrow and the median values of the distribution of bootstrapped parameter values are consistent with the original parameter estimates from the final PK model. Overall the bootstrap results and the VPC indicated that the final PK model for perampanel described the data well and produced well estimated parameters.

The descriptive statistics for Cav,ss by dose and by the presence/absence of inducer concomitant medication are presented in the following table for all studies combined.

Table 7 - Summary Model-Predicted Perampanel Cav,ss (ng/mL) Following Perampanel Daily Dosing by Concomitant Inducer – All Studies

Concomitant Inducer	Dose (mg)	N	Mean	SD	Min	Median	Max	%CV
None	2	174	151.2	73.6	26.1	130.3	405.6	48.6
	4	194	326.9	219.9	56.7	261.2	1215.3	67.3
	6	74	526.3	290.2	169.8	428.6	1612.5	55.1
	8	483	613.1	365.0	115.0	506.0	3028.9	59.5
	10	20	777.8	413.4	322.6	604.2	1729.2	53.2
	12	119	779.0	384.5	217.7	695.4	2007.3	49.4
Carbamazepine	2	128	53.7	22.2	19.4	49.8	136.6	41.3
	4	126	98.4	39.2	32.2	85.4	217.1	39.9
	6	22	170.0	59.6	80.2	160.6	293.1	35.1
	8	330	224.0	121.0	66.0	192.3	1320.7	54.0
	10	16	251.4	81.5	155.3	235.7	387.2	32.4
	12	182	337.3	171.9	125.8	298.2	1056.2	51.0
Oxcarbazepine or Phenytoin	2	109	78.6	33.7	11.4	73.7	200.1	42.9
	4	89	172.3	97.3	39.5	147.8	609.7	56.5
	6	29	235.7	90.8	116.4	233.3	421.6	38.5
	8	234	327.2	226.6	98.9	270.5	1827.4	69.2
	10	20	360.6	95.0	219.1	327.4	614.1	26.3
	12	97	427.7	212.9	133.4	383.1	1193.3	49.8

According to the model, perampanel PK was not affected by seizure type.

The effect of body weight and gender were found to be statistically significant covariates affecting perampanel CL/F. Differences in perampanel CL/F with body weight and between males and females were very small. This was confirmed by simulating perampanel steady state concentration-time profiles (n=1000) following 8mg/day in 50 kg vs. 100 kg body weight subjects and in male vs. female subjects.

PK/PD Analysis

- Perampanel 28-day Average PGTC Seizure Frequency PK/PD Analysis – Study 332

In subjects with PGTC seizures median values for Baseline actual 28-day average PGTC seizure frequency for placebo and treatment groups were 2.5 and 2.6 respectively.

For the final PK/PD model, the parameter values are shown in the table below. The placebo effect in the PK/PD relationship of percent change from Baseline in 28-day average PGTC seizure frequency was not significantly affected by the tested covariates. The diagnostic plots for the model indicated that the model adequately described the change from Baseline in the 28-day average PGTC seizure frequency data. The population and individual predictions versus the observations of log-transformed percentage change in seizure frequency did not show any systematic bias in the predictions. Weighted residuals obtained were evenly distributed versus population predictions or versus the independent variables time in days, and usually less than 2 in absolute value.

Table 8 - Parameter Estimates from Base/Final PK/PD Model for Average PGTC Seizure Frequency – Study 332

Parameter [Units]	Point Estimate	%RSE	95% CI
Placebo effect - β_0	4.36	1.41	4.24-4.48
Perampanel Exposure Effect - β_1	-0.981	31.4	-1.58 – - 0.377
Inter-individual variability (%CV)			
Placebo effect - β_0	8.72	34.6	--
Perampanel Effect - β_1	74.2	39.8	--
Residual variability (%CV)			
Study 332 (proportional)	9.76	12.2	--

%RSE: percent relative standard error of the estimate = SE/parameter estimate * 100, SD=Standard deviation

The model predicts a placebo effect of 31.7% reduction from Baseline in 28-day average PGTC seizure frequency: a subject not taking perampanel with a Baseline of 2.6 seizures per 28 days has a frequency decrease to 1.91 seizures per 28 days due to the effect of placebo alone. The variability between subjects in the placebo effect is mild, with %CV=8.72.

The effect of perampanel Cav,ss on the change from Baseline in 28-day average PGTC seizure frequency is a decrease of 0.981 on the loge scale for an increase of 1 µg/mL in Cav,ss. During maintenance, the seizure frequency in a typical male subject of median body weight (69 kg) not receiving any inducer medication (Baseline of 2.6 seizures per 28 days) is predicted to be reduced by 62.3% to 0.94 seizures per 28 days when treated with 8 mg/day perampanel (predicted Cav,ss of 505 ng/mL). The variability of the slope of perampanel concentration effect between subjects is high, with %CV =74.2.

The following plot displays model-predicting percentage reduction in 28-day average PGTC seizure frequency by dose of perampanel administered for subjects receiving and receiving co-administered inducers in Study 332.

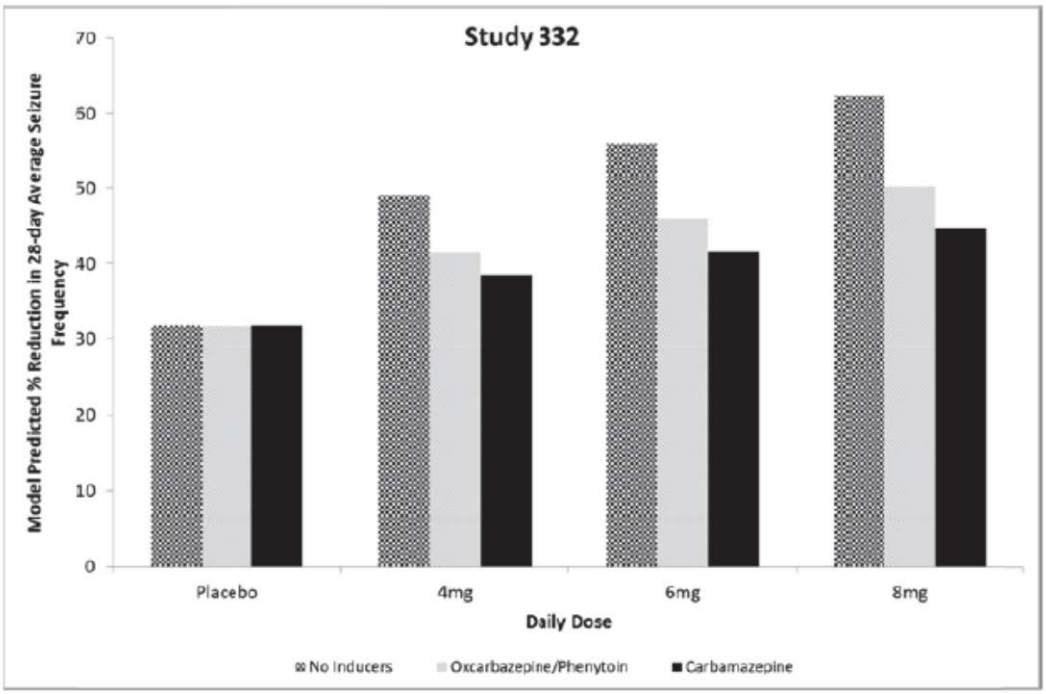


Figure 1 - Plot of Model-Predicted % Reduction in PGTC Seizure Frequency vs. Perampanel Dose Administered for Induced and Non-Induced Subjects – Study 332.

This figure demonstrates an improvement in reduction of 28-day average PGTC seizure frequency with increasing perampanel dose level in the presence and absence of inducer co-administration (carbamazepine, oxcarbazepine and phenytoin). The model-predicted effect of inducer co-administration on the percent change from Baseline in 28-day average PGTC seizure frequency improvement following perampanel administration is less pronounced than their overall effect on perampanel exposure.

The predictive performance of the final PK/PD model was evaluated using the visual predictive check. The majority of the observed data fell within the 90% prediction intervals. The results from the non-parametric bootstrap evaluation (N=1000) indicated that the final PK/PD model for percent from Baseline in 28-day average PGTC seizure frequency was stable and produced well estimated parameters.

The MAH further examined the influence of time and the results showed no improvement on the residual variability with little impact on objective function values.

- Perampanel Response Categorical PK/PD Analysis

The data for the response analysis were the same as described in the PK/PD analysis for 28-day average frequency data. For each time point in the data the subjects were classified as 0 (Non-responder: subject had <50 % decrease of 28-day average PGTC seizure frequency from Baseline) or 1 (responder: subject had ≥50 % decrease of 28-day average PGTC seizure frequency from Baseline).

For the final Categorical PK/PD Model, the final logit model for response data was a sum of constant placebo effect, linear perampanel exposure effect, and random effect to describe between subjects variability.

Table 9 - Logistic Regression Model Parameter Estimates for Response Data – Study 332

Parameter [Units]	Point Estimate	%RSE	95% CI
Placebo effect	1.99	21.9	1.14 – 2.84
Perampanel exposure effect	0.352	23.0	0.193 – 0.511
Inter-individual variability (SD)	1.86	35.2	--

SD – Standard deviation

The probability of an individual to be a responder was significantly increased by perampanel concentration. None of the demographics or concomitant AEDs was found to be a predictor of the probability of response or for affecting the slope for the perampanel exposure effect. The model-predicted probability of being a responder to perampanel was similar with or without inducer co-administration.

The predictive performance of the perampanel-response categorical PK/PD analysis was done using a nonparametric bootstrap evaluation (N=1000). The confidence intervals are generally narrow and the median values of the distribution of bootstrapped parameter values are also consistent with the original parameter estimates. Overall the bootstrap results indicated that the final PK/PD model for categorical response was stable and produced well estimated parameters.

- Perampanel Exposure – Study 332 Safety PK/PD Analysis

The relationship between perampanel Cav,ss and occurrence of treatment emergent adverse events (TEAEs) of special interest in subjects with PGTC seizures in Study 332 was explored graphically as data permitted. Since the incidence of individual TEAEs using narrow Standardised MedDRA Queries (SMQ) terms was small, all individual TEAEs of special interest using both the narrow and broad SMQ terms relating to hostility/aggression (irritability, laceration, agitation, abnormal behaviour, affect lability, aggression, drowning, paranoia, physical abuse) and those relating to psychosis/psychotic events (hallucination, abnormal behaviour, affect lability, delusion, hallucination-visual, illusion, paranoia, speech disorder, hallucination-auditory) as a group were used for the purpose of the exposure-safety assessment. Fifteen subjects receiving perampanel experienced hostility/aggression related adverse events (AEs) for whom PK exposure data was available for 12 subjects. Six subjects receiving perampanel experienced psychosis/psychotic event related AEs for whom PK exposure data was available for 4 subjects.

The median perampanel exposure in subjects who experienced events related to hostility/aggression were higher than those who did not experience such events, though substantial overlap in the concentrations was evident. No exposure relationship was apparent for psychosis/psychotic events. The potential relationship in perampanel exposure and occurrence of hostility/aggression related TEAEs was attempted via modelling using a logistic regression approach as planned, including both perampanel and placebo treated subjects (n=151). However due to high variability in probability of event and overall low incidences of AEs, reliable parameter estimates could not be determined.

2.3.3. Discussion on clinical pharmacology

Study DMPK2013-001

The methods and validation assays used for study DMPK2013-001 were considered acceptable by the CHMP. Perampanel showed no potential inhibition of CYP2B6 up to 30 µmol/L when using bupropion as the probe substrate in human liver microsomes.

Perampanel Pharmacokinetics

The bioanalysis of perampanel in human plasma samples collected in Core Study 332 was carried out in accordance with EMEA/CHMP/EWP/192217/09 Bioanalytical Method validation, using the same LC/MS/MS method as assessed and considered satisfactory in the context of the initial marketing authorisation application.

Population PK analysis was performed on perampanel plasma steady-state concentration data in subjects from Study 332 (PGTC seizures) and from Studies 304, 305, and 306 (refractory POS). The methodology utilised for the modelling was generally appropriate. The CHMP noted that 7 observations (< 1%) were excluded such as below limit of quantification and outlying concentrations. Normally outlying concentrations excluded from analysis should be included at the final step to evaluate their impact. However, in this case only, as there were so few exclusions, these were considered unlikely to be of relevance.

In the absence of CYP3A4/5-inducing AEDs the population estimate of perampanel CL/F was 0.66 L/h. Perampanel PK was not affected by seizure type, thus confirming the appropriateness of pooling PGTC and partial-onset PK data. Perampanel PK was linear since CL/F was dose- and time-independent. In addition, CL/F was not significantly affected by age, race, hepatic (ALT, AST), or renal (CRCL) markers.

Of the extrinsic factors examined, the co-administration of CYP3A4/5 inducing AEDs statistically significantly increased CL/F by factors of 2.75 (carbamazepine), 1.92 (oxcarbazepine) and 1.74 (phenytoin), resulting in perampanel exposure being reduced by similar levels. Perampanel CL/F was also statistically significantly increased by a factor of 1.23 by topiramate, which was considered a mild effect and not clinically important relative to the high variability in perampanel exposures. This small topiramate effect was also observed in the PK assessment of pooled Phase III data in patients with refractory POS only. Perampanel CL/F was not significantly affected by any of the other concomitant AEDs including valproic acid, lamotrigine, clobazam, phenobarbital, levetiracetam and zonisamide.

Of the intrinsic factors, gender was found to affect perampanel CL/F in a statistically significant manner. CL/F was 18% lower in female subjects (0.54 L/h) compared to males (0.66 L/h). Perampanel CL/F was also found to statistically significantly decline with increasing body weight. Both the gender and body weight effects were small, with PK simulations showing large overlaps in exposure between males and females and between small (50 kg) and large (100 kg) subjects when receiving the same dose, regardless of concomitant AEDs. Therefore the effects of gender and body weight were considered by the CHMP to be of no clinical relevance and did not warrant any dose adjustment.

The results from this new population PK analysis are consistent with findings from the previous population PK analyses in subjects with refractory partial seizures and in healthy subjects. A number of additional diagnostic plots and analyses were requested to fully support the MAH conclusions regarding the results of the modelling analysis. The plots were provided and overall supported the conclusions that the model described the data well. There appeared to be a bias towards higher concentrations at later times (e.g., after 16 hours) than predicted by the population PK model, but despite this trend, the CHMP agreed that, when an entire dosing interval is taken into account, the concentrations achieved are well-predicted by the model. Assuming that drug effect is related to exposure over a dosing interval, the noted deviation was considered acceptable.

PK/PD Analysis for Seizure Frequency

Generally, the applied methodology for the PK/PD modelling was considered acceptable by the CHMP. The analysis was conducted on the subject data set from Study 332. Log-transformed percent reduction in PGTC seizure frequency from Baseline was modelled with a placebo effect and a proportional exposure effect. Perampanel administration reduced PGTC seizure frequency with the decrease being proportional (log-linear) to Cav,ss and was independent of time. The decrease in seizure frequency due to placebo was

unaffected by concomitant AEDs and demographics. The effect of concomitant AEDs and demographics on the slope for the effect of perampanel could not be modelled due to the high shrinkage in inter-individual variability for the slope as a result of the high variability in response.

For PGTC subjects, a placebo effect of 31.7% reduction from Baseline in 28-day average seizure frequency, with an effect of perampanel Cav,ss of -0.981 per 1 µg/mL was determined. In a typical male subject, of median body weight (69 kg) treated with 8 mg/day perampanel without concomitant CYP3A4/5-inducing AEDs, seizure frequency was predicted to be reduced by 62.3%, compared to 44.6% reduction with concomitant carbamazepine and 50.1% reduction with concomitant, oxcarbazepine or phenytoin.

The CHMP requested additional displays of diagnostic plots as well as related data presentations, analyses and discussion. These were provided and supported the conclusion that there was no time effect and that the model adequately represents the data.

PK/PD Categorical Analysis for Response

PK/PD analysis of the probability of an individual being a responder to perampanel was conducted on Study 332 data alone. The model for responder probability was a sum of a placebo effect and a $\log_n$-linear perampanel exposure effect. Responder probability increased from 0.390 for placebo to 0.85 for 8 mg/day perampanel in the absence of inducer co-administration compared to 0.80 (carbamazepine) and 0.82 (oxcarbazepine or phenytoin) for inducer co-administration. There was no significant effect for any of the intrinsic and extrinsic factors on the probability of being a responder. Upon request of the CHMP, the MAH provided additional, convincing evidence that the selected model fits the data significantly better than a model with no drug effect and the CHMP endorsed the MAH's conclusions.

Perampanel Exposure – Safety PK/PD Analysis

The median perampanel exposure in subjects who experienced adverse events related to hostility/aggression (n=12) were higher than those who did not experience such events, though substantial overlap in the concentrations was also evident. No exposure relationship was apparent for psychosis/psychotic events. The potential relationship in perampanel exposure and occurrence of hostility/aggression AEs was attempted via modelling using a logistic regression approach as planned, including both perampanel and placebo treated subjects (n=151). However due to high variability in probability of event and overall low incidences of AEs, reliable parameter estimates could not be determined.

2.3.4. Conclusions on clinical pharmacology

With regards to perampanel PK, there were no new findings based on the population PK analysis after pooling the data from patients with PGTC seizures to the previously reported analysis in epilepsy patients with refractory POS. Overall, perampanel PK in epilepsy patients with PGTC were similar to the epilepsy patients with refractory POS. The information in SmPC section 5.2 was updated including revised point estimates of the effects of intrinsic and extrinsic factors on the perampanel exposure due to pooling the data from epilepsy patients with PGTC with epilepsy patients with refractory POS. This was agreed by the CHMP.

No new drug-drug interactions have been identified for perampanel. A pronounced reduction in exposure as well as a reduction of PD effects due to concomitant CYP3A4/5 inducer AEDs was observed. The CHMP considered that the existing warning in SmPC section 4.4 on the use of concomitant enzyme-inducing AEDs and the possible need for dose adjustment was adequate. SmPC section 4.5 was updated to reflect the extent to which perampanel plasma concentrations were affected by concomitant AEDs as calculated with the updated population PK model.

The exposure-AE incidence relationship for hostility/aggression could not be formally modelled. Thus, despite the observation of higher perampanel exposures in subjects who experienced events related to hostility/aggression compared to patients without such events, no firm conclusions could be drawn.

Overall, the CHMP considered that the available clinical pharmacology data were sufficient to support the application for use of Fycompa in the treatment of IGE patients with PGTC seizures.

2.4. Clinical efficacy

In order to demonstrate clinical efficacy in PGTC seizures, the MAH conducted one randomised double-blind Phase III study, Study E2007-G000-332 (also referred to as Core Study 332). The study had an open label extension which was primarily designed to investigate long-term safety, but it also recorded long-term efficacy.

2.4.1. Dose response study(ies)

The MAH proposed treatment of PGTC seizures with perampanel at a dose up to 8 mg/day, which could be further increased up to 12 mg depending on individual clinical response and tolerability.

No dose response studies have been conducted.

Population PK/PD modeling of the perampanel plasma concentration response in Core Study 332 demonstrated the following:

- The percent reduction in 28-day average PGTC seizure frequency from Baseline during maintenance treatment increases as a function of the increase in exposure to perampanel.
- Responder probability was predicted to increase with an increase in exposure to perampanel.

With regards to the choice of the only dose evaluated in Core Study 332 (8 mg/day), this dose was selected considering the efficacy results in previous Phase III POS studies and the expected lesser use of perampanel inducing AEDs in the new target patient population. The 12 mg dose was included in the open label Extension Phase of Study 332 to provide additional safety and efficacy data. The design of Study 332 and, previously, of the Phase III POS studies followed the common clinical practice in epilepsy to titrate to efficacy and tolerability (2 mg to 8 mg titration, see section 2.4.2. for details on the study methods).

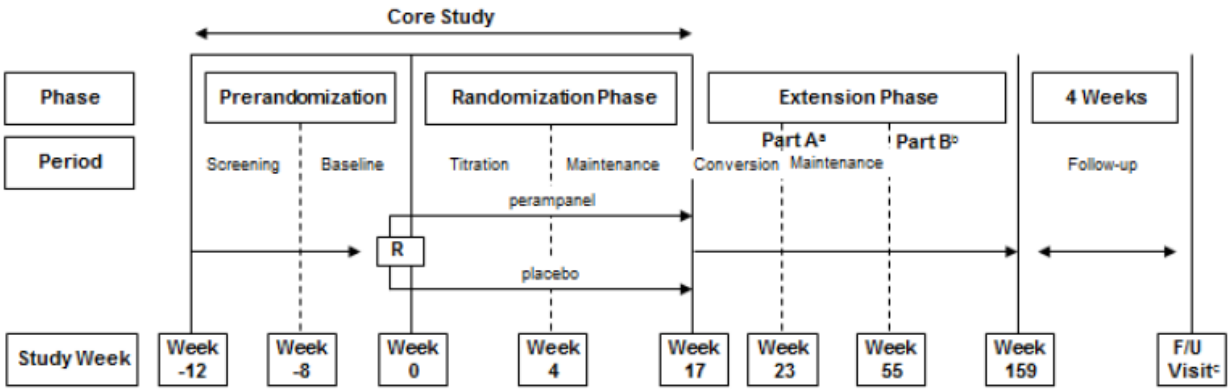
2.4.2. Main study

2.4.2.1. Study E2007-G000-332

Study E2007-G000-332 (Core Study 332) was a double-blind, randomised, placebo-controlled, multicentre, parallel-group phase III trial with an open-label extension phase to evaluate the efficacy and safety of adjunctive perampanel in the treatment of patients 12 years of age and older with primary generalised tonic-clonic seizures.

Methods

Study 332 consisted of 3 phases: Pre-randomisation, Randomisation, and Extension as depicted in the following Figure.



R = Randomization.
F/U = Follow-up.
a = All subjects should be retained in the study through the last visit of Extension Part A.
b = Subjects only need to complete Part B if perampanel is not made available free of charge according to the appropriate local country-specific mechanism (revised per Amendment 03)
c = The Follow-up visit should be conducted for all subjects 4 weeks after their last on-treatment visit.

Figure 2 - Design of Study E2007-G000-332

The Pre-randomisation Phase consisted of 2 periods: Screening Period (up to 4 weeks, depending on how soon the required documentation was obtained) and Baseline Period (4 or 8 weeks, depending on the accuracy of diary-documented seizure frequency during the Screening Period).

Subjects who met all of the inclusion and none of the exclusion criteria at Visit 1 were given a subject seizure diary (paper) to be used for recording seizure count and type on a daily basis by either the subject or the designated caregiver. Subjects must have had at least 8 weeks of consecutive seizure diary data before randomisation (up to 4 weeks could have been obtained from the subject's personal retrospective seizure diary if collected immediately before study entry). To ensure correct seizure classification, the investigator reviewed the subject diary with the subject at Visit 2 and Visit 3.

The Randomisation Phase was up to 21 weeks in duration, and consisted of 3 periods: Titration (4 weeks), Maintenance (13 weeks), and Follow-up (4 weeks, only for those subjects not entering the Extension Phase). Eligible subjects were randomised to receive perampanel or perampanel-matched placebo. Subjects continued to take their Baseline AED medication regimen throughout the Randomisation Phase, and subjects or their designated caregivers continued to complete the subject diary each day.

During the Titration Period, for the perampanel group, the dose was increased at weekly intervals in increments of 2 mg to the target dose of 8 mg/day or highest tolerated dose.

During the Maintenance Period, subjects continued treatment with the study drug dose achieved during the Titration Period, taking the study drug once daily in a blinded fashion. Dose adjustment during the Maintenance Period was not recommended. According to the investigators' clinical judgment, however, subjects with inadequate seizure control were allowed to have their dose increased by one 2 mg increment, and subjects experiencing intolerable AEs were allowed to have their dose down-titrated by only 2 mg, during the Maintenance Period. More than 1 up-titration or down-titration was not allowed during the Maintenance Period unless there was a significant medical reason and the change was approved by the Medical Monitor.

Subjects who completed the Randomisation Phase could enter the Extension Phase and receive open-label perampanel. Subjects who did not continue into the Extension Phase proceeded to the Follow-up Period. During the Conversion Period (Weeks 17-23), all subjects and investigators remained blinded.

Subjects who had been assigned to receive placebo in the Core Study were started on perampanel, whereas subjects assigned to receive perampanel in the Core Study continued to receive perampanel once daily at the dose they received during the Maintenance Period. During the Conversion Period, subjects were allowed to titrate to a total daily dose of 12 mg perampanel (weekly in 2 mg increments) at the investigator's discretion as opposed to 8 mg/day during the maintenance phase. During the Maintenance Period of Part A of the Extension Phase (Weeks 24-55), subjects were unblinded to study treatment and remained on optimal perampanel dose established during the conversion period. Dose adjustment during Maintenance Period was allowed if medically necessary per the investigator's discretion. Subjects who did not tolerate a minimum dose of 2 mg/day during the Extension Period were discontinued from the study. Subjects who elected to participate in Part B were treated until they had at least 52 weeks of total exposure to perampanel in the study. Subjects in a country where an extended access program (EAP) had been activated ended treatment under this protocol and were given the option to enrol in the EAP. If an EAP had not been activated in their country or if the subject did not elect to participate in Part B the treatment was ended and the subject entered the Follow-up Period of the Extension Phase. Subjects who elected not to participate in Part B ended treatment in this study and continued to the Follow-up Period of the Extension Phase.

Subjects entered the Extension Phase on the same concomitant antiepileptic drugs (AEDs) they were receiving at the end of the Core Study. During the Maintenance Period of the Extension Phase, changes to concomitant AED(s) (addition, deletion, or dose adjustment) were allowed, with care taken when switching between an inducer and non-inducer AED.

The Follow-up Period of the Extension Phase spanned the 4 weeks following receipt of the last dose of perampanel. At the end of this period, subjects returned to the clinical site and underwent all end-of-study procedures.

Study participants

Approximately 164 subjects (males and females) with PGTC seizures were planned for enrolment across approximately 95 sites in the US, Europe, and Asia. A review was conducted by an independent group (Epilepsy Study Consortium) of information provided by the investigator regarding the diagnosis and seizure type for each subject who provided informed consent. Only when the accuracy of the diagnosis was approved by the Epilepsy Study Consortium, was a subject eligible for participation in the study.

Inclusion Criteria

Subjects were eligible for participation in the Core Study if they met all of the following inclusion criteria:

1. Aged 12 years and older (in Germany, greater than or equal to 18 years of age [within the course of the study] at the time of the informed consent; in India, less than 65 years of age).

2. Clinical diagnosis of PGTC seizures in the setting of idiopathic generalized epilepsy (with or without other subtypes of primary generalized seizures) and experiencing ≥3 PGTC seizures during the 8-week period prior to randomisation.

3. Had a routine electroencephalogram (EEG) up to 5 years prior to or during the Baseline Period with electroencephalographic features consistent with primary generalized epilepsy; any other concomitant anomaly must have been explained by adequate past medical history. In the case of a normal historical EEG, the EEG was repeated. In the case of another normal EEG upon repeat, the presence or history of myoclonus or typical absence seizure, or first degree relative with PGTC seizures, was required. If the repeat EEG presented abnormalities compatible with PGTC seizures, no further action was required and the subject was eligible for enrolment.

4. On a fixed dose of 1 to a maximum of 3 concomitant AEDs for a minimum of 30 days prior to Baseline Period; only 1 inducer AED (ie, carbamazepine, oxcarbazepine, or phenytoin) out of the maximum of 3 AEDs was allowed.

5. A vagal nerve stimulator was allowed, but must have been implanted ≥5 months prior to Baseline (stimulator parameters were to have remained unchanged for 30 days prior to Baseline and for the duration of the study).

6. Had a computed tomography or magnetic resonance imaging within the last 10 years (for adults) or 5 years (for adolescents) that ruled out a progressive cause of epilepsy.

7. A ketogenic diet was allowed provided the subject had been on this diet for 5 weeks prior to randomisation.

8. All females must have had a negative serum beta-human chorionic gonadotropin test result or a negative urine pregnancy test result at Screening and Baseline. Females of childbearing potential agreed to use a medically acceptable method of contraception (eg, abstinence, an intrauterine device, a double-barrier method such as condom plus spermicide or condom plus diaphragm with spermicide, a contraceptive implant, an oral contraceptive or have a vasectomized partner) throughout the entire study period and for 30 days after study drug discontinuation. The only female subjects who were exempt from this requirement were postmenopausal women (defined as greater than age 50 and having at least 12 months of amenorrhea) or subjects who had been sterilized surgically or who were otherwise proven sterile (ie, bilateral tubal ligation with surgery at least 6 months prior to dosing, hysterectomy, or bilateral oophorectomy with surgery at least 2 months prior to dosing). All women who were of reproductive potential and who were using hormonal contraceptives were required to have been on a stable dose of the same hormonal contraceptive product for at least 12 weeks prior to dosing and must have continued to use the same contraceptive during the study and for 30 days after study drug discontinuation.

9. Provided written informed consent/assent signed by subject or legal guardian prior to entering the study or undergoing any study procedures. If the written informed consent was provided by the legal guardian because the subject was unable to do so, a written or verbal assent from the subject must have also been obtained.

10. Was willing and able to comply with all aspects of the protocol.

Exclusion Criteria

Subjects were not eligible for participation in the Core Study if they met any of the following exclusion criteria:

1. Had participated in a study involving administration of an investigational compound or device within the 30 days prior to Baseline, or within approximately 5 half-lives of the previous investigational compound, whichever was longer.

2. Were pregnant and/or nursing.

3. Had participated in a previous perampanel study(ies).

4. Had a history of status epilepticus that required hospitalization within 12 months prior to Baseline.

5. Had seizure clusters where individual seizures cannot be counted.

6. Had a history of psychogenic seizures.

7. Had any suicidal ideation with intent, with or without a plan, at or within 6 months prior to Visit 2.

8. Had evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could have affected the subject's safety or study conduct.

9. Had a concomitant diagnosis of partial onset seizures.

10. Had progressive neurological disease.

11. Had a clinical diagnosis of Lennox-Gastaut syndrome.

12. Had a history of drug or alcohol dependency or abuse within 2 years prior to Screening.

13. Had multiple drug allergies or a severe drug reaction to an AED(s), including dermatological (eg, Stevens-Johnson syndrome), haematological, or organ toxicity reactions.

14. If felbamate was used as a concomitant AED, subjects must have been on felbamate for at least 2 years, with a stable dose for 60 days prior to Baseline. They must not have had a history of a white blood cell (WBC) count below ≤2500/µL (2.50 109/L), a platelet count <100,000/µL, liver function tests (LFTs) >3 times the upper limit of normal (ULN), or other indication of hepatic or bone marrow dysfunction while receiving felbamate.

15. In case of a history of vigabatrin use in the past, vigabatrin must have been discontinued for approximately 5 months prior to Baseline, and subjects must have had documentation showing no evidence of a vigabatrin-associated clinically significant abnormality in an automated visual perimetry test.

16. Were receiving concomitant use of medications known to be inducers of cytochrome P450 3A (with the exception of carbamazepine, oxcarbazepine, and phenytoin) including, but not limited to: rifampin, troglitazone, St John's Wort, efavirenz, nevirapine, glucocorticoids (other than topical usage), modafinil, pioglitazone, and rifabutin, within 30 days prior to Baseline or were receiving concomitant use of barbiturates (except for seizure control indication) within 30 days prior to Baseline.

17. Had used rescue benzodiazepines intermittently (ie, 1 to 2 doses over a 24-hour period was considered 1-time rescue) more than 2 times within the 30 days prior to Baseline.

18. Were known to be positive for human immunodeficiency virus.

19. Had active viral hepatitis (A, B, or C) as demonstrated by pre-existing positive serology.

20. Had evidence of significant active hepatic disease. Stable elevations of liver enzymes, ALT, and AST due to concomitant medication(s) were allowed if they were <3x ULN.

Subjects who did not tolerate the minimum dose of 2 mg/day during the Core Study were discontinued from the study.

Treatments

Test Treatment: Perampanel was supplied as 2-mg oral tablets. The maximum daily dose was 8 mg in the Maintenance Period and 12 mg in the Extension Phase.

Reference: Placebo oral tablets matching perampanel 2-mg oral tablets.

Subjects in both treatment groups took up to 6 tablets of study drug once daily, by mouth, before bedtime, and with food. While the highest dose to be used during the Core Study was 8 mg/day (2 mg x 4 tablets), a total of 6 tablets were administered during the Core Study in anticipation of maintaining the blind during the Open-label Extension Blinded Conversion Period, which allowed all subjects to titrate to a total daily dose of 12 mg (2 mg x 6 tablets). A subject whose dose was reduced due to intolerable AEs

was allocated a different kit that contained more placebo tablets in order to maintain the same total number of tablets.

Subjects were taking a maximum of 3 marketed AEDs as the Baseline treatment on which they had to be stabile for at least 30 days prior to administration of study medications. Only 1 inducer AED (ie, carbamazepine, oxcarbazepine, or phenytoin) was allowed. No dose changes in concomitant AED(s) were allowed during the Core Study. Additions or deletions of an AED were not allowed during the Core Study. In case of an emergency, subjects could have received other AEDs (including diazepam and other appropriate AEDs) as rescue medications to treat status epilepticus, uncontrolled seizures, or seizure clusters.

Concomitant use of medications known to be inducers of CYP3A (with the exception of carbamazepine, oxcarbazepine, and phenytoin) as well as concomitant use of barbiturates (except for seizure control indication) were not permitted during the study. Benzodiazepine administration, up to a maximum of 1 time per week, was allowed during the Core Study as rescue medication for worsening seizures.

For any drugs known to influence the central nervous system, the dose was to be kept stable during the Core Study.

Objectives

The primary objective of this study was to demonstrate the efficacy of adjunctive perampanel therapy compared to placebo on PGTC seizures.

Secondary study objectives were:

- To evaluate the safety and tolerability of perampanel in subjects with inadequately controlled PGTC seizures.
- To evaluate the efficacy of adjunctive perampanel therapy, compared to placebo, on other subtypes of primary generalized seizure (myoclonic, absence, and all seizures).

Exploratory study objectives were:

- To evaluate the PK of perampanel in subjects with inadequately-controlled PGTC seizures.
- To explore the efficacy of adjunctive perampanel therapy compared to placebo, on the physician-rated Clinical Global Impression of Change scale (CGI-C) and the time from the first dose date to the nth PGTC seizure event, where n = Baseline seizure frequency per 28 days plus 1.
- To explore the relationship between plasma perampanel concentrations, efficacy, and safety using population pharmacokinetic/pharmacodynamic (PK/PD) modeling.
- To evaluate the incremental difference in the percentage change from Baseline in Overall Quality of Life (QOL) in subjects who are “Responders” (ie, ≥50% reduction in seizures) versus “Non-responders”.
- To evaluate the incremental difference in the rates of hospitalization and/ or emergency room visits in subjects who are “Responders” (ie, ≥50% reduction in seizures) versus “Non-responders”.

Efficacy related outcomes/endpoints

Primary Endpoints

The primary efficacy endpoint for EU registration was the 50% responder rate in the Maintenance Period relative to Baseline. For all other regions, this was the key secondary endpoint. Responders were defined

as subjects who experienced a 50% or greater reduction in PGTC seizure frequency per 28 days in the Maintenance Period relative to Baseline (Pre-randomisation Phase).

The primary efficacy endpoint outside the EU was the percent change from Baseline in PGTC seizure frequency per 28 days during treatment. For the EU this was the key secondary efficacy endpoint.

Secondary Endpoints

- Percent change in PGTC seizure frequency per 28 days during the Titration and Maintenance Periods combined relative to Baseline (key secondary endpoint).
- Percent change in other subtypes of primary generalized seizure (i.e., myoclonic, absence, and all seizures) frequency per 28 days in the Titration and Maintenance Periods combined relative to Baseline.
- Responder Rate for other subtypes of primary generalized seizure frequency (i.e., myoclonic, absence, and all seizures) per 28 days in the Maintenance Period relative to Baseline.

Exploratory Endpoints

- Time from the first dose date to the (Baseline seizure frequency per 28 days plus 1)-th PGTC seizure event.
- CGI-C response distribution at Visit 7 (i.e., end of the Maintenance Period).

  The investigator completed the CGI-C questionnaire. The purpose of each questionnaire was to assess the subject's clinical status over the last 4 weeks. This assessment evaluated seizure frequency and severity/intensity, the occurrence of AEs, and overall functional status. Each evaluation was done using a 7-point scale where 1 = very much improved and 7 = very much worse.

Other Endpoints

- Proportion of categorised percent changes in seizure frequency over the Maintenance Period.
- Percentage of subjects who achieved seizure free status (PGTC seizures and all seizures).
- Actual and percent change from Baseline in Patient-Weighted Quality of Life in Epilepsy Inventory 31 (QOLIE-31-P).

  Subjects who were 18 years of age or older at the time of randomisation completed the QOLIE-31-P to assess their quality of life status over the last 4 weeks at the visits. The QOLIE-31-P contained 39 items; 37 items were used to calculate 8 subscales (Energy, Mood, Daily Activities, Cognition, Medication Effects, Seizure Worry, Distress, and Overall QOL) and 1 overall QOLIE-31-P score. One item regarding the health state of the patient was not scored as designated by the developer's official scoring algorithm. This questionnaire was only implemented in the countries where it was available and a validated translation existed for the spoken language(s), and only in the age groups for which it had been validated.
- Monthly rates (per 28 days) per subject for hospitalizations associated with seizures, unscheduled physician visits, and emergency room visits [ie, based on Healthcare Resource Utilization (HCRU) responses].

  HCRU information was collected at the visits using the information on the eCRF (Adverse Event eCRF page for hospitalisation) and subject responses to questions concerning the (1) occurrence (and number) of an unscheduled physician office visit due to a seizure within the preceding 4 weeks and (2) occurrence (and number) of emergency room visits within the preceding 4 weeks, and if any of the emergency room visit(s) resulted in hospitalisation.

Exploratory endpoints related to PK and PK/PD analyses are reported separately and assessed in section 2.3.2.1.

Sample size

Assuming a common Standard Deviation of 60% for the percent change in PGTC seizure frequency per 28 days in the Titration and Maintenance Periods combined relative to the Pre-randomisation Phase, a sample size of 82 subjects in each treatment group in the Full Analysis Set would have >85% power to detect a treatment difference of 30% between the placebo and the perampanel groups based on the Wilcoxon rank-sum test with a 0.05 2-sided significance level.

Based on a sample size of 82 subjects per treatment group, the study had >80% power to detect a treatment difference of 22% in responder rate proportions (35% with placebo and 57% with perampanel) with a 0.05 two-sided significance level using a 2-group chi-square test.

Randomisation

Following the Baseline Period, subjects were assigned to one of the two treatments (1:1) based on a randomisation scheme generated using a computer program. Randomisation was performed centrally by an Interactive Voice Response System vendor that generated a randomisation list with a pseudorandom number generator.

Blinding (masking)

The double-blind design of this study was maintained through the use of placebo tablets that were identical in appearance to the perampanel tablets. All study drugs were packaged and labelled so as to be indistinguishable between the treatment groups.

During the Randomisation Phase, the subject and all personnel involved with the conduct and the interpretation of the study, including the investigators, investigational site personnel and Sponsor staff, were blinded to the treatment codes. Randomisation data were to be kept strictly confidential, filed securely by an appropriate group at the Sponsor or contract research organisation and accessible only to authorized persons until the time of unblinding.

Statistical methods

All statistical analyses were performed by Symbiance, Inc., Princeton Junction, Pennsylvania, US using SAS version 9.1.3.

The **Full Analysis Set (FAS)** included subjects who were randomised to study drug, received at least 1 dose of study drug, and had any post Baseline seizure frequency data during the Randomisation Phase. If a subject received study drug different from that to which he/she was randomised, the subject's efficacy data were analysed "as randomised."

The **Per Protocol (PP) Analysis Set** was a subset of subjects in the Full Analysis Set who did not have any major protocol deviations, were at least 80% compliant with the study medication during the Randomisation Phase, and had diary compliance of at least 80% during the Pre-randomisation and Randomisation Phases. Major protocol deviations were based on selected inclusion criteria related to clinical diagnosis of PGTC seizures and minimum number of PGTC seizures during the Pre-randomisation Phase, discontinuation or interruption of any background AED, and receipt of study drug other than that to which the subject was randomised for longer period of time than receipt of randomised study drug.

The **PK Analysis Set** included subjects receiving perampanel who had at least 1 quantifiable perampanel concentration with documented dosing history.

The **Safety Analysis Set** included subjects who were randomised to study drug, received at least 1 dose of study drug and had at least 1 post-Baseline safety assessment. If a subject received study drug different from that to which he/she was randomised, the subject's safety data were analysed "as treated."

The FAS was the primary analysis set used for the efficacy analyses. The PP Analysis Set was used for sensitivity analysis of the primary and key secondary efficacy endpoints.

Seizure frequency per 28 days was derived from the information recorded in the subject diaries. The percent change from Baseline was analysed over the Titration and Maintenance Periods combined, while Baseline was defined as seizure frequency per 28 days based on all valid diary data during the Pre-randomisation Phase.

The **responder analysis** was carried out using a Cochran- Mantel-Haenszel (CMH) test stratified by country in the FAS. In the Maintenance-LOCF (last observation carried forward) analysis for the responder rate, if a subject had less than 8 weeks of Maintenance Period, the PGTC seizure frequency during the last 8 weeks of the Titration and Maintenance Periods combined (or PGTC seizure frequency during the Titration and Maintenance Periods combined for subjects with less than 8 weeks of Titration and Maintenance Periods combined) was used to impute.

The following sensitivity analyses were conducted for the Responder Rate:

- Analysis of the responder rate using the FAS will be conducted over the Titration and Maintenance Periods combined, and Titration Period, and for the Completers.
- Analysis of the responder rate using the PP Analysis Set.
- The responder analysis counting subjects discontinuing during titration as non-responders in the FAS.

The **percent change in seizure frequency** from Baseline was analysed over the Titration and Maintenance Periods combined in the FAS. PGTC seizure frequency per 28 days (as determined from subject diaries) was calculated as the number of PGTC seizures divided by the number of days in the interval and multiplied by 28. Analysis was conducted using rank analysis of covariance (ANCOVA) with treatment and country as factors, and the Baseline PGTC seizure frequency as a covariate. In this analysis, all PGTC seizure frequency data was first rank-transformed for both Baseline and endpoint PGTC seizure frequencies separately. The ANCOVA will then be conducted based on the rank transformed data.

Due to an expected irregular distribution of PGTC seizure frequency, median was the primary statistic of interest for the primary endpoint. Hodges-Lehmann estimator and 95% confidence interval (CI) for this estimator were displayed for understanding the treatment effect size.

The following sensitivity analyses were conducted for the endpoint of percent change in PGTC seizure frequency:

- Analysis on the Maintenance with LOCF to impute for missing data, and Titration period in the FAS. In the "Maintenance-LOCF" Analysis for the percent change, if a subject has less than 8 weeks of Maintenance Period, the PGTC seizure frequency will be imputed using the same method as in the responder analysis.
- Analysis of the percent change using the PP Analysis Set.
- Analysis of subjects in the FAS who complete the entire study period i.e. have last scheduled double-blind visit completed and is marked by the investigator to have completed the study (Completers).

The following exploratory endpoints were analysed for the FAS:

- The time from the first dose date to the (Baseline seizure frequency per 28 days plus one)- th [nth + 1] PGTC seizure event during the treatment period was analysed using the Kaplan-Meier method with log-rank tests.
- The number and proportion of subjects who remained seizure-free (PGTC seizures and all seizures) during the Maintenance Period were tabulated for the Full Analysis Set (subjects who did not complete the Maintenance Period were considered not to have achieved seizure-free status) and for subjects who completed the Core Study.
- The categorized percentage change in PGTC seizure frequency per 28 days during the Maintenance Period using LOCF was summarized.
- A treatment group difference in the CGI-C was analysed using a CMH test adjusted for pooled country.
- The absolute and percent change from Baseline values were summarized for the following QOLIE-31-P scales for both treatment groups using descriptive statistics: Energy, Mood, Daily Activities, Cognition, Medication Effects, Seizure Worry, Overall QOL, Distress, and Overall Score. Scoring of the QOLIE-31-P was performed in accordance with the Scoring Manual for the QOLIE-31-P: Patient-Weighted Quality of Life in Epilepsy (v.2).
- Descriptive statistics were used to summarize, by treatment group, the accumulated number of subjects at each visit with each HCRU visit type and the number of each type of visits per 28 days averaged across all visits since Baseline.

For the percent change in PGTC seizure frequency and the responder rate, analyses (descriptive statistics only) were performed for the Full Analysis Set based on the following subgroups:

- Age (Age Group 1: ≥12 to <17, ≥17 to <65, ≥65); Age Group 2: ≥12 to <18, ≥18 to <65, ≥65)
- Sex (Male, Female)
- Race (White, Black/African American, Asian/Pacific, Other)
- Country
- Pooled country (the following countries were pooled: Austria/Greece/Serbia/Israel; Lithuania/France; Czech Republic/Poland; all other countries were not pooled)
- Region (North America/Europe, Asia Pacific)
- Baseline AEDs (lamotrigine, valproic acid, levetiracetam, topiramate, zonisamide, ergenyl chrono; these represented the 6 most commonly used concomitant AEDs at Baseline)

Results

Participant flow

Of the 307 subjects who were screened, 143 subjects were screen failures and 164 subjects were eligible to continue in the study. All but 1 of the 164 randomised subjects received at least 1 dose of study drug. This patient assigned to the perampanel group, elected to withdraw from the study prior to the first dose of study drug.

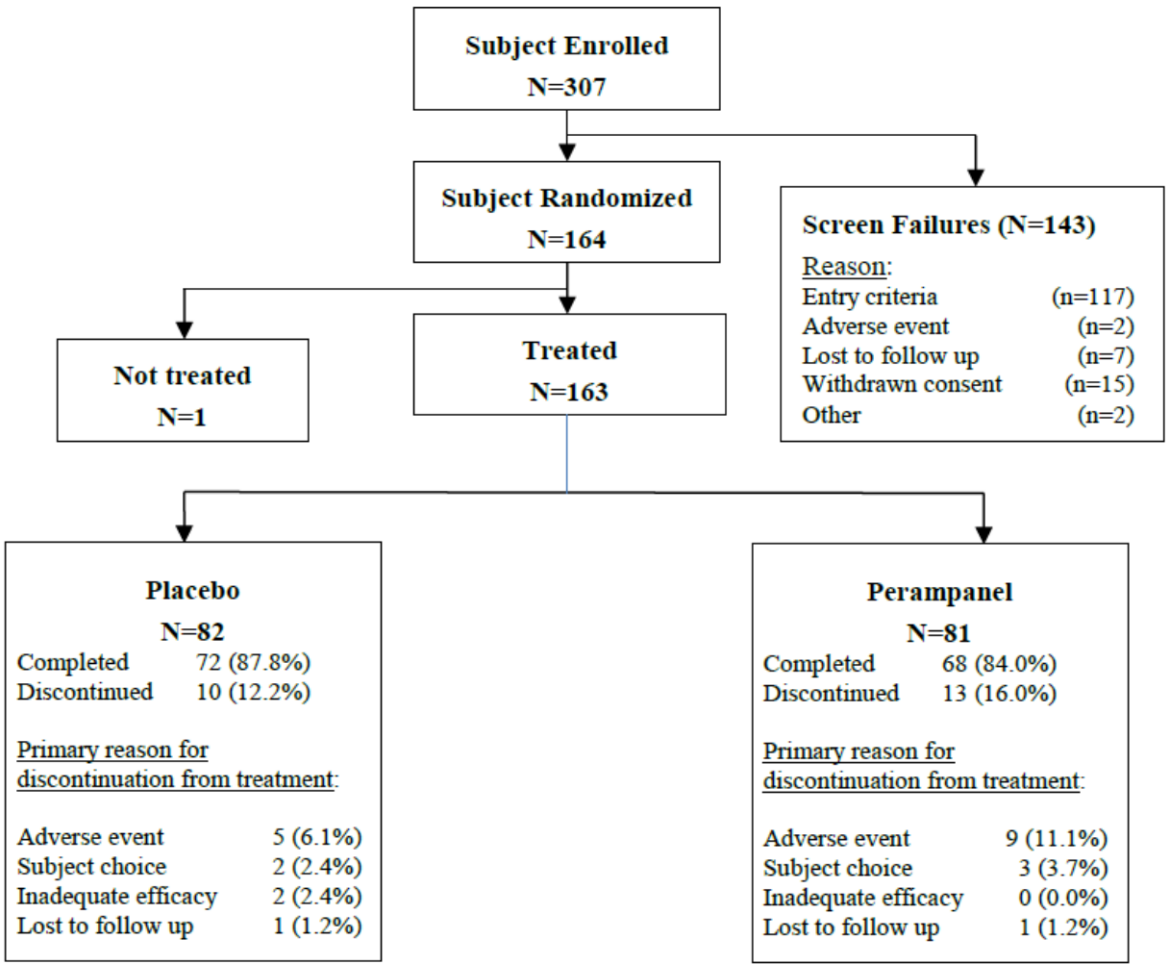


Figure 3 - Subject Disposition and Primary Reason for Discontinuation from Study

Table 10 - Subject Disposition and Primary Reason for Discontinuation from Study – Core Study: All Randomised Subjects

	Placebo	Perampanel
Randomized, n	82	82
Not treated, n	0	1
Treated, n (%)	82 (100.0)	81 (100.0)
Completed Core Study, n (%)	72 (87.8)	68 (84.0)
Discontinued from Core Study, n (%)	10 (12.2)	13 (16.0)
Primary reason for discontinuation[a], n (%)		
Adverse event	5 (6.1)	9 (11.1)
Lost to follow up	1 (1.2)	1 (1.2)
Subject choice	2 (2.4)	3 (3.7)
Inadequate therapeutic effect	2 (2.4)	0
Pregnancy	0	0
Other	0	0

Percentages are based on the number of subjects randomized and treated in the relevant treatment group.
a: As reported on the Subject Disposition Core case report form.

Recruitment

The first subject was enrolled in Study 332 on 13 July 2011 and the last subject visit was 27 May 2014.

Conduct of the study

There were 3 global protocol amendments (27 October 2011, 12 April 2012 and 15 November 2013).

Eleven (11) of 162 subjects who were exposed to study treatments were not eligible to enter in the PP population analysis due to protocol deviations.

The most common reason for exclusion was the major protocol deviation of stopping or interrupting Baseline concomitant AED during the Core Study (3 [3.7%] and 4 [4.9%] subjects in the placebo and perampanel groups, respectively). One subject in each treatment group had a major deviation of <80% compliance with study drug. Additionally, 2 subjects were excluded from the PP Analysis Set for other reasons: perampanel Subject 20071001 for a congenital genetic disorder and placebo Subject 16021002 as a result of prohibited use of a benzodiazepine.

Numbers analysed

The FAS, PP Analysis Set and Safety Analysis Set included 162, 151 and 163 patients respectively.

In addition to one subject assigned to the perampanel group who did not receive any study treatment and was thus excluded from the FAS, another subject, assigned to the placebo group, was not included in the FAS because this subject did not have post-Baseline seizure data. This latter subject died as a result of convulsions on Day 11 prior to the first post-Baseline seizure diary assessment.

Table 11 - Analysis Sets – Core Study 322: All Randomised Subjects

Analysis Set	Placebo (N=82) n (%)	Perampanel (N=82) n (%)	Combined Total (N=164) n (%)
Safety Analysis Set[a]	82 (100.0)	81 (98.8)	163 (99.4)
Full Analysis Set[b]	81 (98.8)	81 (98.8)	162 (98.8)
Per Protocol Analysis Set[c]	76 (92.7)	75 (91.5)	151 (92.1)

Percentages are based on the number of randomized subjects in the relevant treatment group.
a: Safety Analysis Set includes all randomized subjects who provide informed consent/assent, receive at least one dose of study medication, and have at least one postbaseline safety assessment.
b: Full Analysis Set includes all randomized subjects who receive at least one dose of study medication and have any postbaseline seizure frequency data.
c: Per Protocol Analysis Set is the subset of subjects in the Full Analysis Set who do not have any major protocol deviations, are at least 80% compliant with the study medication during the Randomization Phase, and have diary compliance of at least 80% during the Prerandomization and Randomization Phases.

Baseline data

Standard demography parameters collected during the study included date of birth, sex, race, and ethnicity. All pertinent medical history within 2 years, as well as any significant findings noted at screening, was documented for each subject. At screening, physical and neurological examinations were performed.

Most of the 162 subjects in the FAS were 18 to 64 years old. A total of 22 subjects (13.6%) were less than 18 years old (18 [11.1%] subjects were <17 years), and only 1 subject was 65 years of age or older (placebo arm). In the perampanel arm, the age range of patients was 12 to 58 years. The majority of the subjects were White (53.7%); 42.0% (n=68) were Asian (Chinese, Japanese, and Other Asian) and 2.5% were Black/African American. There was a slight imbalance in gender distribution, with females representing 56.2% of the FAS.

The majority of subjects had long-standing epilepsy, with the median time from epilepsy diagnosis to study entry of 14.54 years (range: 1.0, 57.1). Consistent with protocol eligibility criteria, all subjects had tonic-clonic seizures; about one-half of subjects in both treatment groups (50.0% placebo, 51.9% perampanel) also had a history of absence seizures and about 40% (40.2% placebo, 39.5% perampanel) had a history of myoclonic seizures.

Table 12 - Epilepsy-Specific Medical History – Core Study: Safety Analysis Set

Category	Placebo (N=82)	Perampanel (N=81)	Combined Total (N=163)
Time since diagnosis (year)[a]			
n	82	81	163
Mean (SD)	18.63 (12.571)	15.65 (10.755)	17.15 (11.763)
Median	15.90	13.04	14.54
Min, Max	1.0, 57.1	1.9, 53.0	1.0, 57.1
Seizure type, n (%)			
Tonic-clonic	82 (100.0)	81 (100.0)	163 (100.0)
Myoclonic	33 (40.2)	32 (39.5)	65 (39.9)
Absence	41 (50.0)	42 (51.9)	83 (50.9)
Clonic	1 (1.2)	0	1 (0.6)
Tonic	2 (2.4)	0	2 (1.2)
Atonic	1 (1.2)	0	1 (0.6)

Percentages are based on the total number of subjects with non-missing values.
A subject can have more than one seizure type.
Max = maximum; Min = minimum; SD = standard deviation.
a: Time from diagnosis to date of Informed Consent/Assent. If the day or month of diagnosis was missing, the day was imputed to be the 1st of the month and the month was imputed to be January. If imputed date is before the birth date, the birth date was used in place of date of diagnosis.

The percentages of subjects who took prior medications were generally similar for the placebo and perampanel groups. The most commonly taken individual concomitant (non-AED) drugs were classified in the therapeutic subclass of analgesics (13.6% placebo, 24.7% perampanel), and paracetamol was the only concomitant medication, other than AEDs, used by at least 10% of subjects in 1 of the treatment groups (6.2% placebo, 12.3% perampanel).

Overall, 33.7% of the subjects in the Safety Analysis Set were taking 1 AED, 46.0% were taking 2 AEDs, and 19.6% were taking 3 AEDs, and the frequency distribution of the number of AEDs taken was similar for the 2 treatment groups. Table 13 summarises the use of specific AEDs at Baseline for the Safety Analysis Set. Among the 6 most frequently used AEDs for the total Safety Analysis Set (lamotrigine, valproic acid, levetiracetam, topiramate, zonisamide, ergenyl chrono), at least a 2-fold imbalance between the 2 treatment groups was seen in the reported use for topiramate (8.5% placebo; 22.2% perampanel) and zonisamide (15.9% and 7.4%, respectively). Inducer AEDs were used by a small percentage of subjects in the perampanel group (11.1%, 9 patients), consistent with general prescribing

practices for PGTC seizures. The use of an inducer AED, however, was higher in the placebo group (22.0%, 18 patients), largely due to an imbalance in the use of carbamazepine (11.0% placebo; 4.9% perampanel).

Table 13 - Anti-Epileptic Drugs at Baseline – Core Study: Safety Analysis Set

Type of Antiepileptic Drug Antiepileptic Drug	Placebo (N=82) n (%)	Perampanel (N=81) n (%)	Combined Total (N=163) n (%)
Inducer[a]	18 (22.0)	9 (11.1)	27 (16.6)
Carbamazepine	9 (11.0)	4 (4.9)	13 (8.0)
Oxcarbazepine	3 (3.7)	2 (2.5)	5 (3.1)
Phenytoin	6 (7.3)	3 (3.7)	9 (5.5)
Non-inducer[a]	73 (89.0)	79 (97.5)	152 (93.3)
Acetazolamide	0	2 (2.5)	2 (1.2)
Clobazam	3 (3.7)	3 (3.7)	6 (3.7)
Clonazepam	10 (12.2)	4 (4.9)	14 (8.6)
Clorazepic Acid	1 (1.2)	0	1 (0.6)
Ergenyl Chrono	7 (8.5)	8 (9.9)	15 (9.2)
Ethosuximide	3 (3.7)	3 (3.7)	6 (3.7)
Gabapentin	3 (3.7)	0	3 (1.8)
Lacosamide	1 (1.2)	3 (3.7)	4 (2.5)
Lamotrigine	31 (37.8)	33 (40.7)	64 (39.3)
Levetiracetam	21 (25.6)	30 (37.0)	51 (31.3)
Lorazepam	3 (3.7)	0	3 (1.8)
Mesuximide	1 (1.2)	0	1 (0.6)
Phenobarbital	2 (2.4)	5 (6.2)	7 (4.3)
Sultiame	1 (1.2)	0	1 (0.6)
Tiagabine	0	1 (1.2)	1 (0.6)
Topiramate	7 (8.5)	18 (22.2)	25 (15.3)
Valproic Acid	28 (34.1)	27 (33.3)	55 (33.7)
Zonisamide	13 (15.9)	6 (7.4)	19 (11.7)

Percentages are based on the total number of subjects in relevant group. Subjects reporting the same AED more than once are counted only once.
AEDs being taken at the date of randomization are included.
AED = anti-epileptic drug.
a: Inducer AEDs include carbamazepine, oxcarbazepine, phenytoin and eslicarbazepine. All other AEDs are non-inducer AEDs.

Treatment compliance was ascertained from counts of tablets dispensed and tablets returned. Mean compliance was ≥99% in both groups. Based on investigator response, 2 subjects in the placebo group were indicated as having an over-compliance rate of >120% at a single visit.

Outcomes and estimation

Primary Efficacy Results (EU): 50% responder rate

Table 14 summarises the primary efficacy results.

Table 14 – PGTC 50% Responder Rate During Maintenance-LOCF – Core Study: FAS

	Placebo (N=81)	Perampanel (N=81)
Responder		
Yes, n (%)	32 (39.5)	52 (64.2)
No, n (%)	49 (60.5)	29 (35.8)
Total	81 (100.0)	81 (100.0)
P value compared to Placebo[a]		0.0019

A responder is a subject who experienced a 50% or greater reduction in seizure frequency per 28 days during Maintenance-LOCF from prerandomization.
LOCF = last observation carried forward; PGTC = primary generalized tonic clonic
a: The *P* value is based on non-missing values and is from a Cochran-Mantel-Haenszel test stratified by pooled country.

The percentage of subjects who experienced a decrease in seizure frequency of at least 50% relative to Baseline was 39.5% in the placebo group and 64.2% in the perampanel group. The p value for the difference from placebo was 0.0019.

The PGTC responder rate results for all sensitivity analyses (PP Analysis Set, Completers Analysis Set, FAS considering discontinuation during the Titration Period as non-responders as well as FAS considering the Titration and Maintenance Periods combined, and Titration Period) were consistent with those for the primary analysis (Maintenance-LOCF).

As neither the primary and the sensitivity analyses took into account the expected loss of efficacy after treatment withdrawal, the CHMP requested that the primary analysis be repeated with all withdrawals counted as non-responders. The results are presented in Table 15. Ten (10) subjects in the placebo arm and thirteen subjects in the perampanel arm did not complete the study. Of these, 3 subjects in the placebo arm and 5 subjects in the perampanel arm were originally classed as responders.

Table 15 – PGTC 50% Responder Rate during Maintenance with Discontinuation as Non-Responders (FAS)

	Placebo (N=81)	Perampanel (N=81)
Responder		
Yes, n (%)	29 (35.8)	47 (58.0)
No, n (%)	52 (64.2)	34 (42.0)
Total	81 (100.0)	81 (100.0)
P-value compared to Placebo		0.0059

Subgroup analyses are presented in Figure 4 to Figure 7. While several of the subgroups were small, the majority of the results showed a larger PGTC responder rate for the perampanel group compared with the placebo group. No inferential analyses of these subgroup results were performed.

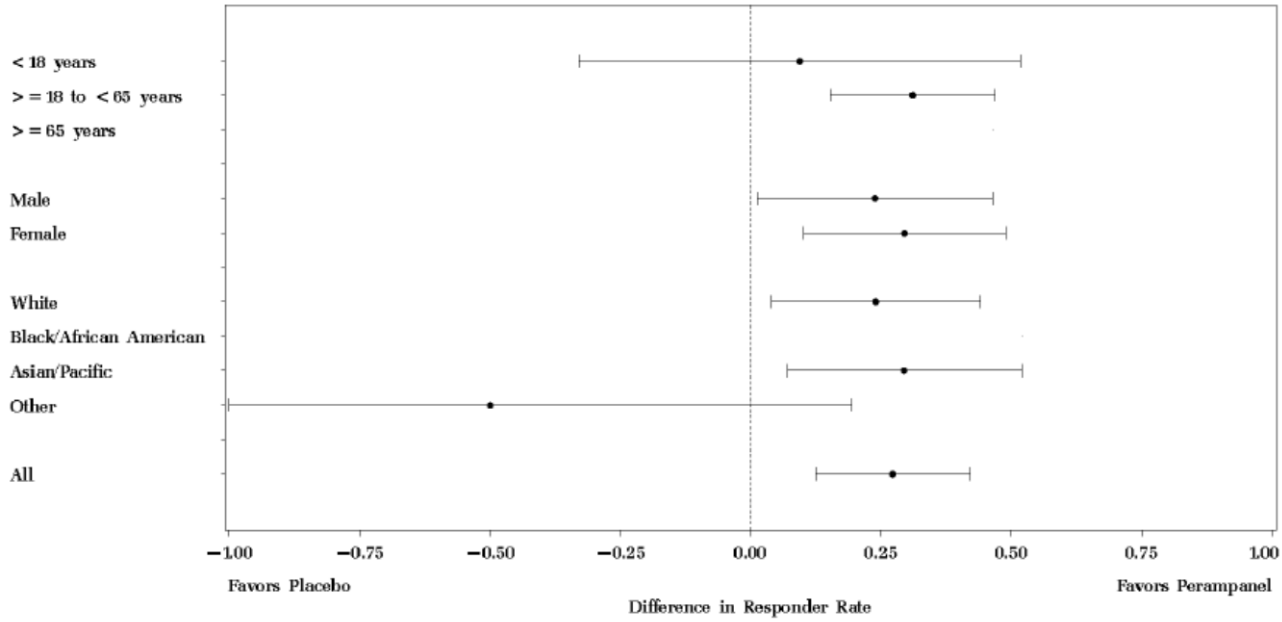


Figure 4 - Forest Plot of Responder Rate, by Age, Sex and Race (FAS)

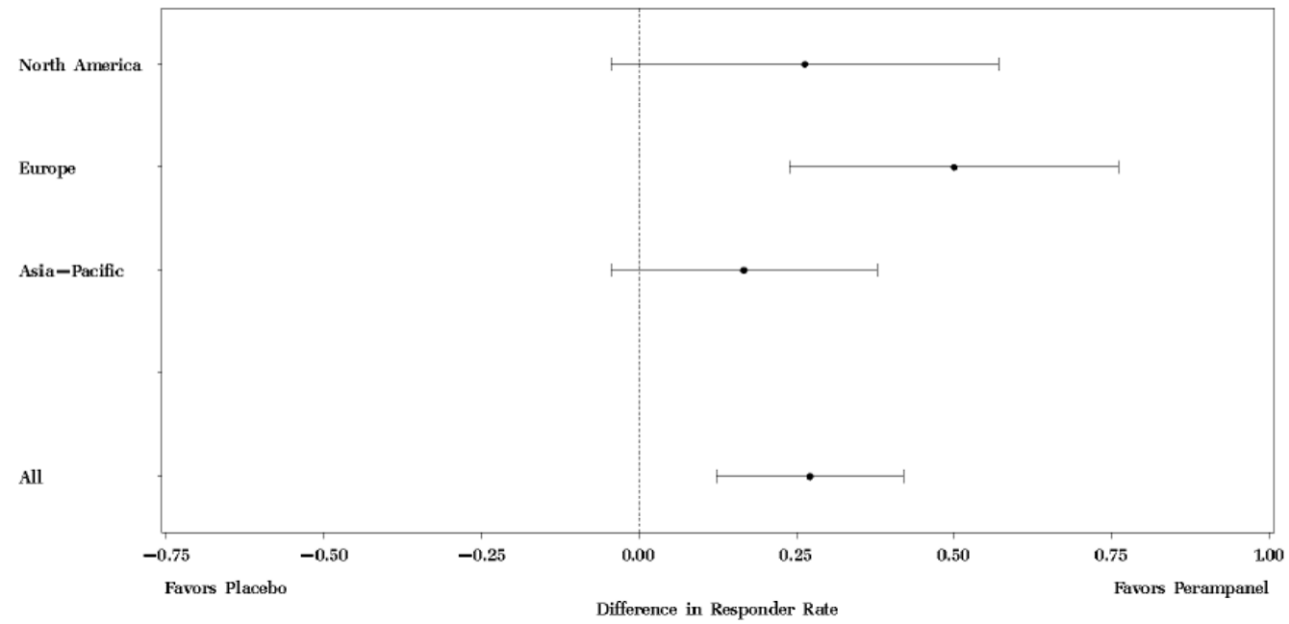


Figure 5 - Forest Plot of Responder Rate, by Region (FAS)

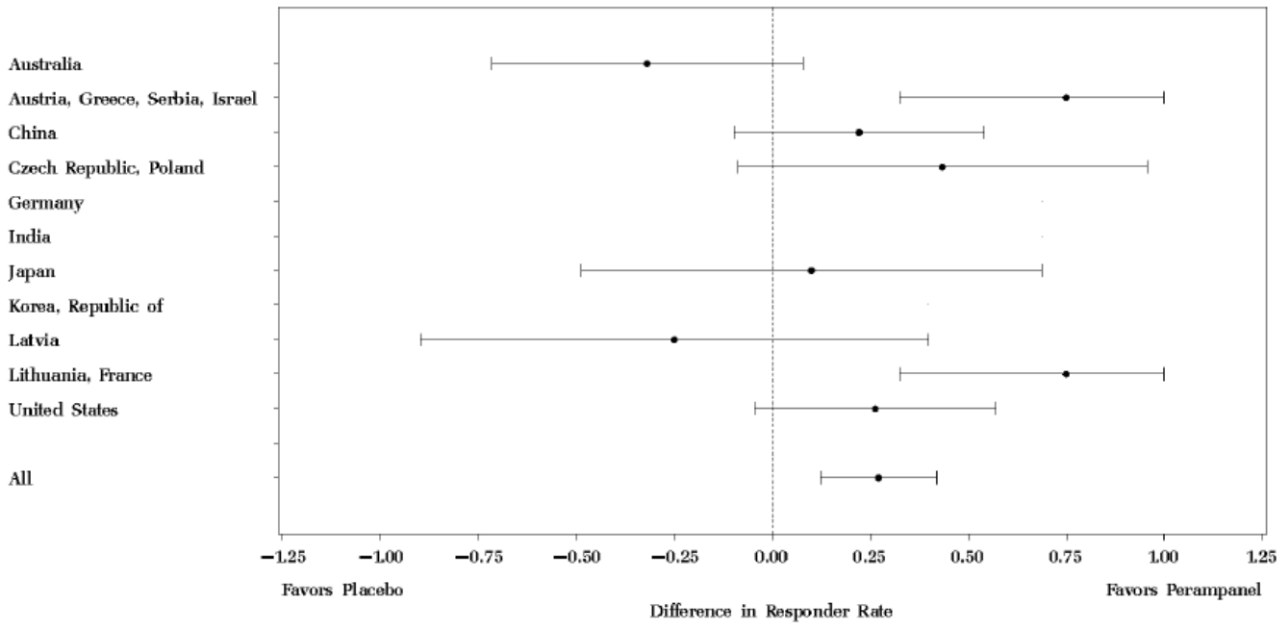


Figure 6 - Forest Plot of Responder Rate, by Pooled Country (FAS)

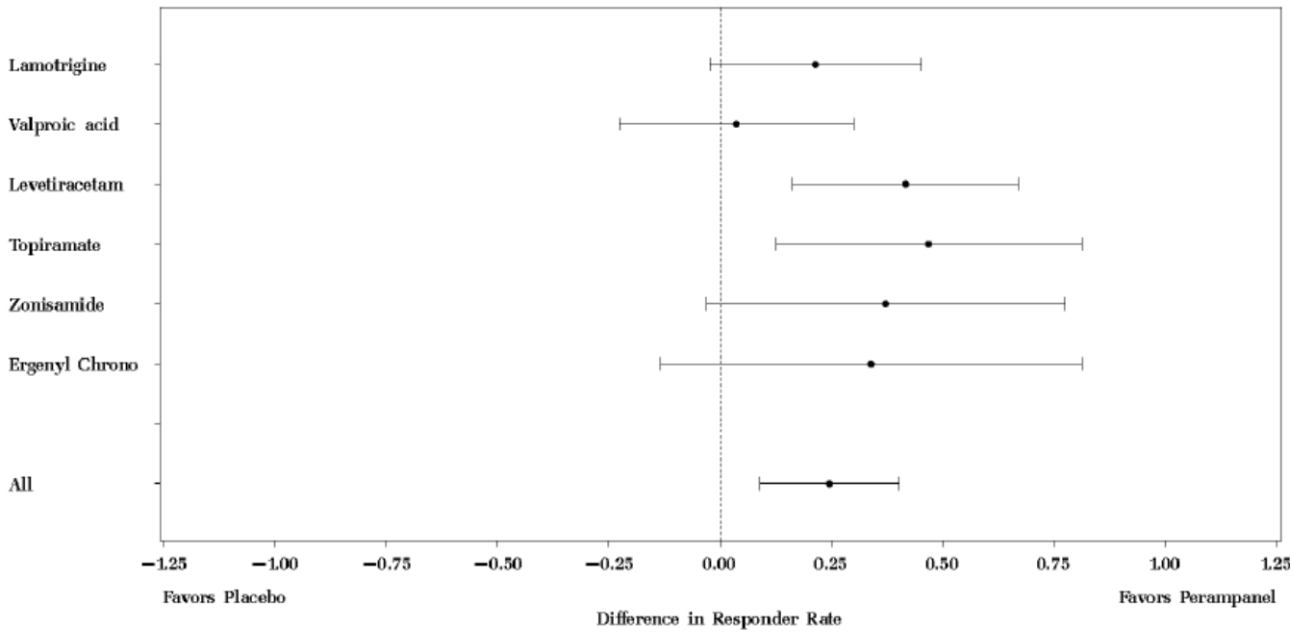


Figure 7 - Forest Plot of Responder Rate, by Baseline AEDs (FAS)

Perampanel was superior to placebo for subjects taking concomitant non-inducer AEDs at Baseline (n=135), while a smaller proportion of perampanel-treated subjects were responders compared to placebo subjects in the subgroup of patients taking concomitant inducer AEDs at Baseline (n=27, 9 patients in the perampanel group and 18 patients in the placebo group). During Maintenance-LOCF, 69.4% of perampanel subjects receiving non-inducer AEDs at Baseline had a reported 50% response, compared with 38.1% of placebo subjects receiving non-inducer AEDs at Baseline. A total of 22.2% of perampanel subjects receiving inducer AEDs at Baseline had a reported response, compared with 44.4% of placebo subjects receiving inducer AEDs at Baseline.

Secondary Efficacy Results

- Main Secondary Endpoint (EU): Percent Change in PGTC Seizure Frequency

Table 16 summarises the percent change in PGTC seizure frequency per 28 days during the Titration and Maintenance Periods (combined) relative to Baseline for the FAS.

Table 16 - PGTC Seizure Frequency per 28 Days and Percent Change During Treatment Summary – Core Study (FAS)

	Placebo (N=81)		Perampanel (N=81)	
Analysis Window Statistic	**Actual**	**Percent Change**	**Actual**	**Percent Change**
Prerandomization Phase				
n	81		81	
Mean (SD)	3.17 (2.000)		3.50 (2.620)	
Median	2.50		2.55	
Min, Max	1.0, 11.7		1.4, 18.5	
Treatment Phase (Titration + Maintenance Periods)				
n	81	81	81	81
Mean (SD)	2.87 (4.740)	-5.85 (184.562)	1.90 (3.303)	-56.88 (50.763)
Median	1.57	-38.38	0.71	-76.47
Min, Max	0.0, 39.1	-100.0, 1546.3	0.0, 22.8	-100.0, 184.5
Median Difference to Placebo[a]				-30.81
(95% Confidence Interval)[a]				(-45.490, -15.244)
P value compared to Placebo[b]				<.0001

Max = maximum; Min = minimum; PGTC = primary generalized tonic-clonic; SD = standard deviation.
a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.
b: The *P* value is based on a rank analysis of covariance with treatment and pooled country as factors, and prerandomization seizure frequency as a covariate.

The median change was -38.38% in the placebo group and -76.47% in the perampanel group. The median treatment difference from placebo was estimated to be -30.81%. Based on rank ANCOVA, the treatment difference was statistically significant (p<0.0001). The median percent change in PGTC seizure frequency at Maintenance-LOCF (FAS) was -37.78% and -74.55% for the placebo and perampanel groups, respectively. The median treatment difference from placebo in this sensitivity analysis was estimated to be -29.63%, and the P value for this difference was <0.0001 (based on rank ANCOVA).

Results for all other sensitivity analyses were consistent with those of the primary analysis and showed that the median percent reduction in PGTC seizure frequency per 28 days during the Titration and Maintenance Periods (combined) relative to Baseline was larger in the perampanel group compared to the placebo group. The estimated median treatment differences from placebo in the PP and Completers Analysis Sets were -29.52% and -30.81%, respectively (p<0.0001 for both sensitivity analyses).

In the subgroup analyses, while several of the subgroups were small, results were generally consistent in showing a larger median percent change in PGTC seizure frequency over the Titration and Maintenance

Periods of the Core Study for perampanel group compared with the placebo. No inferential analyses of these subgroup results were performed.

- Percent Change in All Seizure Frequency

The median percent change in the frequency of all seizures (ie, any type, including PGTC, myoclonic, absence, tonic, and atonic seizures) during the Titration and Maintenance Periods for the FAS was larger for the perampanel group with -43.40% than for the placebo group with -22.87%. The estimated median treatment difference from placebo was -23.45%, and the p value for this difference, based on rank ANCOVA, was 0.0018.

Table 17 - All Seizure Frequency per 28 Days and Percent Change During Treatment – Core Study (FAS)

	Placebo (N=81)		Perampanel (N=81)	
Analysis Window Statistic	**Actual**	**Percent Change**	**Actual**	**Percent Change**
Prerandomization Phase				
n	81		81	
Mean (SD)	33.63 (97.013)		64.39 (197.677)	
Median	4.58		5.50	
Min, Max	1.3, 589.5		1.4, 1404.5	
Treatment Phase (Titration + Maintenance Periods)				
n	81	81	81	81
Mean (SD)	30.21 (85.174)	-13.06 (57.098)	44.89 (121.933)	-9.26 (192.142)
Median	3.29	-22.87	3.29	-43.40
Min, Max	0.0, 498.6	-100.0, 125.7	0.0, 687.9	-100.0, 1366.7
Median Difference to Placebo[a]				-23.45
(95% Confidence Interval)[a]				(-40.668, -8.518)
P value compared to Placebo[b]				0.0018

All Seizures includes PGTC, myoclonic, absence and all other seizures that occur during the study.
Max = maximum; Min = minimum; PGTC = primary generalized tonic-clonic; SD = standard deviation.
a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.
b: The *P* value is based on a rank analysis of covariance with treatment and pooled country as factors, and prerandomization seizure frequency as a covariate.

- Percent Change in Frequency of Primary Generalized Seizure Subtypes

Only a subset of subjects in the FAS experienced absence (60/162, 37.0%) or myoclonic (47/162, 29.0%) seizures during the Pre-randomisation Phase and were included in the analyses. The median percent change in absence seizures was higher for the perampanel group (-41.18%) compared with the placebo group (-7.58%), but the difference did not reach statistical significance (p=0.3478).

For myoclonic seizures, the median percent change was -52.54% for the placebo group and -24.47% for the perampanel group (p=0.6100).

Table 18 - Frequency of Absence and Myoclonic Seizures per 28 Days and Percent Change During Treatment– Core Study (FAS)

	Placebo (N=81)		Perampanel (N=81)	
Subtype Analysis Window Statistic	**Actual**	**Percent Change**	**Actual**	**Percent Change**
Absence				
Prerandomization Phase				
n	33		27	
Mean (SD)	56.67 (138.250)		105.90 (281.325)	
Median	8.15		13.00	
Min, Max	0.4, 572.0		0.4, 1403.0	
Treatment Phase (Titration + Maintenance Periods)				
n	33	33	27	27
Mean (SD)	47.64 (110.305)	8.46 (130.838)	70.03 (136.874)	315.37 (1567.848)
Median	8.96	-7.58	13.76	-41.18
Min, Max	0.0, 498.6	-100.0, 592.4	0.0, 607.3	-100.0, 8088.2
Median Difference to Placebo[a]				-12.25
(95% Confidence Interval)[a]				(-53.054, 26.989)
P value compared to Placebo[b]				0.3478
Myoclonic				
Prerandomization Phase				
n	23		24	
Mean (SD)	24.35 (53.974)		85.73 (191.259)	
Median	3.50		13.75	
Min, Max	0.5, 250.5		0.5, 719.9	
Treatment Phase (Titration + Maintenance Periods)				
n	23	23	24	24
Mean (SD)	25.80 (75.494)	-18.39 (101.154)	65.71 (140.778)	9.23 (131.106)
Median	1.32	-52.54	12.22	-24.47
Min, Max	0.0, 359.5	-100.0, 321.2	0.0, 543.0	-100.0, 482.4
Median Difference to Placebo[a]				24.87
(95% Confidence Interval)[a]				(-15.338, 59.938)
P value compared to Placebo[b]				0.6100

Max = maximum; Min = minimum; SD = standard deviation.

a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

b: The *P* value is based on a rank analysis of covariance with treatment and pooled country as factors, and prerandomization seizure frequency as a covariate.

- Responder Rate for Total Seizures

The responder rate for all seizures (ie, any type, including PGTC, absence, myoclonic, tonic, and atonic seizures) during the Maintenance Period-LOCF for the FAS was numerically higher for the perampanel group (45.7%) than for the placebo group (34.6%). The comparison with placebo was not statistically significant (p=0.1826).

- Responder Rate for Primary Generalized Seizure Subtypes

The 50% responder rate for absence seizures during the Maintenance-LOCF period was 39.4% in the placebo group and 48.1% in the perampanel group. The 50% responder rate for myoclonic seizures was 60.9% (placebo) and 41.7% (perampanel). The p values for the comparison with placebo were 0.4653 for absence seizures and 0.3694 for myoclonic seizures.

Exploratory Efficacy Results

- Time To nth +1 PGTC Seizure Event

The median time to an nth +1 (Pre-randomisation Frequency per 28 Days Plus 1) PGTC seizure event was 43.0 days for the placebo group but was not estimable for the perampanel group as fewer than 50% of subjects in this group experienced a PGTC seizure event. The p value for the comparison with placebo was <0.0001.

- Clinical Global Impression of Change (CGI-C)

At Week 12, 32.9% of the subjects (25/76) in the placebo group and 39.2% of subjects (29/74) in the perampanel group were considered 'much improved' or 'very much improved' by the investigators; the remaining subjects were rated 'minimally improved' to 'much worse'. The p value for the comparison with placebo in the distribution of CGI-C ratings was 0.5639.

Other Efficacy Endpoints

- Categorized Percent Change in PGTC Seizure Frequency

Nearly one-half of subjects in the perampanel group (39/81, 48.1%) had a decrease in PGTC seizure frequency between 75% and 100% compared with 23.5% (19/81) of subjects in the placebo group. The percentage of subjects experiencing an increase in PGTC seizure frequency during the Titration and Maintenance Periods was nearly 3-fold higher for the placebo group (23/81, 28.4%) compared with the perampanel group (8/81, 9.9%).

- Percentage of Subjects who Achieved Seizure-free Status

Among all subjects in the FAS, nearly one-third of subjects in the perampanel group (30.9%, 25/81), compared with 12.3% (10/81) of those in the placebo group, achieved PGTC seizure-free status during the Maintenance Period. Similarly, the percentage of subjects in the FAS who achieved total seizure-free status during the Maintenance Period was substantially higher for the perampanel group compared with the placebo group [4.9% (4/81) placebo vs 23.5% (19/81) perampanel]. In patients with concomitant myoclonic seizures, seizure freedom was reached in 16.7 % (4/24) of perampanel patients compared with 13.0 % (3/23) on placebo, and for concomitant absence seizures, seizure freedom was reached in 22.2% (6/27) of perampanel patients compared with 12.1% (4/33) on placebo.

Similar treatment differences were seen among the subset of subjects who completed the Maintenance Period, with an approximately 3-fold higher percentage of subjects in the perampanel group compared with the placebo group achieving PGTC seizure-free status (36.8% vs 13.9%, respectively) and an approximately 5-fold higher percentage of subjects in the perampanel compared to the placebo group achieving total seizure-free status (27.9% vs 5.6%, respectively). In patients with concomitant absence seizures, seizure freedom was reached in 18.2 % of perampanel patients compared with 13.6 % on placebo, and for concomitant absence seizures, seizure freedom was reached in 28.6 % of perampanel patients compared with 13.8 % on placebo.

- Patient-Weighted Quality of Life in Epilepsy Inventory-31 (QOLIE-31-P)

The median overall QOLIE-31-P score did not differ between placebo and perampanel subjects at Baseline (median scores of 58.09 and 55.48, respectively). The median absolute and percent change in the overall QOLIE-31-P score at Week 17 (end of Maintenance Phase) indicated an improvement in the perampanel group (+3.3 and +4.79% absolute and percent median change, respectively) compared with a worsening in the placebo group (median absolute and percent changes of -1.2 and -1.36%, respectively). Numerically higher median absolute and percent improvements from Baseline at Week 17 were also observed in the perampanel group compared with the placebo group for the following individual QOLIE-31-P domains: Daily Activities (0.0 absolute and 0.00% for placebo group versus +5.0 absolute and

+26.58% for perampanel group), Cognition (+3.1 and +5.83% for placebo versus +4.2 and +32.79% for perampanel), and Distress (0.0 and 0.00% for placebo versus +3.6 and +5.88% for perampanel). For the remaining domains, there were no apparent differences in the median absolute or percent change scores at Week 17 between the perampanel and placebo groups.

- Healthcare Resource Utilization

At Week 17, a smaller percentage of subjects in the perampanel group reported at least 1 emergency room visit since Baseline compared with the placebo group (12.2% placebo, 2.5% perampanel). The percentage of subjects reporting an unscheduled physician visit since Baseline was similar for the placebo and perampanel groups (4.9% and 6.2%, respectively), as was the median number of visits resulting in hospitalisation per 28 days since Baseline (0.00 and 0.00, respectively).

2.4.2.2. Study E2007-G000-332 Extension Phase

Methods

See section 2.4.2.1. for a description of the methods in Core Study 332.

Objectives: The purpose of the Extension Phase was to evaluate the long-term safety, tolerability, and efficacy of perampanel in subjects with PGTC seizures.

Main Criteria for Inclusion:

Male and female subjects were eligible to participate in the Extension Phase if they completed Visit 8 (Week 17, end of maintenance phase) of the Core Study, continued to be treated with a stable dose of 1 to a maximum of 3 approved AEDs; were able to record seizure information in diaries and report AEs (or had a legal guardian who was able to perform these duties) and for females of childbearing potential, had a negative urine pregnancy test at Visit 8 of Core Study and were willing to commit to the consistent and correct use of a medically-acceptable method of contraception for the duration of the study and for at least 30 days after administration of the last dose of study drug.

The number of subjects planned for the extension phase was up to 164 subjects from the Core Study.

Study treatment: Perampanel was supplied as 2 mg or 4 mg tablets. All doses were taken once daily, by mouth, before bedtime, and with food.

Efficacy endpoints and statistical analysis:

The key efficacy endpoints included the percent change in seizure frequency (PGTC and all seizures types) per 28 days during treatment relative to Baseline as well as the proportion of subjects who experienced a 50% or greater reduction in PGTC and total seizure frequency during treatment per 28 days relative to Baseline (responder).

Efficacy analyses were based on the Full Analysis Set (FAS), which comprised all subjects who were eligible to participate in the Extension Phase, received at least 1 dose of perampanel in this phase, and had Baseline seizure frequency data and at least 1 observation of valid seizure diary data during the perampanel treatment duration. Safety analyses were based on the Safety Analysis Set, defined as subjects who received at least 1 dose of perampanel in the Extension Phase and had any on-therapy safety data during this phase (results of the Safety evaluations for this study are presented in the safety section of this assessment report).

Two general approaches were used to analyse efficacy data. The first examined seizure data during the perampanel treatment duration and used the Pre-perampanel Baseline for comparison. The Pre-perampanel Baseline was defined as follows: (i) for subjects who had been assigned to placebo treatment in the Core Study, the Pre-perampanel Baseline was computed from all valid seizure diary data during the

Core Study, and (ii) for subjects who had been assigned to perampanel in the Core Study, the Pre-perampanel Baseline was computed from all valid seizure diary data during the Pre-randomisation Phase plus the 4 weeks prior to the Pre-randomisation Phase of the Core Study. The second approach examined seizure data as a function of randomised treatment group in the Core Study and used the Pre-randomisation Phase of the Core Study as the Baseline for evaluating change. For all efficacy analyses, the perampanel treatment duration consisted of: (i) the Randomisation Phase of the Core Study plus the Extension Phase for subjects assigned to perampanel in the Core Study, and (ii) the Extension Phase for subjects assigned to placebo in the Core Study.

Results

In total, 140 subjects completed the Core Study and were eligible to enter the Extension Phase. Of these, 114 subjects entered the Extension Phase (58 placebo, 56 perampanel) as of the cut-off date for the report submitted by the MAH, representing 81.4% of the 140 subjects who completed the Core Study. All 114 subjects in the Extension Phase received at least 1 dose of perampanel and were included in the Safety Analysis Set.

Table 19 – Subject Disposition and Primary Reason for Discontinuation from Study by Modal Daily Perampanel Dose – Extension Phase (Safety Analysis Set)

	Modal Daily Perampanel Dose				
Category	<4 mg/day (N=4)	4 mg/day (N=7)	>4 to 8 mg/day (N=84)	>8 to 12 mg/day (N=19)	Total (N=114)
Treated, n (%)	4 (100.0)	7 (100.0)	84 (100.0)	19 (100.0)	114 (100.0)
Completed Extension Phase, n (%)	0	0	1 (1.2)	0	1 (0.9)
Discontinued from Extension Phase, n (%)	0	1 (14.3)	10 (11.9)	5 (26.3)	16 (14.0)
Ongoing in Extension Phase, n (%)	4 (100.0)	6 (85.7)	73 (86.9)	14 (73.7)	97 (85.1)
Primary reason for discontinuation[a], n (%)					
Adverse event	0	1 (14.3)	3 (3.6)	3 (15.8)	7 (6.1)
Lost to follow-up	0	0	0	0	0
Subject choice	0	0	2 (2.4)	1 (5.3)	3 (2.6)
Inadequate therapeutic effect	0	0	4 (4.8)	0	4 (3.5)
Withdrawal of consent	0	0	0	1 (5.3)	1 (0.9)
Pregnancy	0	0	1 (1.2)	0	1 (0.9)
Other	0	0	0	0	0

Percentages are based on the number of subjects enrolled and treated in the relevant treatment group.
a: As reported on the Subject Disposition Extension Phase CRF.
CRF = case report form, N = total number of subjects, n = number of subjects with characteristic

The demographic and Baseline epilepsy-specific characteristics for the FAS did not differ as a function of previous treatment in the Core Study with placebo or perampanel.

In total, 36.8% of subjects in the Safety Analysis Set were taking 1 AED, 47.4% were taking 2 AEDs, and 15.8% were taking 3 AEDs at Core Study Baseline, and the most common AEDs taken were lamotrigine (40.4%), valproic acid (32.5%), levetiracetam (27.2%), topiramate (14.9%), ergenyl chrono (10.5%), and zonisamide (10.5%); all other background AEDs were taken by less than 10% of subjects. Of note, 11 subjects (9.6%) were taking carbamazepine, 7 (6.1%) were taking phenytoin, and 5 (4.4%) were taking oxcarbazepine during the Extension Phase.

Treatment compliance, ascertained from counts of tablets dispensed and tablets returned, averaged approximately 98.2% across the entire Extension Phase (mean of 97.7% for blinded Conversion Period and 100.0% for Maintenance Period) for the FAS.

Outcomes and estimation

Efficacy Relative to Pre-perampanel Baseline

The following table summarises the median percent change from the Pre-perampanel Baseline in seizure frequency per 28 days by 13-week interval through Weeks 92 to 104 (end of Year 2).

Table 20 - Summary of Percent Change from Pre-perampanel Baseline in Seizure Frequency per 28 Days and Responder Analysis During Perampanel Treatment Duration – Extension Phase (FAS)

Analysis window/ Statistic	Seizure Type	
	PGTC Seizures	All Seizures
Pre-perampanel – n	114	114
Median seizure frequency	2.39	4.64
Perampanel Treatment Duration		
Weeks 1-13 – n	114	114
Median % change	-84.29	-57.15
Responder rate, n (%)	78 (68.4)	62 (54.4)
Weeks 14-26 – n	94	94
Median % change	-71.20	-63.69
Responder rate, n (%)	67 (71.3)	61 (64.9)
Weeks 27-39 – n	68	68
Median % change	-78.95	-76.33
Responder rate, n (%)	47 (69.1)	45 (66.2)
Weeks 40-52 – n	44	44
Median % change	-81.74	-83.80
Responder rate, n (%)	29 (65.9)	33 (75.0)
Weeks 53-65 – n	34	34
Median % change	-100.00	-90.65
Responder rate, n (%)	27 (79.4)	31 (91.2)
Weeks 66-78 – n	11	11
Median % change	-100.00	-80.46
Responder rate, n (%)	10 (90.9)	9 (81.8)
Weeks 79-91 – n	9	9
Median % change	-100.00	-82.05
Responder rate, n (%)	9 (100.0)	9 (100.0)
Weeks 92-104 – n	1	1
Median % change	-100.00	-83.64
Responder rate, n (%)	1 (100.0)	1 (100.0)

Week 1 begins on the date of first dose of perampanel treatment duration. The perampanel treatment duration starts from the first perampanel dose in the Core Study or Extension Phase and continues to and includes the date of the last dose of perampanel in the Extension Phase. In Part B of the Extension Phase (after Visit 15), the seizure diary was only completed for days on which a seizure occurred. For purposes of the analysis, zero was imputed for non-seizure days. For any given analysis window and seizure type(s), a 50% responder from pre-perampanel is a subject whose seizure frequency per 28 days for that seizure type(s) during that analysis window is 50% to 100% lower than the pre-perampanel baseline seizure frequency per 28 days for that same seizure type(s).
n = number of subjects with event, PGTC = primary generalized tonic-clonic.

Data for age, sex, and race subgroups were generally consistent with those for the overall population in showing a similar stable pattern over time of improvement in PGTC seizure control as reflected by the median percent change in seizure frequency and responder rate.

Efficacy Relative to Core Study Pre-randomisation Phase

The following table summarizes, by previous treatment group (placebo or perampanel), the median percent change in PGTC seizure frequency per 28 days and the percentage of PGTC responders for the Core Study Maintenance Period (when dose was stable), the blinded Conversion Period of the Extension Phase, and by 13-week intervals through Weeks 79 to 91 for the Maintenance Period of the Extension Phase.

Table 21 - Percent Change from Core Study Pre-randomisation Phase in PGTC Seizure Frequency per 28 days and Responder Rate – Extension Phase (FAS)

Analysis Window Parameter	Median Percent Change in Total Seizure Frequency		Responder Rate (n, %)	
	Prior Placebo	Prior Perampanel	Prior Placebo	Prior Perampanel
Seizure Freq. – Prerandomization Phase, n	58	56	58	56
Median	2.50	2.50		
Core Study Maintenance Period, n	58	56	58	56
Median % change or responder rate, n (%)	-41.68	-85.87	23 (39.7)	38 (67.9)
Extension Conversion Period, n	58	56	58	56
Median % change or responder rate, n (%)	-100.00	-100.00	42 (72.4)	42 (75.0)
Extension Maintenance Weeks 1-13, n	47	45	47	45
Median % change or responder rate, n (%)	-79.49	-82.42	34 (72.3)	33 (73.3)
Extension Maintenance Weeks 14-26, n	29	34	29	34
Median % change or responder rate, n (%)	-69.23	-85.91	20 (69.0)	28 (82.4)
Extension Maintenance Weeks 27-39, n	20	27	20	27
Median % change or responder rate, n (%)	-83.52	-100.00	14 (70.0)	19 (70.4)
Extension Maintenance Weeks 40-52, n	9	8	9	8
Median % change or responder rate, n (%)	-100.00	-100.00	6 (66.7)	8 (100.0)
Extension Maintenance Weeks 53-65, n	9	8	9	8
Median % change or responder rate, n (%)	-100.00	-100.00	8 (88.9)	7 (87.5)
Extension Maintenance Weeks 66-78, n	1	2	1	2
Median % change or responder rate, n (%)	-17.95	-100.00	0	2 (100.0)
Extension Maintenance Weeks 79-91, n	1	1	1	1
Median % change or responder rate, n (%)	-100.00	-100.00	1 (100.0)	1 (100.0)

Extension Maintenance Week 1 begins on the date of first dose of the perampanel treatment duration, which starts on the date of the first dose of perampanel in either the Core Study or Extension Phase and continues to and includes the date of the last dose of perampanel in the Extension Phase. In Part B of the Extension Phase (after Visit 15), the seizure diary is only completed for days on which a seizure occurred. For purposes of the analysis, zero was imputed as non-seizure days.
For any given analysis window and seizure type(s), a 50% responder from Core Study Prerandomization is a subject whose seizure frequency per 28 days for that seizure type(s) during that analysis window is 50% to 100% lower than the Core Study Prerandomization baseline seizure frequency per 28 days for that same seizure type(s).
freq = frequency, PGTC = primary generalized tonic-clonic, n = number of subjects with event.

By the end of the blinded Conversion Period of the Extension Phase, subjects who had received prior treatment with placebo showed similar efficacy as subjects who received previous treatment with perampanel.

Ancillary analyses

Not applicable.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. These summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22 – Summary of Efficacy for trial E2007-G000-332

Title: A Double-Blind, Randomised, Placebo-Controlled, Multicentre, Parallel-Group Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Adjunctive Perampanel in Primary Generalized Tonic-Clonic Seizures			
Study identifier	E2007-G000-332 (Study 332) EudraCT Number: 2011-000265-12		
Design	Multicentre, randomised, double-blind, placebo-controlled, parallel-group, adjunctive-therapy study		
	Duration of main phase:		Maintenance (13 weeks)
	Duration of Run-in phase:		Pre-randomisation phase: Screening (up to 4 weeks) and Baseline (4 or 8 weeks) Titration: 4 weeks
	Duration of Extension phase:		Follow-up (4 weeks; only for those subjects not entering into the Extension Phase). Extension Phase: Part A (6-week blinded Conversion Period + 32-week Maintenance and Part B (maximum of 104 weeks Maintenance)
Hypothesis	Superiority of perampanel compared to placebo in the adjunctive treatment of PGTC seizures		
Treatments groups	Perampanel		Once daily oral intake of the highest tolerated dose with a maximum of 8mg/day perampanel (2mg tablets), 4 weeks titration in 2mg/week increments, 13 weeks maintenance, 82 patients randomised (81 in FAS)
	Placebo		Once daily oral intake of placebo tablets over 17 weeks (titration and maintenance), 82 patients randomised (81 in FAS)
Endpoints and definitions	Primary endpoint	50% responder rate	Responders were defined as subjects who experienced a 50% or greater reduction in PGTC seizure frequency per 28 days in the Maintenance Period relative to Baseline (Pre-randomisation Phase).
	Secondary endpoint	% change in PGTC seizure frequency	Percent change in PGTC seizure frequency was calculated per 28 days over the Titration and Maintenance Periods combined compared to Baseline (Pre-randomisation Phase).
Database lock	27 May 2014 (last subject visit)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary analysis was performed on the intent to treat population (full analysis set; FAS) at Week 17 (end of Maintenance Period)		
Descriptive statistics and estimate variability	**Treatment group**	**Placebo**	**Perampanel**
	Number of subject	**81**	**81**
	50% responders, n (%) [a)]	29 (35.8%)	47 (58.0%)

	% change PGTC seizure frequency (median % change) [b)]	-38.38	-76.47
	Min, Max	-100.0, 1546.3	-100.0, 184.5
Effect estimate per comparison	Primary endpoint: 50% responder rate	Comparison groups	Perampanel versus placebo
		P-value [a)]	0.0059
	Secondary endpoint: % change PGTC seizure frequency	Comparison groups	Perampanel versus placebo
		Median difference [b)]	-30.81
		95% Confidence Interval	-45.490; -15.244
		P-value	<0.001
Notes	[a)] For the primary endpoint, the results presented refer to a re-analysis requested by CHMP with all withdrawals counted as non-responders. [b)] Due to an expected irregular distribution of PGTC seizure frequency, median was the primary statistic of interest for this endpoint. Hodges-Lehmann estimator and 95% confidence interval (CI) for this estimator were displayed for understanding the treatment effect size.		
Analysis description	The **responder analysis** was carried out using a Cochran- Mantel-Haenszel (CMH) test stratified by country in the FAS. In the Maintenance-LOCF analysis, if a subject had less than 8 weeks of Maintenance Period, the PGTC seizure frequency during the last 8 weeks of the Titration and Maintenance Periods combined (or PGTC seizure frequency during the Titration and Maintenance Periods combined for subjects with less than 8 weeks of Titration and Maintenance Periods combined) was used to impute. The **percent change in seizure frequency** was based on the PGTC seizure frequency per 28 days (as determined from subject diaries), which was calculated as the number of PGTC seizures divided by the number of days in the interval and multiplied by 28. Analysis was conducted using rank analysis of covariance (ANCOVA) with treatment and country as factors, and the Baseline PGTC seizure frequency as a covariate. In this analysis, all PGTC seizure frequency data was first rank-transformed for both Baseline and endpoint PGTC seizure frequencies separately. The ANCOVA was then conducted based on the rank transformed data.		

2.4.3. Discussion on clinical efficacy

The efficacy assessment for the proposed new indication relied on one single phase III trial, Core Study 332, which involved 164 patients with inadequately controlled PGTC seizures despite the use of 1-3 concomitant AEDs. Supportive data for long-term efficacy was available from the Extension Phase of Core Study 332.

Design and conduct of clinical studies

The general design of the study was acceptable. The selection criteria for the study population were considered appropriate, as was the choice of the endpoints, which were in line with the Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/Rev.2/Corr). With regards to the study population, patients were included based on a clinical diagnosis of PGTC seizures in the setting of idiopathic generalized epilepsy (IGE). The CHMP was therefore of the opinion that the proposed indication of adjunctive treatment of PGTC seizures in patients with epilepsy aged 12 years and older should be amended to clearly refer to patients with IGE in order to correctly reflect the population studied.

The length of all study phases was appropriate including the maintenance phase at 13 weeks. However, the study design did now allow examining whether the patients had a steady rate of seizures or if the frequency was on increase or decrease. The natural variation in the frequency of seizures could have decreased the statistical differentiation of the treatment groups and rendered the results not-significant.

However, the CHMP considered that there was no evidence that this would introduce a systemic bias in favour of one treatment and thus did not further pursue the issue.

The treatment regimen applied in the study was in line with the approved posology for POS. Adjustment of the dose in the maintenance phase as described in the protocol was considered acceptable.

With regards to the EU primary endpoint (50% responder rate), the CHMP was of the view that the analyses defined in the protocol might overestimate the true benefit of treatment as subjects that withdrew during the maintenance phase could still be counted as responders. In order to more accurately estimate the proportion of subjects that continue to benefit from treatment at the end of the maintenance phase, all withdrawals should be counted as non-responders. With regards to the key secondary endpoint (% change in PGTC seizure frequency), since the seizure frequency was expected to follow a skewed distribution, the focus on the median rather than the mean was endorsed by the CHMP. For the same reason the analysis using ranks rather than raw values was accepted.

The CHMP furthermore noted that the FAS should in principle include all patients treated, regardless of whether they had post-Baseline assessments, as the reason for missing the assessments could be treatment related, e.g. due to adverse events. However in the Core Study only one subject was excluded for this reason and this subject belonged to the placebo arm. Thus, no major impact on the study results was to be expected.

The number of subjects in both treatment arms were similar. The rates of discontinuations especially due to adverse events were higher in the active group. However, due to the limited number of such cases it was not possible to statistically analyse these differences and to reach reliable conclusions. At the same time, the lack of therapeutic effect was more frequently the reason for discontinuation of patients in the placebo group and again the number of cases was too small for reliable statistical analysis.

Age distribution showed that the principal percentage of the study subjects were between ≥20 to <40 years old (61.8%) and 22.2% of patients were aged <20 years. This distribution was in line with the distribution in clinical practice of PGTC seizures, which are more frequent at the end of childhood and early adulthood. As the population PK analysis (section 2.3.2.) showed no effect of age on the CL/F, the CHMP considered that the current recommendation that there was no need for dose adjustment in the elderly in SmPC section 4.2 could be maintained. However, the lack of data for perampanel use in patients ≥65 years with PGTC seizures should be reflected in SmPC section 5.2 by providing the age range investigated, i.e. 12 to 58 years.

Concomitant Baseline medication included up to 3 other AEDs and the CHMP noted that such high number of concomitant treatments could potentially cause problems with interactions that may have an impact on the study outcome. However, since the interaction potential with other AEDs was relatively well known for perampanel and since the use of enzyme-inducing AEDs was limited in Core Study 332, the issue was not further pursued.

Use of concomitant AEDs by treatment arms showed an imbalance for topiramate and zonisamide in that topiramate was used by more patients in the perampanel group and zonisamide by more patients in the placebo group. Furthermore, an imbalance was noted in the use of inducer AEDs, which was higher in the placebo group (22.0%) compared to the perampanel group (11.1%), largely due to carbamazepine (11.0% placebo; 4.9% perampanel). The possible impact on the efficacy outcome is discussed below (see ‘efficacy data and additional analyses’).

Baseline seizure types and frequency was balanced between the treatment arms. The actual Baseline frequency of all seizures was higher in the perampanel group due to higher frequency of other types of seizures, while PGTC frequencies were similar between the groups. This imbalance of other seizure types might indicate a difference in the severity and clinical manifestation of the illness between the groups. To address this concern, the MAH performed a number of subgroup analyses which demonstrated that the

differences in the Baseline characteristics were not likely to exhibit any important influence on the results. Using a regression model to adjust for the effect of Baseline PGTC seizure frequency, treatment effect was still significant.

Efficacy data and additional analyses

The results of Core Study 332 showed that adjunctive therapy with perampanel at maximum daily doses of 8 mg was superior to placebo in decreasing the frequency of PGTC seizures in IGE patients with previously inadequately controlled seizure levels. In the perampanel group, the proportion of responders with 50% or more reduction in the seizure frequency compared to Baseline (primary endpoint) was significantly higher than in the placebo group. When withdrawals were counted as non-responders, the 50% responder rate was 58.0% (47/81) in the perampanel arm versus 35.8% (29/81) in the placebo group (p=0.0059). Furthermore, with regards to the key secondary endpoint, perampanel treatment reduced PGTC seizure frequency from a median of 2.55 seizures per 28 days at Baseline to 0.71 seizures per 28 days during the treatment phase (median % reduction of -76.5%). In the placebo arm, the PGTC seizure frequency was reduced from a median of 2.50 to 1.57, corresponding to an improvement of 38.4%. The difference between study arms was statistically significant with -30.8% in favour of perampanel. The CHMP considered these findings clinically relevant.

The findings of the primary and secondary efficacy analyses were confirmed in sensitivity analyses using different analysis populations. Logistic regression analysis of the primary endpoint, performed in response to a CHMP request, adjusting for concomitant treatment, pooled country, Baseline PGTC seizure frequency, Baseline absence seizure frequency, Baseline myoclonic seizure frequency, inducer AED status, number of background AEDs, treatment by inducer AED status interaction and treatment by number of background AEDs interaction resulted on the term for treatment being not statistically significant. However, when the logistic regression was re-run using forward selection for all terms, but including interaction terms, the treatment effect was confirmed to be statistically significant, which was considered sufficiently reassuring by the CHMP.

Results for the 50% responder rate for the subgroup of patients receiving concomitant enzyme-inducing AEDs suggested inferiority of perampanel compared to placebo. However, the size of the subgroup was very limited (only 9 patients treated with perampanel) and the study protocol required capping of the dose at 8 mg/day which could have prevented patients from receiving an optimal therapeutic dose. When combining perampanel data from all subjects on inducers who entered the Extension Phase of study 332 (n=23, including patients receiving placebo in the Core Study) who were allowed a more flexible dose adjustment of up to 12 mg (3 subjects on 12 mg and 1 on 10 mg), the results showed consistent and similar improvements over time for patients on either concomitant inducer or non-inducer AEDs.

Subgroup analyses of the responder rates by concomitant AED treatment furthermore showed a pronounced effect of perampanel in the topiramate subgroup. As topiramate was given more frequently in patients in the perampanel group compared to placebo, it was questioned if this imbalance could have driven the study outcome in favour of perampanel. Logistic regression analyses however did not reveal a significant effect of topiramate on the perampanel treatment response. The same result was found for zonisamide for which as well an imbalance between treatment groups was present at Baseline. Following this additional information the CHMP considered the issue to be resolved.

Finally, subgroup analyses for the responder rate and change in seizure frequency suggested that European patients had significantly better results in favour of perampanel compared to their North American and Asia-Pacific counterparts. However, additional regression analyses with region as covariate did not show statistically significant correlations.

The efficacy of perampanel in reducing PGTC seizure frequency was further supported by secondary,

exploratory and other analyses. Statistical significance was not demonstrated for all of the other endpoints, but the point estimates were generally in line with the primary efficacy findings. The median time to nth + 1 PGTC seizure event was 43.0 days in the placebo group and greater than 120 days but not estimable for the perampanel group, as fewer than 50% of subjects in this group experienced a PGTC seizure event during the Core Study observation period ($p<0.0001$). Furthermore, nearly one-third of subjects in the perampanel group (30.9%) were free of all PGTC seizures during the Maintenance Period, and this percentage was considerably higher than that for the placebo group (12.3%).

Similar results as for PGTC seizures were seen for the 50% responder rate and the change in seizure frequency when counting all primary generalised seizures. Approximately one-quarter of subjects in the perampanel group (23.5%) who completed the Maintenance Period achieved total seizure-free status during the Maintenance Period compared to less than 5% of subjects in the placebo group. However, the results did not support an effect of perampanel specifically on absence or myoclonic seizures, whereby the size of the subgroups of patients with either seizure type were small. The results of the subgroup analyses even seemed to suggest that there was a larger reduction of myoclonic seizures in the placebo group compared to the perampanel group (see section 2.5.1. for related safety discussion). The lack of a demonstrated effect of perampanel on absence and myoclonic seizures was considered relevant by the CHMP given that the target population of IGE patients with PGTC seizures might well also suffer from these other seizure types. The CHMP therefore considered that SmPC section 5.1 should be updated to inform healthcare professional accordingly.

Supportive evidence for sustained efficacy was available from the Extension Phase of Core Study 332, in which patients were treated with perampanel for up to 2 years. Data from the Extension Phase furthermore supported the use of daily doses of more than 8 mg. At the cut-off date for the report provided with this application, 114 subjects had entered the Extension Phase and 19 subjects received perampanel in daily doses of >8 to 12 mg. While the CHMP noted the limitations of the Extension Study (including the open label design, the small number of patients receiving doses of more than 8mg/day and that the number of subjects with available data declining over time) overall, the data suggested that some patients may derived additional benefit from a higher dose than 8 mg/day, including patients on concomitant enzyme-inducing medication. The CHMP also took into account the findings from the PK and PK/PD modelling, suggesting similar profiles of perampanel in epilepsy patients with PGTC seizures and patients with POS and a linear exposure/response relationship, which has been demonstrated for POS over a dose range up to 12 mg/day.

2.4.4. Conclusions on the clinical efficacy

The available clinical data provided convincing evidence that adjunctive therapy with perampanel was effective at doses up to 8 mg/day in the treatment of PGTC seizures in IGE patients, which are not sufficiently controlled despite the use of other AEDs. The observed effect size for the 50% responder rate and PGTC seizure frequency reduction was considered by the CHMP to be clinically meaningful. Limited data suggested that some patients might benefit from further increases of the dose up to 12 mg/day.

Overall, the CHMP considered that there was sufficient evidence with regards to clinical efficacy supporting an extension of the indication for Fycompa to adjunctive treatment of primary generalised tonic-clonic seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy. Suitable updates were introduced to the product information (PI) to adequately inform healthcare professionals and patients/carers of the use of perampanel in the new indication.

2.5. Clinical safety

Introduction

The safety of perampanel in the treatment of PGTC seizures was evaluated in Core Study 332 and it's extension (see section 2.4.2. for a description of the study design and methods). Safety assessments consisted of monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs), discontinuation from treatment, suicidal ideation and behaviour (assessed using Columbia Suicide Severity Rating Scale, C-SSRS), and prior and concomitant medication usage, regular monitoring of haematology, blood chemistry, and urine values, periodic measurement of vital signs, and performance of physical and neurologic examinations. In addition, a Withdrawal Questionnaire was used to assess potential withdrawal signs and symptoms that might be associated with the discontinuation of perampanel.

Additional supportive data were also available from the previous POS program (double-blind adjunctive therapy Phase III studies 304, 305, and 306). The ADR analysis included the PGTC data alone and the PGTC data pooled with the data from the POS double-blind studies.

Patient exposure

All safety analyses were performed on the Safety Analysis Set.

- For Core Study 332, the Safety Analysis Set included subjects who were randomised to study drug, received at least 1 dose of study drug, and had at least 1 post-Baseline safety assessment (N=82 placebo, N=81 perampanel).
- For the Extension Phase of Core Study 332, the Safety Analysis Set included subjects who received at least 1 dose of perampanel in the Extension Phase and had any on-therapy safety data during this phase (N=114). Data were included from the entire perampanel treatment duration, defined as all exposure to perampanel in the Core Study + Extension Phase (subjects who received perampanel in the Core Study) or in the Extension Phase only (subjects who received placebo in the Core Study). Of the 114 subjects in the Extension Phase, 58 had previously received placebo, and 56 had previously received perampanel.

Details on the demographics and Baseline characteristics are provided in section 2.4.2.1.

The mean (SD) duration of exposure in the Core Study was 16.2 (3.54) weeks for subjects in the placebo group and 15.7 (3.57) weeks for subjects in the perampanel group. The median duration of exposure was the same in both treatment groups (17.0 weeks), and ranged from 1.4 to 19.7 weeks for subjects in the placebo group and from 3.7 to 18.1 weeks for subjects in the perampanel group. Treatment duration in the Core Study was greater than 14 weeks for 89.0% of the subjects in the placebo group and 85.2% of the subjects in the perampanel group.

The mean (SD) cumulative duration of exposure to perampanel across both the Core Study and the Extension Phase was 40.3 (28.06) weeks. The median cumulative duration of exposure was 34.9 weeks, and ranged from 0.7 to 123.7 weeks. Cumulative treatment duration was greater than 28 weeks for 64 subjects (56.1%), greater than 40 weeks for 47 subjects (41.2%), and greater than 52 weeks for 36 subjects (31.6%).

Adverse events

- Treatment-Emergent Adverse Events (TEAEs)

The percentages of subjects with TEAEs, treatment-related TEAEs, and TEAEs leading to study drug dose adjustment were higher in the perampanel group than in the placebo group. Overviews of the TEAEs in study 332 and it's extension are provided in Table 23 and Table 24.

Table 23 – Overview of TEAEs – Core Study 332 (Safety Analysis Set)

Category	Placebo (N=82) n (%)	Perampanel (N=81) n (%)
TEAEs	59 (72.0)	67 (82.7)
Treatment-related TEAEs[a]	37 (45.1)	56 (69.1)
Severe TEAEs	6 (7.3)	6 (7.4)
Serious TEAEs	7 (8.5)	6 (7.4)
Deaths	1 (1.2)	1 (1.2)
Other SAEs	6 (7.3)	5 (6.2)
Life-threatening	0	1 (1.2)
Requires inpatient hospitalization or prolongation of existing hospitalization	6 (7.3)	4 (4.9)
Persistent or significant disability or incapacity	0	0
Congenital anomaly / birth defect	0	0
Important medical events	0	0
TEAEs leading to study drug dose adjustment	10 (12.2)	16 (19.8)
TEAEs leading to study drug withdrawal	5 (6.1)	9 (11.1)
TEAEs leading to study drug dose increase	0	0
TEAEs leading to study drug dose reduction	6 (7.3)	8 (9.9)
TEAEs leading to study drug dose interruption	0	1 (1.2)

A TEAE is defined as an adverse event that (1) emerges during treatment, having been absent at pretreatment or (2) re-emerges during treatment, having been present at pretreatment but stopped prior to treatment or (3) worsens in severity during treatment relative to the pretreatment state, when the adverse event is continuous.
For each row category, a subject with two or more adverse events in that category is counted only once.
MedDRA Version 16.1.
MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a: Includes TEAEs considered by the Investigator to be possibly or probably related to study drug or TEAEs with missing causality.

Table 24 - Overview of TEAEs by Modal Daily Perampanel Dose - Extension Phase 1113 2 (Safety Analysis Set)

Category	Modal Daily Perampanel Dose				
	<4 mg/day (N=4) n (%)	4 mg/day (N=7) n (%)	>4 to 8 mg/day (N=84) n (%)	>8 to 12 mg/day (N=19) n (%)	Total (N=114) n (%)
TEAEs	3 (75.0)	7 (100.0)	66 (78.6)	16 (84.2)	92 (80.7)
Treatment-related TEAEs[a]	1 (25.0)	7 (100.0)	58 (69.0)	12 (63.2)	78 (68.4)
Severe TEAEs	0	0	4 (4.8)	4 (21.1)	8 (7.0)
Serious TEAEs	0	0	5 (6.0)	3 (15.8)	8 (7.0)
Deaths	0	0	0	1 (5.3)	1 (0.9)
Other Serious AEs	0	0	5 (6.0)	2 (10.5)	7 (6.1)
Life Threatening	0	0	1 (1.2)	1 (5.3)	2 (1.8)
Requires Inpatient Hospitalization or Prolongs Existing Hospitalization	0	0	4 (4.8)	3 (15.8)	7 (6.1)
Persistent or Significant Disability or Incapacity	0	0	0	0	0
Congenital Anomaly / Birth Defect	0	0	0	0	0
Important Medical Events	0	0	3 (3.6)	1 (5.3)	4 (3.5)
TEAEs Leading to Study Drug Dose Adjustment	0	7 (100.0)	20 (23.8)	8 (42.1)	35 (30.7)
TEAEs Leading to Study Drug Withdrawal	0	1 (14.3)	4 (4.8)	3 (15.8)	8 (7.0)
TEAEs Leading to Study Drug Dose Increase	0	0	1 (1.2)	0	1 (0.9)
TEAEs Leading to Study Drug Dose Reduction	0	6 (85.7)	17 (20.2)	5 (26.3)	28 (24.6)
TEAEs Leading to Study Drug Dose Interruption	0	0	0	1 (5.3)	1 (0.9)

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

For each row category, a subject with 2 or more adverse events in that category is counted only once.

Adverse events were summarized across the entire perampanel exposure. Perampanel exposure consists of the treatment durations of both Core and Extension Phases for subjects on perampanel in Core and Extension Phase only for subjects on placebo in Core.

AE = adverse event, TEAE = treatment-emergent adverse event: an adverse event is treatment emergent if the adverse event started on or after the date of first perampanel dose and prior to or on the day of (date of last dose + 30 days) during the Extension Phase.

a: Includes TEAEs considered by the Investigator to be possibly or probably related to study drug or TEAEs with missing causality.

In a comparison of the overviews of TEAEs for the placebo and perampanel 8 mg/day groups between Core Study 332 and the POS Phase III Double-blind Pool, the drug-placebo difference was generally larger in the POS Pool than in Core Study 332 with respect to TEAEs leading to study drug dose reduction. Otherwise, the results were generally similar for the POS Pool and Core Study 332.

Dizziness, irritability, somnolence, and fatigue were very common TEAEs in both the Core Study and the Extension Phase. The percentages of subjects with dizziness, irritability, and somnolence were similar in the 2 populations. The percentage of perampanel-treated subjects with fatigue was slightly higher in the Core Study (14.8%) than in the Extension Phase (10.5%). All very common TEAEs in Core Study 332 (dizziness, fatigue, headache, irritability, and somnolence,) were also identified as very common TEAEs in the POS Phase III Double-blind Pool, whereby for the POS pool, very common TEAEs were defined as those that occurred in ≥10% of the subjects in any dose group of the pool, ie placebo or perampanel 2, 4, 8, or 12 mg/day. There were no very common TEAEs that occurred in Core Study 332 but that had not occurred in the POS Pool.

In Core Study 332, the overall incidence of TEAEs was lower in adolescents than in adults, in both the placebo and perampanel groups. In the perampanel group, adolescents appeared to have lower incidences of dizziness, fatigue, and somnolence than did adults, and higher incidences of headache and irritability. In the Extension Phase the overall incidence of TEAEs was similar among adolescents and adults.

In the placebo group, the incidences of very common TEAEs overall in the Core Study were comparable for males and females, whereas dizziness, fatigue, and headache occurred in higher percentages of females than males in the perampanel group. The overall incidence of TEAEs in the Extension Phase was similar in males and females.

For the 2 race subgroups with the largest numbers of subjects (white and Asian/Pacific), the incidence of somnolence was higher among white subjects than Asian/Pacific subjects in the placebo group but the opposite occurred in the perampanel group. In the extension phase all TEAEs appeared to occur in higher percentages of white subjects than Asian/Pacific subjects.

Comparative safety data were presented for inducer AEDs (enzyme-inducing AEDs, i.e. carbamazepine, oxcarbazepine, and phenytoin) and non-inducers. In both treatment groups, the number of subjects who were receiving at least 1 inducer AED at Baseline was much smaller than the number of subjects who were receiving only non-inducer AEDs. From the available data no significant difference by Inducer/Non-inducer Status was identified.

Discontinuations Due to Adverse Events

The percentage of subjects with TEAEs leading to treatment discontinuation in the Core Study was higher in the perampanel group (11.1%) compared with the placebo group (6.1%). The percentage of subjects with TEAEs leading to treatment discontinuation in the Extension Phase (7.0%, n=8) was lower than in the perampanel group of the Core Study (11.1%, n=9).

Adverse Events of Special Interest

The following AEs of particular interest were assessed in detail: events related to alertness or cognition, psychiatric disorders, events related to hostility/aggression, suicidal ideation and behaviour, events related to psychosis/psychotic disorders, status epilepticus/ convulsions, events suggestive of abuse potential, events related to drug-related hepatic disorders, events related to falls, injury as a result of a fall, rash, cardiac and electrocardiogram events, events related to orthostatic changes in vital signs, events related to accidents/injury, and events related to laboratory abnormalities.

Events suggestive of cognitive impairment (e.g., somnolence), events related to hostility/aggression, events related to accidents/injury, and falls were seen more frequently in perampanel-treated subjects than those subjects treated with placebo.

The incidence of TEAEs related to suicidal ideation or behaviour was small and similar for the placebo and perampanel groups, and the overall occurrence of suicidality (suicidal ideation and behavior) reports, as assessed by the C-SSRS, was lower for the perampanel group (3.7%) than for the placebo group (6.1%).

A comparison of TEAEs of special interest that occurred in Core Study 332 with those that occurred in the POS Phase III Double-blind Pool did not reveal any clinically meaningful differences.

Adverse Drug Reactions

Adverse drug reactions (ADRs) were defined as TEAEs for which there was 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 other indications. 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 PGTC, the ADR analysis by the MAH included PGTC data alone and the PGTC data pooled with the data from the POS double-blind studies (see Table 25). This analysis revealed no new ADR nor a need for a change in the frequency categorisation of any existing ADR.

Table 25 – ADRs - PGTC and the POS Phase III Double-blind Pool (Safety Analysis Set)

		Perampanel[a]			
MedDRA System Organ Class Preferred Term	Placebo[a] (N=524) n (%)	4 mg/day (N=172) n (%)	8 mg/day (N=512) n (%)	12 mg/day (N=255) n (%)	Total (N=939) n (%)
Subjects with any TEAE	353 (67.4)	111 (64.5)	417 (81.4)	227 (89.0)	755 (80.4)
Ear And Labyrinth Disorders					
Vertigo	6 (1.1)	7 (4.1)	21 (4.1)	12 (4.7)	40 (4.3)
Eye Disorders					
Vision Blurred	8 (1.5)	2 (1.2)	14 (2.7)	11 (4.3)	27 (2.9)
Diplopia	4 (0.8)	2 (1.2)	7 (1.4)	8 (3.1)	17 (1.8)
Gastrointestinal Disorders					
Nausea	24 (4.6)	5 (2.9)	30 (5.9)	20 (7.8)	55 (5.9)
General Disorders And Administration Site Conditions					
Fatigue	26 (5.0)	13 (7.6)	48 (9.4)	31 (12.2)	92 (9.8)
Irritability	15 (2.9)	7 (4.1)	38 (7.4)	30 (11.8)	75 (8.0)
Gait Disturbance	7 (1.3)	2 (1.2)	18 (3.5)	10 (3.9)	30 (3.2)
Injury, Poisoning And Procedural Complications					
Fall	16 (3.1)	3 (1.7)	24 (4.7)	26 (10.2)	53 (5.6)
Investigations					
Weight Increased	9 (1.7)	7 (4.1)	24 (4.7)	11 (4.3)	42 (4.5)
Metabolism And Nutrition Disorders					
Decreased Appetite	8 (1.5)	1 (0.6)	11 (2.1)	11 (4.3)	23 (2.4)
Increased Appetite	5 (1.0)	0	6 (1.2)	7 (2.7)	13 (1.4)
Musculoskeletal And Connective Tissue Disorders					
Back Pain	9 (1.7)	3 (1.7)	8 (1.6)	12 (4.7)	23 (2.4)
Nervous System Disorders					
Dizziness	45 (8.6)	28 (16.3)	163 (31.8)	109 (42.7)	300 (31.9)
Somnolence	35 (6.7)	16 (9.3)	76 (14.8)	45 (17.6)	137 (14.6)
Ataxia	1 (0.2)	1 (0.6)	16 (3.1)	21 (8.2)	38 (4.0)
Balance Disorder	3 (0.6)	0	25 (4.9)	8 (3.1)	33 (3.5)
Dysarthria	0	2 (1.2)	14 (2.7)	9 (3.5)	25 (2.7)
Psychiatric Disorders					
Anxiety	8 (1.5)	3 (1.7)	17 (3.3)	9 (3.5)	29 (3.1)
Aggression	2 (0.4)	1 (0.6)	8 (1.6)	8 (3.1)	17 (1.8)
Anger	1 (0.2)	0	5 (1.0)	7 (2.7)	12 (1.3)

MedDRA = Medical Dictionary for Regulatory Activities; PGTC = primary generalized tonic-clonic; POS = partial-onset seizure TEAE = treatment-emergent adverse event.

a: Subjects treated during the double-blind phase of the study. Dose groups are based on the actual treatment groups.

In Core Study 332, the rate of discontinuation as a result of an adverse reaction was 4.9% in patients randomised to receive perampanel 8 mg, and 1.2% in patients randomised to receive placebo. The adverse reaction most commonly leading to discontinuation (≥2% in the perampanel group and greater than placebo) was dizziness.

Serious adverse event / deaths / other significant events

Two deaths occurred in the Core Study, one in each treatment group, during treatment or within 30 days after the last dose. The death of the placebo-treated subject was considered by the sponsor to be a likely case of sudden unexpected death in epilepsy, and the death of the perampanel-treated subject was due to drowning. There was 1 death during the Extension Phase as of the cut-off date of 1 March 2014, which occurred approximately 2 months after the subject received the last dose of perampanel, and the cause of death was acute pancreatitis. None of the deaths was assessed as related to study treatment.

Treatment-emergent SAE, including fatalities, in the Core Study occurred in 7 (8.5%) subjects in the placebo group and 6 (7.4%) subjects in the perampanel group. With the exception of the 2 subjects who died as a result of the SAE, all subjects in the perampanel group and all but 1 subject in the placebo group (with thermal burn) recovered from their SAE without sequelae.

Most SAEs were considered not related to study drug and did not result in a dose reduction. No individual SAE preferred term occurred in more than 1 subject in the perampanel group.

SAEs assessed as related to study drug were one case of grand mal convulsion in the placebo group and one case each of status epilepticus, suicide attempt, and suicidal ideation in the perampanel group. The latter 3 subjects with related SAEs in the perampanel group were discontinued from study treatment due to the events. The case of suicidal ideation in the perampanel was considered an SAE because it was severe in intensity, the subject had 2 previous TEAEs of suicidal ideation that were moderate, and hospitalization was required. Three additional subjects in the placebo group had TEAEs of suicidal ideation that the investigators did not consider to be SAEs. These events were mild or moderate in intensity and did not lead to hospitalization.

A comparison of the incidences of SAEs occurring in Core Study 332 with those in the POS Phase III Double-blind Pool showed similar results. The most frequently occurring SAEs were those related to epilepsy. In both Core Study 332 and the POS pool, these occurred in a larger number of subjects in the placebo group than the perampanel group. In study 332, SAEs related to epilepsy (ie, convulsion, grand mal convulsion, and status epilepticus) occurred in 4 (4.9%) subjects in the placebo group and 2 (2.5%) subjects in the perampanel group. Most of these epilepsy-related TEAEs were considered SAEs because they resulted in hospitalization.

Treatment-emergent SAEs (including fatalities) occurred in 8 (7.0%) of the 114 subjects in the Extension Phase. Two of the 8 subjects had the same SAE in both the Core Study and the Extension Phase (1 with convulsion and 1 with constipation). A treatment-emergent SAE of ‘abortion spontaneous incomplete’ occurred in the Follow-up period of the Extension Phase. Convulsion and suicide attempt occurred in 2 subjects each in the Extension Phase. With the exception of the subject who died as a result of the SAE and one subject with retinal detachment, all subjects recovered from their SAEs with no sequelae.

The SAEs in the Extension Phase that were assessed as related to study drug were aggression in 1 subject, mental status changes in 1 subject, suicide attempt in 1 subject, and both suicide attempt and depression in 1 subject. The dose of perampanel was reduced due to an SAE in the subject with mental status changes. The SAEs led to discontinuation of treatment in the subject with suicide attempt and the subject with both depression and suicide attempt.

Laboratory findings

No placebo- or perampanel-treated subject met the criteria for drug-induced liver injury (Hy's Law) at any single visit or over the course of treatment in the Core Study or in the Extension Phase.

Electrocardiogram tracings were not obtained in Study 332.

Photosensitivity was not evaluated in Study 332.

Across all subjects regardless of age, there was a larger mean change in body weight at the end of treatment in the perampanel group (+1.8 kg) compared with the placebo group (+0.1 kg). The mean change from Baseline to the end of treatment in the perampanel group was less among adults (≥17 years: +1.69 kg for perampanel group; +0.02 kg for placebo group) than among adolescents (≥12 to <17 years: +2.58 kg for perampanel group; +0.37 kg for placebo group).

The percentage of subjects with at least 1 post-Baseline triglyceride value above 50 or 100 mg/dL was higher in the perampanel group than in the placebo group among adult subjects (≥17 years), while no such pattern was seen among the 18 adolescent subjects. Treatment-emergent markedly abnormal elevations in triglycerides were seen in only 1 subject in the perampanel group whose Baseline triglyceride value was above the normal range.

Safety in special populations

Safety data as relevant for age, sex and race has been presented in previous sections as relevant. No effect of geographic location on the safety profile was noted.

No additional data has been collected to add to the evaluation of the effects of concomitant illnesses on TEAEs in subjects receiving perampanel.

Safety related to drug-drug interactions and other interactions

There was no evidence to suggest that co-administration of perampanel with other AEDs increased the occurrence of TEAEs (based on the 6 most commonly taken Baseline AEDs, which were all non-inducers).

In the population PK analysis of pooled PK data (studies 332, 304, 305, and 306), a pronounced reduction in perampanel exposure due to concomitant CYP3A inducers (carbamazepine, oxcarbazepine, and phenytoin) was observed. A mild effect on exposure due to concomitant topiramate (a weak CYP3A inducer) was observed, which was not considered to be clinically important relative to the high variability in observed perampanel exposure as presented and discussed in sections 2.3.2 and 2.3.2.

Post marketing experience

As of 22 July 2014, the cumulative worldwide post-marketing patient exposure to perampanel from the International Birth Date was estimated to be over 2,000,000 patient-days of exposure, based 8 mg as the defined daily dose. Commercial launch has taken place in 19 of the 39 countries: United Kingdom, Germany, Sweden, Austria, Norway, Denmark, Ireland, Switzerland, Lichtenstein, Canada, United States, Iceland, Malta, Finland, Spain, Israel, Russia, Netherlands, and France.

There have been a total of 26 post-marketing reports with events that fell under the MedDRA SMQ of suicide/self-injury, with 17 reports which met serious criteria and including reports of suicidal ideation and suicide attempts where the temporal association suggested a possible causal link to perampanel therapy.

No new emerging safety issues in the clinical development program or marketing data with perampanel were identified in the most recent periodic safety update reporting period, and there were no changes to the previous knowledge of efficacy and safety of perampanel. Generally, there were no significant changes in the frequency and severity of previously identified adverse reactions or important risks.

2.5.1. Discussion on clinical safety

Safety data for the use of perampanel in the treatment of PGTC seizures were available from the Core Study 332 for 81 patients. Additional data were available from the Extension Phase for 114 patients treated with perampanel including 58 patients who previously received placebo in the Core Study. Only limited information was available for long-term use (36 patients with exposure of 52 weeks or more) and for daily doses of >8 mg – 12 mg. No children less than 12 years of age with PGTC seizures were included in Study 332. However, 13.6% of the study population was younger than 18 years of age and the safety findings were similar to the total population. Only 1 elderly patient (≥65 years) was included in Study 332 and assigned to the placebo group, but as previously discussed, the age distribution in Study 332 was in line with the observed frequency of PGTC epilepsy which are more frequent at the end of childhood and early adulthood. Furthermore, the safety of perampanel in the elderly population has previously been assessed in studies in other indications (Parkinson's disease and neuropathic pain).

Overall, the CHMP considered the extend of the exposure in patients with PGTC seizures acceptable, taking into account the additional existing data in other patient populations, in particular POS. Additional data for long-term safety in the treatment of PGTC seizures are expected to become available in June 2016 with the full study report of the Extension Phase of Study 332.

In the population of epilepsy subjects with PGTC seizures in the Core Study 332, 82.7% of subjects treated with perampanel had TEAEs (compared with 72.0% of placebo-treated subjects) and 69.1% of subjects experienced TEAEs that were reported as treatment-related (compared with 45.1% of placebo-treated subjects). Treatment-emergent SAEs (including fatalities) were reported for 7.4% of perampanel-treated subjects and 8.5% of placebo-treated subjects. TEAE-related treatment discontinuation occurred in 6.1% of the subjects in the placebo group and 11.1% of the subjects in the perampanel group. These rates are consistent with those seen in patients with refractory POS for which Fycompa has previously been approved.

The incidence and type of TEAEs in Core Study 332 were not significantly influenced by age, sex, race, geographic location, or concomitant AED use. For the effect of enzyme-inducing AEDs see sections 2.3.2. and 2.4.

The incidence of TEAEs related to suicidal ideation or behaviour was small and similar for the placebo and perampanel groups, and the overall occurrence of suicidality reports (suicidal ideation and behaviour), as assessed by C-SSRS, was lower for the perampanel group (3.7%) than for the placebo group (6.1%). However, there have been post-marketing reports of suicidal ideation and suicide attempts for which a temporal association was found suggesting a possible causal link to perampanel therapy. On the basis of these post-marketing reports and the known AED class risk, it was agreed that the risk of suicide should be considered an important identified risk in the risk management plan (RMP), rather than a potential risk, and section 4.8 of the SmPC was updated to include "suicidal ideation" as well as "suicide attempt" in the list of ADRs. Both events were included as uncommon ADRs, as the integrated analyses of PGTC and POS data revealed an incidence of 0.2% and 0.1% for suicidal ideation and suicide attempt, respectively. The product information already included the AED class warning on suicide in SmPC section 4.4, which was considered sufficient by the CHMP.

Another question, while not arising directly from the safety assessment, but rather the efficacy analyses, was if perampanel, like some other anticonvulsants, may worsen/induce myoclonic seizures. In Core

Study 332, the reduction of myoclonic seizure frequency was larger in the placebo group compared to the perampanel group (see section 2.4.2.1.). To address this point, the MAH provided additional supportive analyses showing an interaction between treatment effect and Baseline myoclonic seizure frequency, which was unbalanced in favour of placebo. Furthermore, when taking into account the full categorisation of seizure worsening in the strict sense of an increase in frequency (i.e. > 0% to 25%, > 25% to 50%, > 50% to 75%, > 75% to 100% and > 100%), the data showed a similar pattern for both the perampanel and the placebo arm with 7 patients in each arm (29.2% and 30.4%, respectively) experiencing seizure worsening, including 3 patients each with a seizure frequency increase of >100%. The CHMP was reassured by these data and agreed that at the time of this report, there was no strong evidence showing that perampanel would induce or worsen myoclonic seizures.

Except for the upgrading of suicidality from an important potential to an important identified risk, no new safety issues have been identified and there were no significant changes in the frequency or severity of previously identified ADRs based on cumulative safety data from the clinical development program and from the worldwide post-marketing experience.

The data on vital signs presented, including weight increase, were in line with the previous assessment for the POS indication. Likewise, the data on laboratory evaluations, including increases in triglyceride values, did not raise any new concerns compared to the previous POS evaluation.

Overall, the CHMP was of the view that the data presented in support of the proposed indication in the treatment of patients with PGTC seizures did not significantly alter the established safety profile of the product. The product information has been updated with relevant safety data.

2.5.2. Conclusions on clinical safety

Overall, the CHMP was of the opinion that the available safety data including the integrated analysis of PGTC and POS data, were sufficient to support this application for an extension of the indication of Fycompa to adjunctive treatment of primary generalised tonic-clonic seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy. The product information has been adequately updated with relevant safety information.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.2 was acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The safety specifications have been updated to upgrade “Suicidality” as an important identified risk (new wording shown in **bold**, deleted wording ~~in strikethrough~~):

Safety concerns

Table 26 – Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Dizziness • Somnolence • Aggression • Balance disorder, ataxia and falls (particularly in the elderly) • Interaction with levonorgestrel-containing contraceptives, and unintended pregnancy exposures • Weight gain • Blurred vision • **Suicidality**
Important potential risks	• Drug abuse, misuse, dependency and withdrawal • Off-label usage • Skin photosensitivity • ~~Suicidality~~
Missing information	• Use in patients <12 years of age • Impact on cognition and growth in the paediatric population • Long-term safety in adolescents and adults • Use in human pregnancy and lactation • Long term effects of perampanel binding to elastin, melanin and hepatic cells • Use in patients with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction or any evidence of risk factors for QT prolongation • Use in patients with a history of psychotic disorder or suicidal behaviour in the previous 2 years • Use in patients with hepatic insufficiency whether related to concomitant medications or underlying liver disease • Use in patients with a history of drug or alcohol dependency • Use in patients who are taking vigabatrin • Use in patients with clinically significant renal or respiratory disease • Idiosyncratic reactions related to reactive metabolites • Use in the elderly with epilepsy, with particular monitoring of dizziness, balance disorders and falls • Non-CYP3A drug-drug interactions

In addition, section VI.2.1. of the RMP has been added to include discussion of the proposed new indication. Section VI.2.4. has been completed in compliance with the EMA guideline "Guidance on format of the risk management plan (RMP) in the EU". The table in VI.2.6. "planned Post-Authorisation Development plan" has been updated to include the studies from the summary tables in Part III and Part IV as requested. Other minor editorial changes have also been introduced.

2.7. Update of the Product information

As a consequence of this application for a new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet (PL) has been updated accordingly. In addition, minor editorial changes and amendments to improve the clarity and readability of the information was implemented throughout the PI. Some information in relation to POS was re-arranged and moved from SmPC section 4.4 to section 5.1, where it was considered better placed.

The main changes introduced to the SmPC (sections 4.1, 4.2 and 4.4) were the following (new text is shown in **bold**, deletions are shown as ~~strikethrough~~):

- SmPC section 4.1:

Fycompa is indicated for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in **adult and adolescent** patients **from 12 years of age** with ~~epilepsy aged 12 years and older~~.

Fycompa is indicated for the adjunctive treatment of primary generalised tonic-clonic seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy (see section 5.1).

- SmPC section 4.2:

Posology

Adults and adolescents

Fycompa must be titrated, according to individual patient response, in order to optimise the balance between efficacy and tolerability.

Perampanel should be taken orally once daily ~~before~~ **at** bedtime.

Partial Onset Seizures

Perampanel at doses of 4 mg/day to 12 mg/day has been shown to be effective therapy in partial-onset seizures.

Treatment with Fycompa should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg~~/day~~ **(either weekly or every 2 weeks as per half-life considerations described below)** to a maintenance dose of 4 mg/day to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased by increments of 2 mg/day to 12 mg/day. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

***Primary* Generalised Tonic-Clonic Seizures**

Perampanel at a dose up to 8 mg/day has been shown to be effective in primary generalised

tonic-clonic seizures.

Treatment with Fycompa should be initiated at a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg (either weekly or every 2 weeks, as per half-life considerations described below) to a maintenance dose of up to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased up to 12 mg/day, which may be effective in some patients (see section 4.4). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

(...)

- SmPC section 4.4:

(...)

Concomitant CYP 3A inducing anti-epileptic medicinal products

Response rates after addition of perampanel at fixed doses were less when patients received concomitant CYP3A enzyme-inducing anti-epileptic medicinal products (carbamazepine, phenytoin, oxcarbazepine) as compared to response rates in patient who received concomitant non-enzyme–inducing anti-epileptic medicinal products. ~~The 50% responder rates in the 4 mg, 8 mg and 12 mg groups were respectively 23.0%, 31.5%, and 30.0% in combination with enzyme inducing antiepileptic medicinal products and were 33.3%, 46.5% and 50.0% when perampanel was given incombination with non-enzyme-inducing anti-epileptic medicinal products.~~ Patients' response should be monitored when they are switching from concomitant non-inducer anti-epileptic medicinal products to enzyme inducing medicinal products and vice versa. Depending upon individual clinical response and tolerability, the dose may be increased or decreased 2 mg at a time (see section 4.2).

Other concomitant (non- anti-epileptic) cytochrome P450 inducing or inhibiting medicinal products

Patients should be closely monitored for tolerability and clinical response when adding or removing cytochrome P450 inducers or inhibitors, since perampanel plasma levels can be decreased or increased; the dose of perampanel may need to be adjusted accordingly.

~~Monotherapy~~

~~Two to 6.5% of the patients on perampanel in the clinical studies became seizure free during the last 28 days of treatment compared with 0% - 1.7% on placebo. There are no data regarding the effects of withdrawal of concomitant anti-epileptic medicinal products to achieve monotherapy with perampanel.~~

(...)

For all other changes, including changes to the PL, please refer to the attached PI.

Changes were also made to the PI to bring it in line with the current SmPC guideline, which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Belgium, Luxembourg and Malta.

2.7.1. User consultation

No new user testing was considered necessary by the CHMP.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Efficacy of Fycompa in the adjunctive treatment of PGTC seizures that are not sufficiently controlled despite the use of other AEDs was demonstrated in one double-blind, randomised clinical Phase III trial (Core Study 332) with supportive data from its open label extension. Additional supportive data for the use of perampanel in patients with PGTC seizures were derived from PK/PD modelling and a population PK analysis which included three Phase III studies in POS patients.

Overall, the design of Core Study 332 was considered acceptable and the study population was generally representative of the new target population. However, the CHMP noted that patients were selected based on an underlying diagnosis of IGE. Therefore, the CHMP considered that the indication should refer to PGTC seizures in patients with IGE in order to correctly reflect the population in which a beneficial effect has been demonstrated.

The results of Core Study 332 showed that more patients responded to adjunctive therapy with perampanel at daily doses of up to 8 mg compared to placebo, as measured by the proportion of patients with 50% or more reduction in PGTC seizure frequency compared to Baseline. When withdrawals were counted as non-responders, the 50% responder rate was 58.0% (47/81) in the perampanel arm versus 35.8% (29/81) in the placebo group ($p=0.0059$). Perampanel was also superior to placebo in reducing PGTC seizure frequency per 28 days with a median treatment difference of 30.8% less seizures in the perampanel arm. These findings in a refractory population were considered clinically relevant.

Furthermore, nearly one-third of subjects (30.9%) became free of all PGTC seizures during treatment with perampanel, and this percentage was considerably higher than that for the placebo group (12.3%). The median time to an nth + 1 PGTC seizure event was 43.0 days in the placebo group and greater than 120 days but not precisely estimable for the perampanel group, as fewer than 50% of subjects in this group experienced a PGTC seizure event during the Core Study observation period ($p<0.0001$).

Similar results were observed for the change in all seizure frequency and in the 50% responder rate for all seizures. Approximately one-quarter of subjects in the perampanel group (23.5%) who completed the Maintenance Period of the study achieved total seizure-free status compared to less than 5% of subjects in the placebo group.

Support for sustained efficacy was provided by data from the Extension Phase for up to 2 years. Some patients in the Extension Phase appeared to benefit from doses of >8 mg to 12 mg/day, including, but not limited to patients receiving concomitant inducer AEDs. While the data from the Extension Phase were limited, use of doses up to 12 mg/day was further supported by population PK and PK/PD analyses suggesting a linear exposure/response relationship of perampanel. Population PK and PK/PD analyses generally suggested that perampanel PK in epilepsy patients with PGTC seizures were similar to the epilepsy patients with refractory POS. A pronounced reduction in exposure as well as a reduction of PD effects due to concomitant CYP3A4/5 inducing AEDs was observed, which was in line with previous findings for POS only. Therefore, the CHMP considered that the existing warning in SmPC section 4.4 on the use of concomitant enzyme-inducing AEDs and the possible need for dose adjustment was adequate and no further update was needed.

Uncertainty in the knowledge about the beneficial effects

While generally the age distribution in the pivotal trial reflected the fact that PGTC seizures occur more frequently at the end of childhood and early adulthood, the CHMP noted that there were no data for elderly patients (≥65 years) receiving perampanel treatment. However, since the population PK analysis suggested that CL/F did not depend on age, the CHMP agreed that there was no need for dose adjustment in the elderly.

The CHMP furthermore considered the effect of perampanel on absence and myoclonic seizures, as IGE patients might well suffer from other primary generalised seizure types in addition to PGTC seizures. While generally similar results as for PGTC seizures were observed when counting all primary generalised seizure types, analyses for absence and myoclonic seizures, respectively, did not show a convincing effect of perampanel on either seizure type. The CHMP considered that this information was relevant to prescribers and therefore decided that SmPC section 5.1 should be updated to inform about the lack of a demonstrated effect on absence and myoclonic seizures.

Risks

Unfavourable effects

In Core Study 332, 82.7% of subjects treated with perampanel had TEAEs, compared with 72.0% of placebo-treated subjects, and 69.1% of subjects experienced TEAEs reported as treatment-related, compared with 45.1% of placebo-treated subjects. Treatment-emergent SAEs, including fatalities, were reported for 7.4% of perampanel-treated subjects and 8.5% of placebo-treated subjects. TEAE-related treatment discontinuation occurred in 6.1% of the subjects in the placebo group and 11.1% of the subjects in the perampanel group. These rates were consistent with those seen in patients with refractory POS.

Based on cumulative data from the clinical development program and from the worldwide post-marketing experience, there were no significant changes in the frequency or severity of previously identified ADRs. The available data did not suggest an effect of age, sex, race, geographic location, or concomitant AED use on the safety profile. No new drug-drug interactions have been identified for perampanel.

Safety data from Study 332 for suicidal ideation or behaviour were generally in line with previous safety assessments for Fycompa. However, when taking into account the totality of the available data accumulated over time, including post-marketing reports of suicidal ideation and suicide attempts for which a temporal association suggested a possible causal relationship to perampanel use, as well as the known AED class risk, the CHMP considered that the safety concern in the RMP should be upgraded from an important potential to an important identified risk. Consequently, suicidal ideation as well as suicide attempt were included in the list of ADRs in SmPC section 4.8.

Uncertainty in the knowledge about the unfavourable effects

Overall, the CHMP considered the extend of the exposure in patients with PGTC seizures acceptable, albeit there were limited data in some age groups and with regards to long-term treatment. No children less than 12 years of age with PGTC seizures were included in the Core Study, which was acceptable given that the indication was restricted accordingly. With regards to adolescent patients, 13.6% of the study population was younger than 18 years of age and the safety findings were similar to the total population. No elderly patients received perampanel treatment in Study 332. The safety in the elderly has however previously been demonstrated in studies in other indications. A total of 1324 subjects aged 65 or more were included in studies in Parkinson's disease and neuropathic pain, with no evidence for different adverse reactions in patients in this age group.

Data for perampanel exposure of 52 weeks or more were only available for 36 patients. Additional data for long-term safety in the treatment of PGTC seizures were expected to become available in June 2016 with the full study report of the Extension Phase for study 332.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Support for a favourable treatment effect of perampanel in the adjunctive treatment of PGTC seizures originated from an appropriately designed and executed study in patients of a suitable clinical profile. A statistically significant benefit compared to placebo was demonstrated for relevant endpoints, i.e. 50% responder rate and reduction in seizure frequency, in line with the Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/Rev.2/Corr). More than half of the patients receiving perampanel responded to treatment, which was considered clinically relevant.

The safety profile for perampanel for treatment of patients with PGTC seizure was generally in line with the previously established profile in refractory POS. The risk of suicidality was upgraded to an important identified risk in the RMP based on cumulative safety data including post-marketing reports in POS patients. Overall, the risks of perampanel treatment were considered manageable given the updates to the product information and the RMP.

Benefit-risk balance

The CHMP considered that a beneficial effect has been demonstrated for perampanel up to daily doses of 8 mg/day, which could be further increased to 12 mg/day for some patients with PGTC seizures. Treatment related risks were generally in line with the established safety profile of Fycompa prior to this report. Therefore, based on the updated product information, the CHMP concluded that the benefits of perampanel outweighed its risks in the adjunctive treatment of primary generalised tonic-clonic seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy. Overall, the benefit-risk profile of Fycompa remained favourable.

Discussion on the Benefit-Risk Balance

There was limited information for long-term use of perampanel in patients with PGTC seizures and for daily doses above 8 mg and up to 12 mg. However, overall, the available data suggested maintenance of the effect and that at least some patients, including those with concomitant inducer AEDs, might benefit from doses above 8 mg/day. Additional data were expected by June 2016 when the full study report of the Extension Phase for study 332 is expected.

No convincing effect on absence and myoclonic seizures was shown for perampanel compared to placebo. These finding were considered important in the population of IGE patients who might well also suffer from generalised seizure types other than PGTCs, and the CHMP considered that healthcare professionals should be informed accordingly (SmPC section 5.1.)

With regards to safety, the upgrade of the risk of suicidal ideation or behaviour to an important identified risk and related labelling changes was not triggered directly by data from patients with PGTC seizures, but rather reflecting a cumulative review of the available data at the time of this report. The related class warning for AEDs had already been included in SmPC section 4.4 prior to this report.

Overall, suitable updates were introduced to the product information to adequately inform healthcare professionals and patients/carers of the use of perampanel in the new indication.

4. Recommendations

The application for the extension of the indication for Fycompa for adjunctive treatment of primary generalised tonic-clonic seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy is approvable since all concerns have all been resolved.

Final Outcome

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

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 and IIIB

Extension of indication to include a new indication for Fycompa for adjunctive treatment of primary generalised tonic-clonic seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy. Consequently, the MAH proposed an update of sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC. In addition, minor editorial changes and amendments to improve the clarity and readability of the information was implemented throughout the product information.

The Package Leaflet was proposed to be updated accordingly.

In addition, the MAH took the opportunity to updates the contact details of the local representatives of Belgium, Luxembourg and Malta.

The variation proposed amendments to the Summary of Product Characteristics and 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

Extension of indication to include a new indication for Fycompa for adjunctive treatment of primary generalised tonic-clonic seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy. Consequently, the MAH proposed an update of sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC. In addition, minor editorial changes and amendments to improve the clarity and readability of the information was implemented throughout the product information.

Summary

Review of the results from a randomised controlled clinical trial and from a computer model to predict the fate and effects of perampanel in the body after administration showed that adjunctive treatment with Fycompa was effective in reducing the frequency of primary generalised tonic-clonic seizures in patients with idiopathic generalised epilepsy. More than half of the patients responded to treatment and had only half as many seizures or even less than before treatment. The safety profile was generally in line with the

previously established profile in patients with treatment resistant partial onset seizures and the benefit-risk balance was considered favourable.