



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/424476/2012

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fycompa

perampanel

Procedure No.: EMEA/H/C/002434

Note

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



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List of abbreviations

AEDs	antiepileptic drugs
AMS	accelerator mass spectrometry
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BID	twice daily
DB	double blind
CHMP	Committee for Medicinal Products for Human Use
ECG	electrocardiogram
EEG	electroencephalogram
EMA	European Medicines Agency
E2007	perampanel
GCP	Good Clinical Practice
ITT	Intent-To-Treat
LOCF	Last observation carried forward
MTD	maximum tolerated dose
NRU	neutral red uptake
OC	oral contraceptive
OLE	open-label extension
PD	pharmacodynamics
PK	pharmacokinetics
POMS	Profile of Mood States
PSV	peak saccadic velocity
QD	once daily
QTc	corrected QT interval
VAMS	Bond and Lader Visual Analog Mood Scale
VAS	visual analog scale
PVT	Psychomotor Vigilance Test
KSS	Karolinska Sleepiness Scale
POMS	Profile of Mood State
SUDEP	Sudden unexpected death in epilepsy
STM	Sternberg short term memory scanning task

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eisai Europe Ltd. submitted on 24 May 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Fycompa, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 October 2010.

The applicant applied for the following indication: the treatment of partial-onset seizures.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicant's own tests and studies and bibliographic literature supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/79/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/79/2010 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 applicant 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.

New active Substance status

The applicant requested the active substance perampanel contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 14 October 2005, 24 January 2007, 24 January 2008 and 25 June 2009. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer of the active substance

Eisai Co., Ltd.
Kashima Plant
22 Sunayana
Kamisu-shi
Ibaraki-ken 314-0255
Japan

Manufacturers of the finished product

Eisai Co Ltd
1 Kawashimatakehaya-machi
Kakamigahara
Gifu 501-6195
Japan

Eisai Manufacturing Ltd.
European Knowledge Centre
Mosquito Way
Hatfield, Herts AL10 9SN
United Kingdom

Manufacturer responsible for batch release

Eisai Manufacturing Ltd.
European Knowledge Centre
Mosquito Way
Hatfield, Herts AL10 9SN
United Kingdom

1.3. Steps taken for the assessment of the product

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

Rapporteur: **Robert James Hemmings**

Co-Rapporteur: **Pierre Demolis**

CHMP Peer reviewer: Pieter Neels

- The application was received by the EMA on 24 May 2011.
- The procedure started on 22 June 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 September 2011 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 September 2011 (Annex 2).
- During the meeting on 17-20 October 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 October 2011 (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 December 2011.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 January 2012 (Annex 4).
- During the CHMP meeting on 13-16 February 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 5).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 March 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 April 2012 (Annex 6).
- During the CHMP meeting on 16-19 April 2012, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the applicant (Annex 7).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 April 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 May 2012 (Annex 8).
- The Rapporteurs circulated the Final Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 May 2012 (Annex 9).
- During the meeting on 21-24 May 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Fycompa on 24 May 2012.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Epilepsy is a common neurological disorder affecting individuals of all ages, which is defined by the recurrence of spontaneous/unprovoked seizures. It is characterized by excessive electrical discharges in the brain. More than 50 million adults and children suffer from epilepsy world-wide.

For epidemiological purposes, the definition requires more than one unprovoked seizure of any type.

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

Half of the epilepsies begin before the age of 18 and one quarter of these are intractable, having severe social and cognitive consequences. The majority of paediatric epilepsies consist of age-dependent epilepsy syndromes whose manifestations are affected by ongoing brain maturation. Another major difference in paediatric and adult epilepsies is that some syndromes carry a grave prognostic for cognitive outcome due to the impact of epilepsy (epileptic encephalopathies).

Antiepileptic drugs (AEDs) are the main treatment option. Over the past 15 years, several AEDs have been developed with the objective of improving efficacy, tolerability, and ease of use when compared with classic currently-used AEDs such as carbamazepine, phenytoin, valproic acid, Phenobarbital, and benzodiazepines. Approximately 60% of newly diagnosed patients are seizure-free with monotherapy and an additional 10-20% with polytherapy. It follows that about 30% of patients are not satisfactorily controlled. In addition many patients suffer from significant adverse effects.

Thus, there remains a need for new AEDs with improved efficacy and tolerability profiles, as well as for greater mechanistic diversity.

2.1.2. About the product

Perampanel is a selective, non-competitive antagonist of the ionotropic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor. Glutamate is the primary excitatory neurotransmitter in the central nervous system and is implicated in a number of neurological disorders caused by neuronal overexcitation. Activation of AMPA receptors by glutamate is thought to be responsible for most fast excitatory synaptic transmission in the brain. AMPA antagonists could potentially reduce excessive excitatory activity and excitotoxicity, and thus exhibit anticonvulsant and potentially antiepileptogenic effects.

2.2. Quality aspects

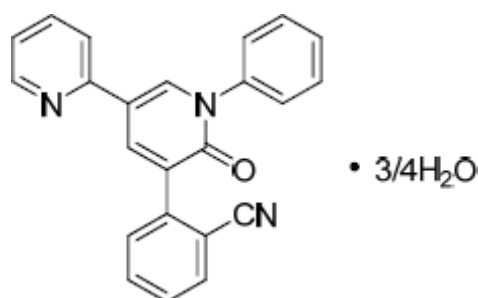
2.2.1. Introduction

Fycompa is presented as film-coated tablets containing 2, 4, 6, 8, 10, and 12 mg perampanel (as the $\frac{3}{4}$ hydrate) as active substance. The composition is described in section 6.1. of the SmPC.

The product is available in clear PVC blister film and Al lidding foil, with heat seal lacquer.

2.2.2. Active Substance

Perampanel is a white to yellowish white non-hygroscopic powder. Perampanel is practically insoluble in water, with a slight improvement at acidic pH. The chemical names are 2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2 dihydropyridin-3-yl)benzonitrile hydrate (4:3) or benzonitrile, 2-(1',6'-dihydro-6'-oxo-1'-phenyl[2,3'-bipyridin]-5'-yl), and the structural formula is as follows:



Perampanel has a non - chiral molecular structure and therefore, it does not exhibit stereoisomerism. Polymorphism has been observed for perampanel. It exists in five anhydrous polymorphic forms and one hydrate. Among them, three anhydrous forms and the hydrate have been isolated, and the manufacturing process of perampanel consistently affords the hydrate. The crystal form is routinely checked in the drug substance by x-ray powder diffraction (XRPD).

Manufacture

Perampanel is synthesized in two main steps by one manufacturing site.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Batch analyses data are provided on batches produced with the proposed synthetic route, and the batch analyses data show that the active substance can be manufactured reproducibly.

Specification

The active substance specification includes tests for: description (appearance), identification (IR), X-ray power diffraction, heavy metals, related substances (HPLC), residual solvents (GC), residual elements (ICP-AES), residue on ignition (Ph Eur), water content (Karl Fischer), particle size, assay (HPLC, 98.0 – 102.0%) microbial limits (Ph Eur).

Batch analysis data (n=25) of the active substance are provided. The results are within the specifications and are consistent from batch to batch.

Stability

Three production scale batches of the active substance packed in a heat sealed linear low-density polyethylene bag contained in an aluminium laminate bag stored under long term conditions (25°C/60%RH) and at 5°C for up 48 months, and under accelerated conditions (40°C/75%RH) for up 6 months stability testing (ICH conditions).

Stress testing in solid state was also conducted by exposure to light, heat, humidity and oxidation using one pilot scale batch. Photostability testing was performed according to ICH Q1B in one batch.

The parameters tested were: appearance, identification, polymorphic form, related substances, water content and assay.

The stability results justify the proposed retest period.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The product development has taken into consideration the physicochemical characteristics of the active substance. The low solubility of the active substance in water together with the low percentage content of perampanel in the finished product, suggests particle size may have an influence on the drug product. The applicant investigated the effect of different particle sizes of perampanel on content uniformity and dissolution and consequently employed a defined control particle size limit.

The manufacturing process development was focused on the critical steps of the process. A wet granulation method was preferred to ensure the content uniformity of core tablets because of the comparatively low concentration of perampanel in the finished product.

With consideration to the desired final market presentation, a film coated tablet was preferred. The formulation factors which may impact product quality were identified and classified. Each factor was assessed for its potential impact on quality attributes of the finished product. The compatibility of the active substance with excipients was also evaluated. All these studies resulted in the choice of the proposed formulation for commercial production.

Bioequivalence studies were performed showing bioequivalence between the clinical formulation and the proposed commercial formulation.

The excipients have been selected taking into account rapid disintegration and dissolution and acceptable manufacturability and are typical for an immediate release tablet formulation. The chosen excipients were lactose monohydrate (diluent), low-substituted hydroxypropyl cellulose (disintegrant),

povidone (binder), magnesium stearate (lubricant), microcrystalline cellulose (disintegrant in the 6, 8, 10 and 12 mg tablets), hypromellose, talc, macrogol 8000, and colorants.

All excipients are controlled according to the current monograph in the Ph.Eur except low-substituted hydroxypropyl cellulose which is not the subject of a monograph in the Ph.Eur. or a pharmacopoeia of a Member State. This excipient meets the requirements of the current National Formulary (NF). Appropriate in house specifications have been proposed for the colorants.

The primary packaging proposed is PVC/aluminium blisters. These materials have been tested according to USP <661>, physico-chemical tests –Plastics and polyethylene containers and have been shown compliant. In addition, IR spectra of HDPE are provided under this section. Suitability of this packaging has been shown also by stability of perampanel film-coated tablets.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Magnesium stearate is of vegetable origin.

Manufacture of the product

The manufacturing process consists of seven main steps: mixing, granulation, drying, sizing, lubrication, tableting and film-coating.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and is satisfactory. The validation data provided is acceptable for registration purposes, considering the compositions of the 6mg to 12mg strengths are very similar (different levels of drug substances, which is compensated by different levels of the lactose monohydrate to maintain the same tablet weight for all strengths). However, for GMP purposes, an additional two batches of the 8mg and 10mg tablets should be validated and validation data, along with a remedial plan of action, should only be provided to the EMA in the case of out of specification results. The in process controls are adequate for this film-coated tablet preparation.

The batch analysis data on three full scale batches shows that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The finished product specifications include appropriate tests (at release) with the tests in brackets: appearance, identification (HPLC, UV spectrum), assay (95.0-105.0%, HPLC), related substances (HPLC), dissolution (Ph. Eur.), content uniformity (Ph. Eur.), and microbial limits (Ph. Eur.).

Batch analysis results in a great number of batches confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability data of three batches for 2mg and 4 mg film-coated tablets stored for 48 months and three batches for 6 mg and 12 mg film-coated tablets and one batch for 8 mg and 12 mg tablets stored for up to 12 months under long term conditions (5°C and 25°C/60%RH) and for up to 6 months under accelerated conditions at 40°C/75%RH according to ICH requirements were provided. The batches were packed in the primary packaging proposed for marketing. Samples were tested for description, identification, related substances, assay, dissolution, and microbial quality.

Forced degradation testing at 60°C and photostability testing as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products were additionally performed.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Further validation of the manufacturing process on two batches of 8 mg and 10 mg tablets, after placing the product on the market. Any out of specification results together with a remedial action plan should be reported.

2.3. Non-clinical aspects

2.3.1. Introduction

Perampanel is an orally active, noncompetitive antagonist of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor that has been developed as an antiepileptic agent for subjects with partial-onset seizures. Nonclinical testing of perampanel encompassed pharmacology, safety pharmacology, pharmacokinetic, and toxicology studies designed to support safe clinical use. The performed studies conform to the study types and designs recommended by relevant International Conference on Harmonisation (ICH) guidances and satisfy the requirements of Article 8.3 of EC Directive 2001/83 (as amended).

The applicant received Scientific Advice from the CHMP on 24Jan2008 on non-clinical general aspects of the dossier.

All pivotal toxicology studies and the core battery of safety pharmacology studies were conducted in accordance with Good Laboratory Practice (GLP) regulations.

The primary pharmacodynamic effects of perampanel were evaluated in *in vitro* binding and cell-based assays, and *in vivo* in various animal models of seizures. In addition, *in vivo* studies in animal models of neuropathic pain, multiple sclerosis, and Parkinson's disease were conducted to evaluate whether perampanel has any potential effects on these neurologic disorders in which excitatory amino acid have been implicated.

The secondary pharmacodynamic effects of perampanel were evaluated in binding specificity and immune response assays *in vitro*, and motor coordination assays *in vivo*.

Safety pharmacology of perampanel was evaluated by analysis of the effects on tail currents of the human ether-à-go-go related gene (hERG) channel *in vitro*, and on heart rate, blood pressure and electrocardiogram (ECG) *in vivo* in conscious dogs. Additionally, effects of perampanel on central nervous system (CNS) and respiratory function were evaluated in rats.

The pharmacokinetics of perampanel was evaluated *in vivo* in mice, rats, dogs, and monkeys following single or repeated doses. These species were also used in pharmacology or toxicology studies. Mass balance studies and tissue distribution of radioactivity in rats and monkeys were assessed with [¹⁴C]perampanel. Additionally, distribution of radioactivity into pigmented tissues was evaluated up to 106 weeks post-dose. Plasma protein binding and distribution to red blood cells were determined *in vitro*. For assessment of metabolic characteristics of perampanel, *in vitro* studies were conducted using liver sub-cellular fractions including liver microsomes, the 9000×g supernatant (S9 fraction) of homogenized liver containing microsomes and cytosol, complementary deoxyribonucleic acid (cDNA)-expressed recombinant human metabolizing enzymes, and cultured hepatocytes. Species differences of perampanel metabolism were assessed using plasma or excreta obtained from *in vivo* studies. The potential of drug interaction for perampanel on drug metabolizing enzymes and transporters was evaluated *in vitro*. Bioanalytical assay methods for perampanel in plasma were developed and validated using high performance liquid chromatography.

The toxicity of perampanel was evaluated in a comprehensive set of toxicology studies encompassing all appropriate toxicologic endpoints based on relevant regional and ICH guidances. All pivotal toxicology studies were performed in accordance with GLP regulations, while preliminary and dose-range finding studies were generally non-GLP studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro, perampanel was shown not to exhibit any binding affinity to the AMPA binding site but inhibited AMPA-induced increase in cellular calcium in cultured rat cortical neurons. *In vivo*, oral administration of perampanel (1.25 – 5 mg/kg) prolonged seizure latency in AMPA-induced murine seizure models in a dose-dependent manner. These results suggest that perampanel might be a non-competitive AMPA antagonist.

Perampanel showed potent anticonvulsant activities in several animal models of seizures. The anticonvulsant activity of perampanel was demonstrated in the murine audiogenic seizure model (ED₅₀ = 0.47 mg/kg) and maximal electroshock seizure model (ED₅₀ = 0.1.6 mg/kg). Perampanel was

more potent than carbamazepine and valproate (positive controls) in both models. Perampanel protected mice from myoclonic seizures in the pentylenetetrazol-induced seizure model ($ED_{50} = 0.94$ mg/kg).

In the rats kindling model, an animal model of temporal epilepsy, perampanel elevated the afterdischarge threshold (10/mg/kg), suggesting that perampanel can affect initiation of localized seizures. Perampanel also reduced seizure severity and afterdischarge duration. Perampanel often abolished motor seizures without affecting afterdischarge duration. The separation between reduction of seizure severity and afterdischarge duration suggests that perampanel may inhibit the propagation of seizures to other brain areas. Perampanel had no effect in the GAERS model in which valproate had a clear effect, suggesting that perampanel may have limited effect on absence epilepsy.

Even though the anticonvulsant effects of perampanel have been well demonstrated on various classical animal models, its mechanism of action remains elusive. Indeed, no interaction with any of the molecular targets investigated, including AMPA receptors, could be found. Therefore it is recommended that the applicant pursue the understanding of the mechanism of action.

Because glutamate is a major excitatory neurotransmitter in the CNS, AMPA-antagonists are thought to affect motor coordination in addition to their anti-seizure activity. As expected, perampanel caused motor incoordination at comparable doses that produced potent anticonvulsant activity in various seizure models. In 1993 Yamaguchi et. al. reported a similar narrow protective index for both non-competitive and competitive AMPA receptor antagonists, suggesting this is inherent to AMPA receptor blockade. The clinical significance of this narrow therapeutic index cannot be determined by non-clinical studies alone. Refer to the clinical assessment report for further details.

Secondary pharmacodynamic studies

In two rodent models of neuropathic pain, perampanel at oral doses of 3 and 6 mg/kg dose-dependently increased the paw-withdrawal threshold. In the experimental autoimmune encephalomyelitis (EAE) rodent model, oral perampanel decreased disease scores without affecting either peripheral antibody production or central nervous system (CNS) perivascular cuffing. In rat and primate animal models of Parkinson's disease, oral administration of perampanel enhanced the effect of L-dopa. The clinical significance of these findings remains unknown at the time of this assessment.

Further secondary pharmacology studies demonstrated that perampanel did not significantly inhibit the production of cytokines and chemokines from human peripheral blood mononuclear cells which suggests that it does not have anti-inflammatory properties.

Safety pharmacology programme

The safety pharmacology profile was investigated in a series of *in vivo* studies in rats and dogs and one *in vitro* study.

No perampanel-related effects on the cardiovascular system (including QT intervals) were noted in an *in vivo* study in the conscious dog at doses up to 10mg/kg and hERG activity was weak (IC_{50} : 5.52 μ g/mL). A safety factor of >100 is calculated between effect in preclinical (hERG: weak effect at 5.52 μ g/mL) and highest plasma concentration of Perampanel in clinical use (799 ng/mL, corresponding to a free drug concentration of approximately 36 ng/mL [free drug concentration adjusted for protein binding which is approximately 95.5% in Humans]).

Perampanel induced slight and reversible depressant effects on CNS function in rats at 5 mg/kg (high dose), and had no effect on body temperature in rats at oral doses up to 5 mg/kg. Perampanel had slight and reversible effects on respiratory frequency in rats at all doses tested. The investigator

concluded that these changes were most likely associated with depressant effects of the drug on the CNS and not due to a direct effect on respiratory function. This hypothesis was supported further by the fact that there was no evidence of clinical distress.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been submitted.

2.3.3. Pharmacokinetics

- **Absorption**

Following single dose administration perampanel was characterised by a low to moderate clearance and a moderate to large volume of distribution in rats, dogs, and monkeys. T_{max} ranged from 0.5 - 1.5 hours) and oral absorption was complete, resulting in good bioavailability (36% - 74.5%). Systemic exposure of Perampanel after repeated administration was not changed in animals. The protein binding of Perampanel in mouse (94.1% - 94.6%), rat (86.8% - 87.5%), dog (88.8% - 90.1%), monkey (90.1% - 90.6%) and human (95.3% - 95.8%) was moderate. Half-lives range from 1.4 to 2.2 hours in the rat, 5.3 to 6.9 hours in the dog, and 6.9 to 7.6 hours in the monkey.

- **Distribution**

In tissue distribution studies the radioactivity was widely distributed to tissues and eliminated rapidly from most tissues except the aorta in rats and pigmented tissues in rats (eyeball) and cynomolgus monkeys (ocular tissues). The terminal half-lives of radioactivity in the aorta and eyeball were extremely long, estimated to be 110 and 45 weeks, respectively, in rats. The slow elimination of radioactivity from the aorta and the pigmented tissues could be attributable to covalent or tight binding of radioactivity to elastin, a component of aorta, and to melanin (a pigmentation component in the eye tissues) respectively. The applicant has stated that there were no reported pathological changes in the aorta and eyes in repeated-dose toxicology studies in rats and monkeys, therefore the accumulation of perampanel-derived material could be considered a toxicologically insignificant characteristic of perampanel.

The non-extractable radioactivity in rats and cynomolgus monkey livers at 24 hours and 7 days (respectively), after dosing suggested covalent binding of radioactivity to endogenous macromolecules, however, no hepatic toxicity was observed in the repeated-dose toxicity studies in both animal species. Thus, this type of covalent binding in the liver may also be toxicologically insignificant. The clinical relevance of the slow elimination of perampanel from the liver, aorta and pigmented tissues cannot be fully established from non-clinical studies alone.

In pregnant rats, perampanel (radioactivity) was distributed to the fetus suggesting that perampanel crosses the placenta, although the amount of radioactivity transferred was low ($\leq 0.09\%$ of the dose administered). Perampanel was secreted into milk in lactating rats.

- **Metabolism**

In metabolism studies, there were no qualitative species-species differences of metabolic pathways and aside from metabolite M14 (that was only identified in human urine) there were no human-specific metabolites formed in any of the studies cited. The primary oxidative metabolism of perampanel was mediated by cytochrome P450 (CYP) 3A4 and/or CYP3A5 based on the results of metabolism by recombinant human CYPs and inhibition studies using anti-CYP3A4 and ketoconazole in human liver microsomes.

The main metabolic pathway of perampanel was primary oxidation at the pyridine, benzene, or benzonitrile ring, and sequential conjugation. The metabolites formed were: hydroxylated metabolites (M1, M3, M4, and M5) and their glucuronides (M12, M13, and M14), rearrangement of pyridine ring (M6) to carboxylic acid metabolite (M2), dihydrodiol metabolites (M7) likely mediated by epoxide (M19), and N-acetyl cysteine conjugate of perampanel (M15). In primary pharmacology study **M09014**, metabolites M1, M3, M4, M5 and M7 had antagonistic effect on AMPA-type glutamate receptor, but the effect was weaker than perampanel by 44-, 3.0-, 3.8-, 7.7- and 27-fold, respectively. No activity was observed with M2 up to 10 µmol/L.

The applicant has highlighted the fact that metabolites with structural concerns were found. These metabolites included an epoxide (M19) *in vitro*, dihydrodiol (M7) as an end product of the epoxide *in vitro* and *in vivo*, and N-acetyl cysteine conjugate (M15) *in vivo*. These metabolites were generated in humans, as well as in rats and monkeys. The dihydrodiol and the N-acetyl cysteine conjugate were detected in rats, and an *in vivo* rat bone marrow micronucleus assay of perampanel was negative. The presence of the dihydrodiol metabolite in rats indicates that the epoxide was also transiently formed *in vivo*. The epoxide is rapidly converted to the less chemically reactive form, the dihydrodiol, by spontaneous or enzymatic hydrolysis (i.e., epoxide hydrolase). The dihydrodiol is not registered as a structural alert in the *in silico* DEREK system. The N-acetyl cysteine conjugate of perampanel (M15) is also negative in structural alerts analysis using the DEREK system. Furthermore, perampanel administered at MTD did not demonstrate any carcinogenic potential in the 2-year carcinogenicity studies using mice and rats. The current data are sufficient to evaluate the mutagenic potential of perampanel, the epoxide, the dihydrodiol, and the N-acetyl cysteine conjugate and that no further *in vitro* evaluation is necessary.

In rats and monkeys, unchanged perampanel was the major component in plasma with minor metabolites observed as the circulating metabolites. The exposures of the circulating metabolites were much less than that of perampanel and in humans perampanel was the dominant component in plasma. The Applicant has also stated that no circulating disproportionate metabolites were observed in clinical studies (please refer to the clinical assessment report for further details). Therefore, in accordance with ICH guidance document M3, the absence of further quantification of circulating metabolites and toxicological evaluation of these metabolites in animals is not required. This is acceptable from a non-clinical perspective.

- **Excretion**

In excretion studies it was reported that following oral administration of ¹⁴C-perampanel to rats and monkeys, the excretion of radiolabelled material was virtually complete within 7 days. The faecal excretion was the predominant route of elimination of the radioactivity and accounted for 87.8% and 56.7% of the dosed radioactivity in rats and monkeys, respectively. Faecal excretion was mediated by biliary excretion in rats.

No human excretion studies data have been presented for comparison (the reader is referred to the clinical assessment report for further information).

- **Drug interactions**

In human liver microsomes, perampanel at high concentration (30 µmol/L) inhibited CYP2C8 and UGT1A9 among major hepatic CYPs and UGTs. In cultured human hepatocytes, perampanel induced CYP2B6 and CYP3A4/5. However, induction potencies were weak compared to corresponding positive controls.

In vitro it was demonstrated that perampanel is not a substrate but was a weak inhibitor of OAT1 (inhibition constant (K_i): 21.9 µmol/L), OAT3 (K_i: 8.5 µmol/L), OCT1 (K_i: 18.2 µmol/L), P-gp (IC₅₀: 12.8 µmol/), and BCRP (IC₅₀: 18.1 µmol/) for the transporters tested.

The enzymes induced by CBZ, which are not UGT but with a reduced exposure of perampanel by two-thirds, are not in line with the low involvement of CYP3A4 and should be further characterised. Providing that the drug-drug interaction potential of perampanel is properly characterized through the battery of clinical pharmacology studies no further non-clinical drug-drug interaction data would be warranted.

2.3.4. Toxicology

Single dose toxicity

Clinical signs observed in rodents were pharmacology-based CNS effects and consisted of abnormal gait and decreased activity, prostration, dyspnea (mice only), bradypnea (rats only), hypothermia (rats only), and mydriasis (dead rats only). In rats, drug-related CNS clinical signs were more evident in females than in males and the applicant's explanation that this was probably due to the noted gender difference in drug exposure (female>male) is plausible.

The oral MTD of perampanel was 3 mg/kg in dogs, and 2 mg/kg in monkeys since the animals given these doses exhibited severe pharmacology-based CNS clinical signs such as ataxia and prostration.

Repeat dose toxicity

In rodents, perampanel was administered orally for up to 13 weeks in mice and 26 weeks in rats at doses up to 1000 and 300 mg/kg/day, respectively. Perampanel was administered orally in non-rodents for up to 13 weeks in dogs and one year in monkeys at doses of up to 10 and 8 mg/kg/day, respectively

Significant findings related to perampanel in repeated-dose toxicity studies in all animal species were generally limited to pharmacology-based clinical signs consisting of abnormal gait, decreased activity, sedation, and prostration that are expected findings for an AMPA antagonist. These dosage-related clinical signs were mainly related to C_{max}. There were no drug-related histopathological lesions at any dose in the repeated-dose toxicity studies in rats, dogs or monkeys; although a dose-dependant decrease of corpora lutea was observed in the mice receiving ≥100 mg/kg. Cynomolgus monkey was selected as a non-rodent species for chronic repeated-dose toxicity studies in order to achieve higher systemic exposures.

The NOAELs were primarily the low doses in these studies. No significant toxicological findings were observed at 10 mg/kg in mice (C_{max} approximately 1100 ng/mL), at 1 mg/kg in rats (C_{max} ~ 250 ng/mL), at 1 mg/kg or 10 mg/kg in male and female dogs, respectively (C_{max} ~ 50 and 130 ng/mL, respectively), or at 0.6 mg/kg in monkeys (C_{max} ~ 240 ng/mL).

Genotoxicity

Perampanel was not genotoxic in the standard battery of genotoxicity studies.

Carcinogenicity

There was no evidence of carcinogenicity of perampanel in mice and rats.

Reproduction Toxicity

The range of studies conducted was in line with current guidance and provides a suitable package of reproductive toxicity studies.

In the rat male and female fertility study (**S01011**), prolonged and irregular oestrous cycles and consecutive dioestrus were observed at 30 mg/kg in females. The investigators have stated that the effects on the oestrous cycle have been reported for glutamate receptor involving AMPA type and hence the effects in this study are expected to be non-specific to the test-item, but moreover related to excessive pharmacological effects of a glutamate receptor antagonist. No drug-related effects on fertility and early embryonic development were noted at any dose.

In the rat (**200420**) and rabbit (**250520**) embryo-fetal development (EFD) studies, decreased body weight and food consumption were observed in maternal animals at the doses of 3 and 10 mg/kg. Drug-related CNS clinical signs were observed in rats at ≥ 1 mg/kg, and CNS clinical signs and premature delivery (3 dams) in rabbits at 10 mg/kg. A significant delay in ossification was noted in proximal phalanx of forepaws in the rat mid-dose group and the number of ossified proximal phalanx of forepaws in the rabbit high-dose group was significantly lower than controls. However, as there was no dose relationship between treated groups in rats and since neither changes in the number of ossified cases in any other bone was observed in rabbits, these findings were explained as incidental.

In the rat pre- or postnatal development study, abnormal delivery and nursing conditions were observed in some dams (3 or 10 mg/kg), and increased number of stillbirth, reduced birth and viability indexes were observed in the offspring. The NOAEL was 1 mg/kg. Clinical relevance of these effects cannot be determined at this stage. Therefore the proposed SmPC text in section 4.6 includes a statement that does not recommend the use of perampanel during pregnancy. This is accepted as there were no human margins of safety at the reported NOAEL in the rat pre- and post-natal development study.

Juvenile toxicity

For the rat study **901163** the treatment regimen was considered to be equivalent to the development in humans from birth to 18 years of age and hence supported the proposed clinical age for treatment. The Applicant has not stated the corresponding human age for the one-month juvenile dog (6 week old animals) study (**901978**).

In rats, a reduction in growth progression (body weights, crown-to-rump lengths, femur and tibia lengths, delayed preputial separation and vaginal opening) was observed at 3 mg/kg or higher, however, it was hypothesised that the findings were most likely secondary to the pharmacologically-based clinical signs (including decreased activity and lying on side/prostration) that may have resulted in decreased suckling time prior to weaning and lower food consumption during the post weaning period, and not due to direct effects of the test article. The effect upon growth progression showed signs of recovery following cessation of treatment. However, reduction in body weight was still significantly lower than controls by pp Day 118 (dosing ended on pp Day 90). It seems plausible that growth retardation (which was also significantly reduced in the recovery period) and delayed physical development could be secondary to perampanel-related toxicity. Furthermore, it is reassuring that there were no effects on measures of learning or behaviour, and the animals demonstrated normal reproductive function. The Applicant has compared exposures in juvenile and adult animals. At the MTD, C_{max} and AUC values were comparable between adult and juvenile rats. The C_{max} exposures at MTD in adult rats were generally equivalent or slightly higher than that observed in the clinic and AUC values were lower. In a 33-week toxicity study in juvenile dogs (Study **901979**), the C_{max} and AUC exposures in juvenile and adult (Study **S01009**) dogs were similar at all doses (males and females)

with no evidence of increased sensitivity to perampanel-related toxicities in juvenile dogs. It is, therefore, accepted that juveniles are generally equally sensitive to perampanel.

Toxicokinetic data

Increases in C_{max} and AUC were not always dose-proportional but did primarily increase with dose and accumulation was apparent. compared with the exposure at the maximum proposed human dose of 12 mg (C_{max}: 799 ng/mL, AUC: 7899 ng·h/mL) reported in clinical Study **E2007-A001-013**, exposure levels (AUC) at the NOAELs in the non-clinical repeated-dose studies are several-fold lower than or equivalent to (in 13 week mouse study only) that expected at the proposed maximum human dose.

Exposure to perampanel was higher in humans than in toxicology species and hence no human safety factor for the reported CNS-related toxicities can be established. It is, however, accepted that perampanel-related adverse effects were primarily attributed to pharmacologic effects and there was no systemic or organ toxicity and hence the risk/benefit ratio for perampanel as a treatment for epilepsy is positive, from a non-clinical perspective, as both non-clinical and clinical data support safe clinical usage. These findings are appropriately represented in the SPC.

Local Tolerance

Not applicable

Other toxicity studies

- **Dependency**

Nonclinical data suggests perampanel may have the potential to cause physical dependence (in rats) and reinforcing effects (in monkeys) although it was weak when compared with positive controls. Clinical evaluations have indicated that there is also abuse potential in humans, therefore, the risk benefit of this abuse potential will be definitively assessed clinically. No further non-clinical studies are required at this stage.

- **Combination toxicology**

Following 13-week rat and monkey studies enhancement of toxicity by concomitant administration of levodopa and carbidopa (LD/CD) with perampanel was evident in CNS-related clinical signs and probably related to the increased exposure level of perampanel in rats and monkeys.

- **Phototoxicology**

The 'battery' of phototoxicology studies conducted suggests that the risk for photoirritation, photoallergy, and photocarcinogenicity is low. Furthermore there are no clinical signals of photosensitivity. Therefore no further assessment is required from a toxicological perspective.

2.3.5. Ecotoxicity/environmental risk assessment

Table 1. Summary of main study results

Substance (INN/Invented Name): perampanel			
CAS-number: 380917-97-5			
PBT screening		Result	Conclusion
<i>Bioaccumulation potential- log K_{ow}</i>	OECD107	2.86	Potential PBT (N)
PBT-assessment			
Parameter	Result relevant		Conclusion

	for conclusion				
Bioaccumulation	log K_{ow}	2.86	not B		
	BCF		B/not B		
Persistence	DT50 or ready biodegradability		P/not P		
Toxicity	NOEC or CMR		T/not T		
PBT-statement :	The compound is not considered as PBT				
Phase I					
Calculation	Value	Unit	Conclusion		
PEC _{surfacewater} , default or refined (e.g. prevalence, literature)	0.009	µg/L	>0.01 threshold (N)		
Other concerns (e.g. chemical class)			(N)		
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results	Remarks		
Adsorption-Desorption	OECD 106 or ...	$K_{oc} = 2.71$	List all values		
Ready Biodegradability Test	OECD 301	no significant degradation of perampanel (1-2%)			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT _{50, water} = DT _{50, sediment} = DT _{50, whole system} = % shifting to sediment =	Not required if readily biodegradable		
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/ <i>Species</i>	OECD 201	NOEC	>1200	µg/L	<i>Pseudokirchneriella subcapitata</i>
<i>Daphnia</i> sp. Reproduction Test	OECD 211	NOEC	220	µg/L	
Fish, Early Life Stage Toxicity Test/ <i>Species</i>	OECD 210	NOEC	60	µg/L	<i>Pimephales promelas</i>
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	>1x10 ⁶	µg/L	

Perampanel is not a PBT substance.

An environmental risk assessment has been carried out and the studies conducted thus far indicate that perampanel does not pose a risk to the environment.

However, the Applicant calculated the PEC_{surfacewater} within Phase I of the ERA, using a refined F_{pen} which is based on prevalence data on epilepsy in Europe (Forsgren et al. 2005). The median prevalence value of 4.1 per 1000 inhabitants in children >10 years was used for the calculation instead of the overall median prevalence for children and adults of 5.2 per 1000 inhabitants. Furthermore, according to the current question-and-answer document (EMA/CHMP/SWP/44609/2010), in Phase I F_{pen} calculations, 100% medication compliance is always assumed. Furthermore, according to the SmPC perampanel should be taken once daily. If 365 days of treatment per year are assumed and the prevalence value of 5.2 is taken as the basis for F_{pen} refined, the calculated PEC_{surfacewater} exceeds the action limit of 0.01 µg/L. Although the applicant provided a phase II ERA for the active substance perampanel including the full study reports, further testing would be recommended.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation: The applicant should perform, post approval, an OECD 308 (aerobic system) study, and depending on the results, to perform an OECD 218 (sediment dwelling organism) study.

2.3.6. Discussion on non-clinical aspects

The applicant has conducted an acceptable range of nonclinical studies for Fycompa. No major objections were raised.

In vitro models support the hypothesis that perampanel might be a non-competitive AMPA antagonist. Perampanel showed potent anticonvulsant activities in several animal models of seizures. Even though the anticonvulsant effects of perampanel have been well demonstrated on various classical animal models, its mechanism of action remains elusive. Therefore it was recommended that the applicant pursue the understanding of the mechanism of action. In addition, it was requested that the Applicant elaborate further on the clinical relevance of the long tissue retention in the eyeball, especially given the common eye disorders seen in the clinic and assess a potential association between the slow elimination of radioactivity from the aorta and the cardiovascular adverse events observed in the clinical studies. No effects on ElectroRetinoGraphy (ERG) were noted in chronic toxicology studies in monkeys or dogs and these findings were supported by published data that suggested the binding of drugs to eye melanin is not predictive of ocular toxicity. With respect to the cardiovascular effects, no histopathologic findings in the aorta in any of the repeated-dose toxicology studies were noted.

The safety pharmacology profile was investigated in a series of in vivo studies in rats and dogs and one in vitro study. No non-clinical issues were raised.

The pharmacokinetics of perampanel was essentially well-characterised in toxicology species. Non-clinical concerns relating to the pharmacokinetic drug interactions were addressed in non-clinical sections of the SmPC. Specifically, it was requested that a warning with digoxin and dabigatran, both probe P-gp substrates and the levels of which may increase, should be included in the SPC. Further characterisation enzymes(s) participating in the metabolism of perampanel are to be addressed in the clinical assessment.

In single dose toxicology studies Clinical signs observed in rodents were pharmacology-based CNS effects. The oral MTD of perampanel was 3 mg/kg in dogs, and 2 mg/kg in monkeys. Repeat dose studies of up to 26 week in rodents, up to 13 weeks in dogs and one year in monkeys were conducted. Significant findings were generally limited to pharmacology-based clinical signs consisting of abnormal gait, decreased activity, sedation, and prostration that are expected findings for an AMPA antagonist. These dosage-related clinical signs were mainly related to C_{max}. The NOAELs were primarily the low doses in these studies. At the NOAELs exposure was measured and calculated to be several-fold lower than or equivalent to (in 13 week mouse study only) that expected at the proposed maximum human dose and hence no human safety factor for the reported CNS-related toxicities can be established. It is, however, accepted that perampanel-related adverse effects were primarily attributed to pharmacologic effects and there was no systemic or organ toxicity and hence the risk/benefit ratio for perampanel as a treatment for epilepsy is positive, from a non-clinical perspective, as both non-clinical and clinical data support safe clinical usage. These findings are appropriately represented in the SPC.

Perampanel was not genotoxic or carcinogenic in the standard battery of studies.

In reproductive toxicology and developmental studies, no drug-related effects on fertility and early embryonic development were noted at any dose. Incidences of embryo-fetal development toxicity, though drug-related, were not dose-related and were explained as incidental. In the rat pre- or postnatal development study, abnormal delivery and nursing conditions were observed in some dams, and increased number of stillbirth, reduced birth and viability indexes were observed in the offspring. As the clinical relevance of these effects cannot be determined the SPC text in section 4.6 includes a statement that does not recommend the use of perampanel during pregnancy. This is accepted as

there were no human margins of safety at the reported NOAEL in the rat pre- and post-natal development study.

Juvenile toxicology studies were conducted, and it was concluded that juveniles are generally equally sensitive to perampanel as adults.

An environmental risk assessment has been carried out however further studies are recommended to be conducted post-approval. Therefore an assessment of the impact of perampanel on sediment dwelling organism according to the CHMP Questions and Answers document should be performed.

The proposed wording in the SPC can be accepted as representative of the reported non-clinical profile.

2.3.7. Conclusion on the non-clinical aspects

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

In the fertility study in rats, prolonged and irregular oestrous cycles were observed at the maximum tolerated dose (30 mg/kg) in females; however, these changes did not affect fertility and early embryonic development. There were no effects on male fertility.

The excretion into breast milk was measured in rats at 10 days post-partum. Levels peaked at one hour and were 3.65 times the levels in plasma

In a pre- and postnatal development toxicity study in rats, abnormal delivery and nursing conditions were observed at maternally toxic doses, and the number of stillbirths was increased in offspring. Behavioural and reproductive development of the offspring was not affected, but some parameters of physical development showed some delay, which is probably secondary to the pharmacology-based CNS effects of perampanel. The placental transfer was relatively low; 0.09% or less of administered dose was detected in the foetus.

Juvenile toxicology studies were conducted, and it was concluded that juveniles are generally equally sensitive to perampanel as adults.

Perampanel was not genotoxic or carcinogenic in the standard battery of studies.

2.4. Clinical aspects

2.4.1. Introduction

The applicant received Scientific Advice from the CHMP on 24 January 2008, 08 May 2008 and 25 June 2009. The following clinical aspects related to studies included in the application were discussed in the above mentioned Scientific Advice letters: the design of the Phase III studies, endpoints, use of comparator, length of the maintenance period, duration of the follow-up and population for the primary efficacy analysis.

The applicant presented data obtained from 19 Phase 1 studies in healthy subjects, 3 phase II studies conducted in patients with partial-onset seizures, 3 open-label extension studies conducted in patients with partial-onset seizures, the pooled analysis of the controlled Phase III studies conducted in patients with partial-onset seizures and analysis of samples collected in adolescent patients aged 12 to 17.

In addition, studies have been conducted to evaluate the effect of impaired hepatic function and age on the PK of perampanel. Clinical studies have been conducted to evaluate possible drug-drug interactions between perampanel and drugs that might be co-administered with perampanel:

ketoconazole, carbamazepine, midazolam, ethinylestradiol and levonorgestrel-containing oral contraceptives, levodopa and alcohol.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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 pharmacology studies

Study Category

Study No.	Perampanel Doses Evaluated	Study Type/Population
Single-dose PK and PD studies in healthy subjects		
E2007-E044-001	0.2, 0.5, 1, 2, 4, 6, and 8 mg	Ascending dose study/adult males
E2007-E044-003	1 mg	Food effect/adults
E2007-E044-007	2 mg	Mass balance/elderly
E2007-A001-008	2 mg	Bioequivalence/adults
E2007-J081-010	0.25, 0.5, 1, 2, 4, 6, and 8 mg	Dose evaluation/Japanese males
E2007-E044-016	4 mg	Bioequivalence/adults
E2007-E044-017	8 mg	Bioavailability and mass balance/adult males
E2007-E044-028	4 mg	Bioavailability/adults
E2007-E044-037	12 mg	Bioequivalence/adults
E2007-A001-039	6 mg	Bioequivalence/adults
E2007-A001-040	12 mg	Bioequivalence/adults
Multiple-dose PK and PD studies in healthy subjects		
E2007-E044-002	1, 2, 4, and 6 mg QD	Ascending-dose study/adult males
E2007-E044-009	6 mg single dose	Food effect/adults
	6, 8, and 10 mg QD	Morning vs. evening dosing/adults
E2008-J081-026	2 and 4 mg QD	Ascending-dose study/Japanese males
Studies of PK and PD in epileptic patients		
E2007-E049-203	1 and 2 mg QD	Epileptic adults with partial-onset seizures
E2007-J081-231	2, 4, 6, 8, 10, and 12 mg QD	Epileptic adults with partial-onset seizures
Evaluation of intrinsic factors on PK and PD: studies in special populations		
E2007-E044-004	1 and 2 mg single dose	PK and PD in healthy elderly subjects
E2007-E044-015	1 mg single dose	PK in adults with hepatic impairment vs. healthy adults
Effect of extrinsic factor on PK: drug-drug interaction (DDI) studies		
E2007-E044-005	1 mg	Ketoconazole comparator/healthy adult males
E2007-E044-006	2 mg	Carbamazepine comparator/healthy adult males
E2007-A001-014	6 mg QD	Midazolam comparator/healthy adults
E2007-E044-019	2 and 4 mg QD	Microgynon® 30 ED comparator/healthy premenopausal females
E2007-E044-029	6 mg single dose; 4, 8, and 12 mg QD	Microgynon® 30 ED comparator/healthy premenopausal females
E2007-E044-025	4 mg QD	Levodopa comparator/healthy adults
E2007-E044-030	4, 8, and 12 mg single dose and QD	Alcohol study/healthy adults
Special studies in healthy subjects		
E2007-A001-013	6, 8, 10, and 12 mg QD	QT interval study/healthy adults
E2007-E044-020	2 and 6 mg QD	Phototoxic potential study/healthy adults
E2007-A001-023	8, 12, 16, 20, 24, 28, 32, and 36 mg single dose	MTD and abuse liability/recreational polydrug users
E2007-A001-024	8, 24, and 36 mg single dose	Abuse liability/recreational polydrug users

- Tabular overview of clinical safety and efficacy studies

Study ID	No. of study centres/ locations	Design	Study Objective	Study Posology	Sbjs by arm.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
PHASE 2 STUDIES									
E2007-A001-206	43; EU and US	RD, DB, PLA-controlled, parallel-group. 3 phases: 4-w baseline, 12-w DB (8-w titration, 4-w maintenance), 2-w transition	To determine the maximal tolerated dose	PLA	51	12 w	23/28 38.1 y 22/29 41.2 y	18-70 y Uncontrolled POS receiving 1 or 2 marketed fixed-dose AEDs	Proportion of 50% responders during maintenance period
				PRP QD (1 to 4 mg/d, flexible dosing)	51				
E2007-G000-208	17; EU	RD, DB, PLA-controlled, parallel-group. 3 phases: 4-w baseline, 16-w DB (12-w titration, 4-w maintenance), 4-w Follow-up	Safety and tolerability of doses up to 12 mg	PLA	10	16 w	5/5 18/20 41.7 y	18-70 y Uncontrolled POS receiving 2 or 3 marketed fixed-dose AEDs	Proportion of 50% responders during maintenance period
				PRP (2 to 12 mg; flexible dosing)	38				
E2007-J081-231	9; Japan	OL. 2 phases: 4-w observation, 10-w ttt (6-w titration, 4-w maintenance), 4-w follow-up	Safety and tolerability of doses up to 12 mg co-administered with other AEDs	PRP (2 to 12 mg; dosing to MTD)	30	10 w	16/14 35.4 y	20 to < 65 y Uncontrolled POS receiving 1 or 3 marketed fixed-dose AEDs	Seizure frequency, CGIC, PGIC
CONTROLLED PHASE 3 STUDIES									
E2007-G000-304	77; Argentina, Canada, Chile, Mexico, US	RD, DB, PLA-controlled, parallel-group. 3 phases: 6-w pre-randomisation, 19-w DB (6-w titration, 13-w maintenance), 4-w follow-up	Efficacy and safety	PLA	121		54/67	≥ 12 y Uncontrolled POS receiving up to 3 marketed fixed-dose AEDs	Non-EU: % change in frequency of all POS per 28 days during ttt relative to baseline EU: proportion of 50% responders
				PRP 8 mg	133		65/68		
				PRP 12 mg	134		69/65		
E2007-G000-305	84; Australia, EU, India, Israel, Russia, South Africa, US	RD, DB, PLA-controlled, parallel-group. 3 phases: 6-w pre-randomisation, 19-w DB (6-w titration, 13-w maintenance), 4-w follow-up	Efficacy and safety	PLA	136		71/65	≥ 12 y Uncontrolled POS receiving up to 3 marketed fixed-dose AEDs	Non-EU: % change in frequency of all POS per 28 days during ttt relative to baseline EU: proportion of 50% responders
				PRP 8 mg	129		65/64		
				PRP 12 mg	121		50/71		
E2007-G000-306	116; Argentina, Australia, Canada, Chile, China, EU, Hong Kong, India, Malaysia, Philippines, Russia,	RD, DB, PLA-controlled, parallel-group. 3 phases: 6-w pre-randomisation, 19-w DB (6-w titration, 13-w maintenance), 4-w follow-up	Efficacy and safety	PLA	185		95/90	≥ 12 y Uncontrolled POS receiving up to 3 marketed fixed-dose AEDs	Non-EU: % change in frequency of all POS per 28 days during ttt relative to baseline EU: proportion of 50% responders
				PRP 2 mg	180		85/95		
				PRP 4 mg	172		88/84		
				PRP 8 mg	169		77/92		
				QD at bedtime			33.8 y		

Serbia,
South
Korea,
Taiwan,
Thailand,
Ukraine

OPEN-LABEL EXTENSION STUDIES

E2007- G000- 307	283	Ongoing, OL 3 phases: 16- w blinded conversion, 256-w maintenance, 4-w follow-up	Safety and tolerability Maintenan ce of effect	PRP (2 to 12 mg, flexible dosing) QD at bedtime	1186	5 y	598/ 588 34.4 y	Subjects with POS who completed studies 304, 305, or 306	% change in frequency of all POS per 28 days compared to baseline of preceding study or pre-PRP baseline Proportion of 50% responders
E2007- A001- 207	48	Ongoing, OL 3 phases: 12- w titration, 424-w maintenance, 4-w follow-up	Safety and tolerability Maintenan ce of effect	PRP (2 to 12 mg, flexible dosing) QD at bedtime	138	436w	58/80 40.7 y	Subjects with POS who completed studies 206 or 208	% change in frequency of all POS per 28 days compared to pre-PRP baseline Proportion of 50% responders
E2007- J081- 233	9, Japan	Ongoing, OL 112-w ttt, 4-w follow-up	Safety and tolerability Long-term efficacy	PRP (2 to 12 mg, flexible dosing) QD at bedtime	21	116w	11/10	Subjects with partial seizures who completed 231	% change in frequency of all POS per 28 days compared to baseline of study 231 Proportion of 50% responders

AEDs: antiepileptic drugs

BID: twice-a-day dosing

DB: double-blind

MTD: maximum tolerated dose

OL: open-label, ttt: treatment

PLA: placebo

POS: partial-onset seizures

PRP: perampanel

QD: once-a-day dosing

RD: randomised

w: week

y: years

2.4.2. Pharmacokinetics

Absorption

Population PK analysis of the nineteen Phase I studies was performed.

The PK population consisted of 606 subjects, including 479 Caucasians, 28 Black/African Americans, 20 Asians, 60 Japanese, and 19 subjects of other races. There were 436 males and 170 females.

The population age and weight ranged from 18 to 76 years (median = 28.0 years) and 48 to 107 kg (median = 72.5 kg), respectively. The population BMI ranged from 18 to 46 kg/m² (median = 24.1 kg/m²).

After administration of single oral doses, perampanel was rapidly and almost completely absorbed. After C_{max} was reached, perampanel was eliminated from plasma in an apparent bi- or tri-exponential manner with a long apparent terminal disposition phase. Secondary peaks 24 hours after drug administration were also noted.

With once daily multiple-dose administration of perampanel under fasting conditions, a prominent absorption phase and an initial rapid disposition phase are also evident. When perampanel is administered under fasting conditions to healthy male subjects, peak to trough ratios (C_{min}/C_{max} x 100%) ranged from 57% to 82% over a 1 mg to 6 mg o.d. dose range (Study 002). In another study involving healthy Japanese male volunteers (Study 026), peak to trough ratios were 67% and 74% for 2 mg and 4 mg o.d. doses, respectively.

Reported mean terminal elimination half-lives ranged from 53 to 136 h across studies and dose groups. Except for $t_{1/2}$ and V_d/F , inspection of the PK parameter estimates across studies for the same dose level are reasonably consistent, the dose dependent PK parameters (C_{max} and AUC) increase with increasing dose, and the dose-independent PK parameters (i.e., CL/F) are similar across doses and studies.

The relatively low systemic clearance is due in part to relatively high plasma protein binding (unbound fraction about 5%, Studies B00033 and 017,) as well as low intrinsic clearance. In vitro studies demonstrated that human serum albumin is the principal binding protein in human plasma (Study AE-4737-G), and that the blood to plasma ratio of perampanel ranges from 0.55 to 0.59 (Study B06013).

Administration of perampanel with food consistently slows drug absorption (lower C_{max} and later t_{max} ; Studies 003 and 009) but does not change the extent of absorption. Administration of perampanel with food reduces peak to trough fluctuations (PTF) (Study 009).

- **Bioavailability**

Two bioavailability studies have been conducted:

- [E2007-E044-028](#) (*Relative Bioavailability; Suspension vs. Formulation C Tablet*)
- [E2007-E044-017](#) (*Absolute BA and Metabolite Identification Study*)

Biopharmaceutical studies have demonstrated that following oral administration, perampanel is almost completely absorbed with low oral systemic clearance and high relative BA (compared to suspension, Study 028) and high absolute BA (Study 017).

The oral clearance of perampanel based on blood levels is substantially lower than hepatic blood flow (1500 mL/min), consistent with a low hepatic extraction ratio and the observed high absolute BA of perampanel.

The rate of perampanel absorption for the oral suspension was slower than that of the tablet as shown by a prolonged t_{max} and an associated reduction in C_{max} . The extent of absorption (AUC_{0-t}) was similar for both perampanel formulations.

- **Bioequivalence**

Four tablet formulations have been used in perampanel clinical trials (A, B, C, and D). Formulation C and D tablets are proposed for commercial use. Formulation C (2-, and 4-mg tablets), which was used in the Phase 3 program, was developed to make the tablets distinguishable among all the tablet strengths by changing the color of the 2 mg film-coated tablet from yellow (Formulation B) to orange (Formulation C) and by producing a 4 mg tablet of different color and size. Formulation D (6-, 8-, 10-, and 12-mg tablets) was developed to permit convenient dose escalation. Compared with Formulation C, the amount of low-substituted hydroxypropyl cellulose in the tablet core of Formulation D was reduced and microcrystalline cellulose was added.

Four studies evaluated the bioequivalence (BE) of Formulation C and D dosed in healthy adult subjects (Studies 016, 037, 039, and 040).

Bioequivalence has been demonstrated between the 2X2mg, 2X3mg, 6X2mg and the equivalent single dose formulations.

Study 040 demonstrated bioequivalence between the 12mg and the 2mgx6 tablets. C_{max} was still lower when compared with the reference but the results were within the Confidence interval of 80-125%.

Perampanel oral suspension 4 mg failed to demonstrate bioequivalence with the corresponding dosage in tablets. The oral suspension had a much slower rate of absorption (prolonged t_{max} and reduction in C_{max}). The extent of absorption (AUC_{0-t}) was similar for both perampanel formulations. The applicant is not applying for an oral suspension.

Distribution

In vitro studies demonstrated that human serum albumin is the principal binding protein in human plasma (Study AE-4737-G), and that the blood to plasma ratio of perampanel ranges from 0.55 to 0.59 (Study B06013).

Study B00033 investigated the protein binding of perampanel in rat, dog and human plasma taken under fasting conditions. The protein binding was constant across the three dosages assayed (20 mg, 200 mg and 2000 mg). In humans, perampanel was 95.3-95.8% bound.

In Study 017 blood and plasma were analyzed at specific time points to determine plasma protein binding. The proportion of perampanel bound to plasma protein in vivo was $95.9 \pm 1.36\%$ at 1 hour postdose.

The results of Study AE-4737-G indicated that ¹⁴C-perampanel mainly bound to HSA and α -1-acid glycoprotein, and partially to HG in human serum. Saturable binding was found in α -1-acid glycoprotein.

Elimination

Perampanel is primarily eliminated by oxidative metabolism followed by conjugation and faecal and urinary excretion of perampanel metabolites.

The elimination half-life of perampanel is long (ca 105 hours) in healthy subjects. Given the long t_{1/2} in the absence of inducing AEDs, the Applicant has provided simulations to support the suitability of the proposed dose increment interval of one week. The simulations support weekly dosage adjustment in patients with median effective half-lives (83 h) or shorter, but raise concerns of unexpected tolerability problems as a result of dosage adjustments that are too frequent relative to the half life of the drug in patients with longer half-lives.

Perampanel appears to exhibit an essentially linear relationship between dose and plasma concentrations. Intra-subject variability of perampanel exposure appears to be moderate (15-30 %). The pharmacokinetics of perampanel is similar in healthy volunteers and patients.

Following oral administration of a microtracer dose of perampanel, 70% of the dose was recovered with 22% and 48% of radioactivity recovered in urine and faeces, respectively. Of radioactivity circulating in plasma, greater than 90% corresponded to parent drug. Although there are deficiencies in the supporting studies, from the available data, perampanel appears to be extensively metabolised, with little unchanged drug eliminated in urine or faeces.

- **Quantitation of the metabolic pathways of perampanel in vivo.**

The excretion balance study (007) was deficient for a number of reasons, most importantly because metabolic profiling was carried out on samples from single time points representing in total approximately 5% of the dose. The Applicant has highlighted data available from another study (017)

that qualified/quantified metabolites after administration of a radiolabelled dose of perampanel. The objective of the study was to evaluate the absolute bioavailability of perampanel following concomitant administration of an IV microdose of ¹⁴C-perampanel solution and a single oral dose of perampanel and to investigate the metabolite profile of perampanel in plasma, urine and faeces, and characterise metabolites where appropriate. These data are accepted as supportive since (1) there is reasonable evidence that the absolute bioavailability of perampanel is high with a minimal first pass effect and (2) in contrast to study 007 (conducted in healthy elderly subjects), the absolute bioavailability study (017) was conducted in young healthy volunteers, arguably more appropriate for extrapolation of data to other populations.

The metabolic profiling carried out in study 017 was more informative than that in study 007 since (1) three urine and three faecal samples spaced in time were used for the profiling and (2) almost 50% of the dose was represented in these samples (5% in urine and 42% in faeces). For comparison, the standard expected for an excretion balance study is that metabolic profiling is carried out on samples representing greater than 80% of excreted radioactivity. Although representing a smaller % of the dose than ideal, it is reassuring that the samples were spread over time and that the metabolite patterns were similar in the latter two sample collection intervals.

Although more informative than study 007, study 017 failed to adequately characterise the metabolic profile of perampanel, due to the very low extraction efficiencies of faecal samples (less than 20%). Extraction efficiencies of greater than 90% would typically be expected. Nevertheless, the metabolic profiles, particularly those in faeces, are reassuring in that there appear to be many metabolites at low levels (unidentified) in addition to the identified metabolites. And as the three samples used for profiling are well spaced through the elimination profile, it is unlikely that there are additional, as yet unidentified, metabolites of quantitative importance.

Thus, study 017 provides a greater insight and is reassuring that there are no unidentified major metabolites of perampanel, although the quantitative contribution of individual metabolites is not completely elucidated.

- **Enzymes responsible for perampanel metabolism.**

CYP3A4/5 has been shown to be involved in the metabolism of perampanel, but the involvement of other enzymes cannot be ruled out and requires further investigation. The data supporting the involvement of CYP3A4/5 in perampanel metabolism include in vitro evaluations, in vivo metabolic profiling, two in vivo drug-drug interaction studies, a population pharmacokinetic analysis and Simcyp simulations.

While the data generally support CYP3A4 an elimination pathway, there are sufficient inconsistencies and gaps that do not eliminate the possibility of other metabolic pathways of sufficient importance to be of concern for drug-drug interactions. Gaps include (1) lack of data for inhibitors of enzymes other than CYP3A4 (i.e. perampanel was incubated with human liver microsomes in the presence and absence of ketoconazole and a CYP3A antibody, but not inhibitors of other enzymes), (2) the metabolic pathway responsible for the production of the in vivo metabolite M5 is unknown and (3) the quantitative importance of M5 in vivo is not known because of the deficiencies in studies 007 and 017.

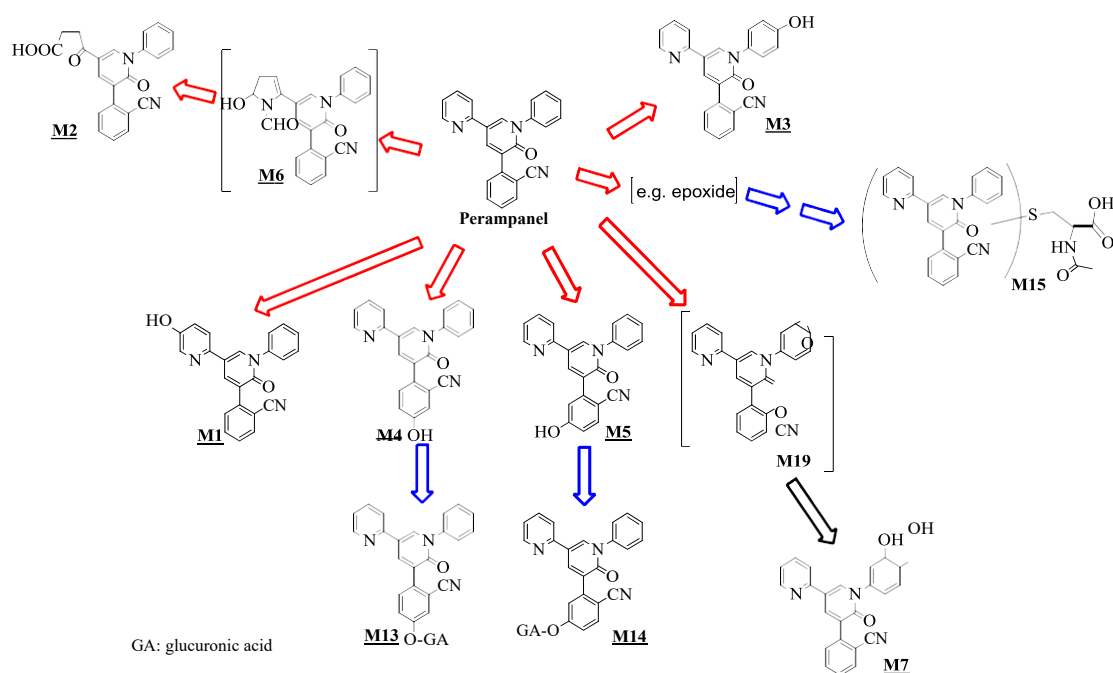
Ketoconazole co-administration (400 mg once daily for 10 days and 1 mg perampanel on day 3) increased perampanel exposure by only 20%. Although slow metabolism by CYP3A4 can be expected to reduce the extent of interaction expected for an inhibitor with a short half life (depending on study design), an extent of interaction that is almost within the range of bioequivalence is not expected. Additionally, the PBPK simulations predict a greater increase in AUC than observed with ketoconazole and a smaller decrease in AUC than observed with carbamazepine. PBPK simulations also showed that

a greater extent of interaction cannot be ruled out for CYP3A inhibitors with longer half-lives (e.g. itraconazole) or when co-administration is continued for a longer period of time (> 10 days).

The population PK analysis for perampanel showed interactions with the enzyme inducers carbamazepine, phenytoin, oxcarbazepine and topiramate. While these inducers are known to induce CYP3A4, they also induce other enzymes. This finding of an interaction is consistent with CYP3A4 as an elimination pathway, but not conclusive that it is the only pathway.

- **Formation of reactive metabolites**

The metabolism of perampanel is summarised qualitatively in the scheme below. Of note are two metabolites, M7 and M15, formed from reactive intermediates. The quantitative importance of reactive metabolic pathways is unknown for perampanel because of the deficiencies in studies 007 and 017. CYP3A4/5 plays a role in the formation of the reactive intermediates, M7 and M15, which are thought to result from an epoxide intermediate, as they were found as metabolites of perampanel when incubated in human microsomes and their formation was inhibited when ketoconazole or CYP3A antibody was added. However, as there was no study of the formation of these metabolites in the presence and absence of other inhibitors (in human microsomes), other pathways cannot be ruled out.



The formation of reactive metabolites is considered worthy of particular attention since there is a history of idiosyncratic immune-mediated adverse drug reactions for antiepileptic drugs which may be mediated through the formation of reactive metabolites, there is evidence from the literature that mortality from serious skin reactions with anti-epileptic drugs is significantly greater for drugs with long half-lives (> 24 h) and perampanel has a long half-life.

- **Implications for the safety of perampanel**

A mechanistic approach to drug-drug interactions is predicated on an understanding of the mechanisms/enzymes responsible for the elimination of a drug. For perampanel, uncertainty around the enzymes responsible for its metabolism precludes reassurance that the drug-drug interactions that could lead to increased formation of reactive metabolites or increased exposure to perampanel can be anticipated. This incomplete understanding adds uncertainty around the safety profile of perampanel.

The phase III studies for perampanel involved co-administration with a variety of other antiepileptic drugs, some of which are known enzyme inducers. The population PK analysis quantified the impact of co-administration of enzyme inducing antiepileptic drugs on perampanel exposure. Carbamazepine resulted in the greatest decrease in perampanel exposure (3-fold), while phenytoin was associated with a 2-fold decrease. Inconsistent with the impact on perampanel exposure, co-administration with carbamazepine resulted in little reduction in efficacy, while phenytoin showed a pronounced effect. The reason for this inconsistency is not understood.

As the safety and efficacy of perampanel was well documented in these studies the benefit/risk of perampanel is considered to be sufficiently established for adjunctive treatment of partial onset seizures. The continued uncertainty around the safety of perampanel with co-administration of other drugs is considered on balance to be manageable through additional clinical pharmacology studies undertaken as part of the risk management plan and through appropriate SmPC wording regarding with co-administration of strong inhibitors of enzymes other than CYP3A until these data are available.

The studies should include in vitro, in silico (simulations) and if needed in vivo investigations to characterise the enzymes involved in the formation of all identified metabolites (including M5), further elucidate the contribution of pathways other than CYP3A and better inform the SmPC regarding risk of drug-drug interactions. A stepwise approach will be necessary, with the results of in vitro studies potentially informing the final model used for additional PBPK simulations and the necessity of further in vivo studies (e.g. additional drug-drug interaction studies).

Dose proportionality and time dependencies

PK Data from Studies 009, 026, and 013, which collectively evaluated single and multiple dose ranging from 2 to 12 mg, did not reveal evidence of significant nonlinearities. Two additional studies utilized doses that ranged from 8 mg to 36 mg of perampanel in healthy poly-drug users (Studies 023 and 024). In the exploratory study (Study 023), C_{max} values increased less than proportionally with dose, whereas AUC (0-72 h) values increased roughly proportionally to dose. Over the 4.5-fold dose range, C_{max} values increased 2.7-fold and AUC (0-72 h) values increased 4.3-fold. In the definitive abuse liability study (Study 024), C_{max} and AUC (0-t) values increased less than proportionally with dose. Over the 4.5-fold dose range, C_{max} values increased 2.88-fold and AUC(0-t) values increased 3.41-fold.

In general agreement with the study-specific data presented above, definitive population PK analyses of plasma data from healthy subjects (0.2 to 36 mg) did not find evidence of significant PK nonlinearities (Study CPMS-E2007-2011-002).

Perampanel exhibits essentially linear PK over the dose range studied (0.25mg to 12 mg).

Special populations

- **Impaired hepatic function**

Because perampanel is eliminated primarily by oxidative metabolism, the effect of hepatic impairment on perampanel PK was evaluated in a prospective study:

- E2007-E044-015 (PK in adults with hepatic impairments vs. healthy adults)

In the hepatically impaired population, T_{1/2} was longer in mildly impaired (306h vs 125h) and moderately impaired (295h vs. 139h) when compared to the matching healthy subjects. Since Perampanel is primarily eliminated by oxidative metabolism followed by glucuronidation and fecal and urinary excretion of its metabolites it is therefore to be expected that its clearance

should be reduced in patients with hepatic dysfunction as confirmed by the results above. Consequently caution is advised in the proposed SmPC with regard to use in hepatic impairment.

- **Impaired renal function**

A clinical study examining the effect of renal impairment on perampanel PK has not been conducted. The population PK analysis for data from the controlled Phase III studies showed that clearance of perampanel was not significantly affected by mild renal impairment. There were insufficient patients with moderate renal impairment to support dosing in this population and use in patients with moderate and severe renal impairment cannot be supported.

- **Gender**

The results obtained from the 19 Phase I studies in healthy subjects, demonstrated no effect of sex on perampanel clearance.

The results from the controlled Phase III studies showed that perampanel CL/F was slightly lower in a typical female subject (0.605 L/h) than in a typical male subject (0.730 L/h), both with a median fat body mass of 17.1 kg and not taking any AEDs found to have a statistically significant effect on perampanel clearance.

- **Elderly**

Two studies have been conducted in the elderly:

- E2007-E044-007 (mass-balance study)
- E2007-E044-004 (PK and PD in healthy elderly subjects)

Study 004 was a randomised, double-blind, placebo controlled, three treatments, three group study evaluating the safety, tolerability, PK and PD of perampanel in elderly subjects.

The study included 24 elderly subjects (12 male and 12 female) aged 65 to 76 years old.

Three groups of eight subjects per group (four men and four women) received single oral doses of either 1 mg or 2 mg of perampanel (administered in escalating dose order) or placebo while fasted.

There was no apparent gender effect on the pharmacokinetics of perampanel.

Perampanel was safe and well tolerated following administration of single oral doses of 1mg and 2mg in healthy, elderly male and female subjects.

There were no deaths or serious adverse events, and no subjects were withdrawn from the study due to adverse events.

There was no evidence of significant sedation being induced by single doses of 1mg or 2mg perampanel in this elderly male and female population.

From the data above it can be concluded that there's no effect of age on the PK of perampanel. The SmPC doesn't require any dose adjustment for the elderly and this is acceptable.

- **Adolescents**

In the population PK analysis for data from the controlled Phase III studies (age range: 12 to 74 years), no effect of age on perampanel clearance was found (CPMS-E2007-2011-003).

A separate population PK analysis was conducted for adolescent subjects in the Phase III studies 304,305 and 306 (CPMS-E2007-2011-004). After selecting subjects aged <18 years old, with complete dosing and sampling information for perampanel and concomitant AEDs, the perampanel PK

adolescents population includes 74 subjects; the PK/PD population for efficacy and safety analysis includes 105 subjects.

The age ranged between 12 and 17 years of age, with median 15 years. Body weight ranged from 25.0 to 102 kg and BMI from 12.9 to 39.7 Kg/m². There were 57.1% males and 42.9% females. There were 85 Whites, 3 Blacks, 12 non-Chinese Asians and 5 others.

Approximately two thirds of all subjects of the PK population were administered at least one known, pre-specified, inducer AED, carbamazepine, oxcarbazepine, phenobarbital or phenytoin.

The result of the analysis showed that the clearance value in adolescents (0.787 L/h; similar for males and females) (CPMS-E200702011-004) was comparable to that for adult subjects with partial-onset seizures (0.730 L/h in males, 0.605 L/h in females).

Perampanel clearance increases in presence of co-administered carbamazepine and oxcarbazepine by approximately threefold and twofold respectively.

In the adolescent population, the increase of perampanel clearance due to co-administration of carbamazepine and oxcarbazepine was comparable to that estimated in the larger population analyzed (27). However, no significant effect of phenytoin (co-administered to 6 subjects treated with perampanel) was detected, likely due to the small number of subjects.

There were no differences in response to perampanel with sex, race, age, and co-administration of AEDs.

The pharmacokinetic parameters in the elderly were found to be similar to both those in the younger age groups studied. It seems unlikely therefore that age alone has any clinically significant impact on the PK of perampanel.

Pharmacokinetic interaction studies

Drug-drug interactions were evaluated in individual in vitro studies, studies in healthy volunteers and in a population PK analysis based on the pool of the double-blind, Phase III studies (CPMS-E2007-2011-002 and CPMS-E2007-2011-003).

- **Carbamazepine**

One open label, three treatment, fixed sequence three-way crossover study evaluated the effect of the CYP3A4 inducer carbamazepine on the PK, PD, safety and tolerability of perampanel (study - E2007-E044-006).

The treatment period comprised of three phases:

Days 1-10: A single dose of Perampanel ('E2007 alone')

Days 11-31: Repeated dosing with carbamazepine ('CBZ alone')

Days 32-42: A single dose of Perampanel in the presence of steady-state carbamazepine ('E2007+CBZ')

During the first phase subjects received a single 2 mg dose of perampanel on Day 1. In the second phase, carbamazepine dosing was started on Day 11 at 100 mg b.i.d. for one week (Days 11-17) then the dose was escalated to 200 mg b.i.d. for one week (Days 18-24) and 300 mg b.i.d. for one week (Days 25-31).

Carbamazepine dosing was continued at 300 mg b.i.d. for 10 days during the third phase (Days 32-41) with a single dose of perampanel being co-administered on Day 32.

Twenty healthy men were included in the study. 14 subjects completed the three treatments phases: perampanel alone, carbamazepine alone and perampanel+ carbamazepine.

It has been shown that co-administration of Perampanel with carbamazepine caused an increase in oral clearance of Perampanel and a corresponding reduction of Perampanel half-life and exposure. This finding is not surprising since carbamazepine is a known potent CYP3A4 inducer (in addition to CYP2C19).

The pharmacodynamic response was increased when perampanel was co-administered with carbamazepine. This confirms not only a PK interaction but also a pharmacodynamic interaction between Perampanel and carbamazepine.

Initial analysis of Study 006 indicated that there was a change in AEs when perampanel was administered alone or in combination with carbamazepine. The increase of central nervous system AEs during the co-administration phase are comparable to the AEs reported during carbamazepine only administration and consistent with the known AEs profile for carbamazepine.

In Study 006, the highest increase in ALT, AST and GGT values appeared during the co-administration phase. When carbamazepine was administered alone, the increase of these values was sporadic and lower than the combination. Perampanel alone didn't cause any significant increase in ALT, AST and GGT. From the data above, it seems that the co administration of perampanel and carbamazepine at steady state causes an increase in these values. Further analyses of Study 006 concluded that the elevations of liver enzymes could reasonably be attributed to carbamazepine. However, pooled analysis of the Phase III studies does not show a worse safety profile when perampanel was co-administered with carbamazepine than with another AEDs.

There is an increase in musculoskeletal and connective tissue disorders when Perampanel is co-administered with carbamazepine than with the 2 drugs administered alone.

- **Ketoconazole**

One open label, 2-way crossover study to evaluate the interaction between Perampanel and ketoconazole (Perampanel 1mg and ketoconazole 400mg) has been conducted (study - [E2007-E044-005](#)).

Twenty-six (2X13) patients were enrolled and analysed.

Co-administration of ketoconazole with perampanel caused a slight prolongation of perampanel half-life with a corresponding increase in total exposure. Mean perampanel half-life was 8 h (15%) longer and total exposure was approximately 20% higher when perampanel was co administered with ketoconazole than when perampanel was taken alone . Perampanel C_{max} and t_{max} showed no apparent differences when perampanel was administered alone or co-administered with ketoconazole.

From PBPK simulations it was shown that a higher extent of interaction could result from co-administration of inhibitors with longer half-lives (e.g. itraconazole) or for longer than 10 days, because of the long half-life of perampanel.

- **Estradiol and Levonorgestrel**

Two DDI studies (study 019 and 029) were conducted to evaluate the effect of perampanel on the PK of the components of an oral contraceptive (OC) pill in healthy premenopausal women.

Study 019

This open-label, three treatment, fixed sequence crossover study utilized a perampanel dose of 4 mg o.d. to evaluate the effect of perampanel on the PK of the components of Microgynon 30 ED (ethinylestradiol 30microgram and levonorgestrel 150microgram).

Perampanel 4 mg had no effect on the plasma levels of either component of the OC, AUC (0-t) and C_{max} were similar between treatments for both ethinylestradiol and levonorgestrel, and the 90% CIs of the ratios of these parameters were within the equivalence interval (80% to 125%).

Study 029

This open-label, non-randomized, fixed sequence study investigated the effect of steady-state perampanel on the PK of the components of a single dose of Microgynon-30 (ethinylestradiol 30microgram and levonorgestrel 150microgram (Part A) and the effect of repeated dosing of this OC on the PK of a single dose of perampanel (Part B).

The secondary objective for Study Part A was to investigate the effect of steady-state perampanel on QT interval duration relative to predose baseline.

PK Results, Part A:

Steady-state concentrations of perampanel following multiple doses of 8 mg perampanel had no statistically significant effect on the PK (C_{max} and AUC (0-24h)) of ethinylestradiol or levonorgestrel compared to the OC administration alone.

Steady-state concentrations of perampanel following multiple doses of 12 mg perampanel induced a decrease of C_{max} and AUC (0-24h) of levonorgestrel to 58% and 60 % (Or approximately 40%) compared with OC administration alone.

The combined effects of perampanel on ethinylestradiol and levonorgestrel suggest that 12 mg of perampanel increased the rate of levonorgestrel metabolism, but the induction did not appear to be CYP3A4-dependent

PK Results, Part B: Co administration of an OC containing ethinylestradiol and levonorgestrel did not affect the PK (bioequivalent) of a single dose of perampanel 6 mg.

- **Population PK Findings**

The population PK analysis using data from the pivotal Phase III studies evaluated the effect of commonly co-administered AEDs on perampanel PK. The following co-administered drugs (number of patients) were evaluated: carbamazepine (n=379), lamotrigine (n=357), valproate (n=350), levetiracetam (n=330), topiramate (226), oxcarbazepine (n=201), clobazam (n=115), zonisamide (n=94), phenytoin (n=91), clonazepam (n=82), phenobarbital (n=54), and primidone (n=18). Three known CYP3A4-inducer AEDs increased perampanel CL/F. Carbamazepine treatment increased perampanel CL/F approximately 3-fold. Oxcarbazepine or phenytoin treatment (at a median phenytoin concentration of 16.2 µg/mL), increased perampanel CL/F approximately 2-fold. Co-administration of perampanel with topiramate also slightly increased perampanel CL/F by 23% to 29%. None of the other concomitantly administered AEDs had an effect on perampanel clearance. The results of the population PK analysis should be viewed with caution, given the deficiencies noted in the methodology.

- **Effect of perampanel on other drugs**

Perampanel was found to have no impact on midazolam exposure and a small (15%) increase in C_{max} following 6 mg perampanel QD for 20 days. In a multiple-dose study, 4 mg of perampanel QD did not alter the PK of levodopa.

Pharmacokinetics using human biomaterials

In Vitro Drug Transporter Studies have shown that the inhibition percentages of perampanel for CYP2C8 and CYP3A4 were 40.7% and less than 14% at the 30 µmol/L, respectively. From these results, perampanel had inhibitory effect for CYP2C8 but not potent. On the other hand, perampanel showed virtually no or weak inhibitory effect for CYP3A4 up to 30 µmol/L. The inhibitory effect of perampanel for CYP3A4 increased with the pre-incubation of perampanel. The K_{inact} and perampanel concentration at 50% of K_{inact} (KI) were estimated to be 0.0360/min and 40.6 µmol/L, respectively (AE-4739-G).

Perampanel inhibited UGT1A9 and UGT2B7, as approximately 44% and 13% inhibition, respectively, at 30 µmol/L. There was little or no evidence of inhibition of UGT1A1, UGT1A4 or UGT1A6 by perampanel up to 30 µmol/L.

The IC₅₀ for these enzymes were reported as greater than 30 µmol/L.

Perampanel (up to 30 µmol/L) had little to no effect on UGT1A1, UGT1A4, UGT1A6, UGT1A9 and UGT2B7 activity.

2.4.3. Pharmacodynamics

Mechanism of action

Perampanel is described as an orally active, non-competitive and highly selective Alpha-amino-3-Hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist. AMPA receptors mediate cortical glutamatergic transmission; therefore AMPA antagonists could potentially reduce excessive excitatory activity and excitotoxicity. This effect could translate as an anticonvulsant and potentially antiepileptogenic effect.

However, it is still not entirely clear with what mechanism Perampanel exerts its antiepileptic effect. Until the precise mechanism is fully elucidated appropriate wording is included in SmPC (section 5.1)

Primary and Secondary pharmacology

- **Primary pharmacology**

This potential anticonvulsant activity has been studied and demonstrated in various seizures models in rodents.

The effects of perampanel on brain electrical activity were assessed in two Phase I studies in healthy volunteers (Studies 002 and 009) where effect on Delta, Theta and Beta waves was seen.

Increases in delta, theta, and, to a lesser extent, alpha activity were apparent at times corresponding to maximum perampanel plasma concentrations for doses greater than 1 mg. High beta activity was also increased at times corresponding to maximum plasma concentrations. These effects were global (i.e., across the whole cortex) and appeared to be dose-dependent.

These changes in waves activity, which are normally apparent during sleep, chemical sedation and drowsiness, could be translated in a reduction of excitatory activity and therefore a potential antiepileptic effect.

Perampanel related changes were similar after a single dose and after repeated dosing, suggesting the development of tolerance to perampanel effects over time.

- **Secondary pharmacology**

The effect of perampanel on sedation, saccadic eye movement or patient reported subjective mood scores have been evaluated in eight of the Phase I clinical pharmacology studies in healthy volunteers and one Phase II study in epileptic patients using a variety of scales (Studies 001,002,003,004,006,009,010, 026, 203).

Other sedation-related assessments (*Psychomotor Vigilance Task (PVT)*, *Karolinska Sleepiness Scale (KSS)*, and the fatigue and vigor items on the *Profile of Mood States (POMS)*) were performed to evaluate the PD of perampanel when administered alone and with alcohol (Study 030).

Psychomotor Performance, Cognitive Function and Postural Stability were also assessed.

Doses up to 1 mg produced no consistent difference from placebo with regard to effects on PD measures of sedation, including PSV (peak saccadic velocity) and VAMS (Visual Analogue Mood Scale) (Study001). PSV showed a dose-related reduction, indicative of a sedative effect, at 2 and 4 hours post dose among subjects who received 4, 6 and 8mg doses of perampanel.

The relationship between perampanel plasma concentrations and PSV at the 2 highest dose levels suggest that the maximum reductions in PSV occurred at or near the time of C_{max} (t_{max}), with PSV values subsequently returning toward predose levels as the plasma concentrations decreased.(Studies 001, 010,)

Study 002 (ascending dose, multiple dose study) confirmed that once daily doses up to 1 mg show no difference from placebo with regard the effects on PD measures of sedation and that the maximal effect for doses above 2 mg was apparent around C_{max} time.

The multiple dose administration showed that the effects of a particular dose were similar on Day1, 7 and 14 of dosing despite higher plasma concentration after repeating dosing. This would suggest a tolerance to this effect over time.

Electroencephalographic changes were largest in the 6mg dose group on day 14. No clear dose- response was observed for the lower dose levels.

Study 009 showed that repeated dosing with perampanel caused sedation in a dose-related manner. Evening dosing produced less daytime sedation than morning dosing.

Study 026 (ascending-dosing, multiple dosing) showed that repeated daily doses of perampanel did not result in any notable change from pre-treatment or vs., placebo in the VAMS anxiety, dysphoria and sedation sub-scores. Perampanel single and repeated daily administration was associated with decrease in PSV compared with placebo.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Absorption

Following oral administration, perampanel is rapidly and almost completely absorbed. The mean T_{max} ranges from 0.5 to 4.0 hours. The pharmacokinetic analysis of pooled data from the 19 Phase I studies showed that the mean t_{1/2} of perampanel is approx. 105 hours. Accumulation therefore occurs and steady state is reached after approximately 14 days of once daily dosing.

An interval of one week is recommended before dose increases in patients who are taking concomitant medicinal products that shorten the half-life of perampanel. An interval of two weeks is recommended before dose increases in patients who are taking concomitant medicines that do not shorten the half-life of perampanel. This information is mentioned in the SmPC (Section 4.2).

Perampanel exhibits essentially linear PK over the dose range studied (0.25mg to 12 mg).

Administration of perampanel with food has the effect of delaying absorption and reducing C_{max}. This information is mentioned in the SmPC (Section 5.2).

- **Bioavailability**

The oral bioavailability of Perampanel is close to 100%.

Perampanel oral suspension 4 mg failed to demonstrate bioequivalence with the corresponding dosage in tablets. The oral suspension had a much slower rate of absorption (prolonged t_{max} and reduction in C_{max}). The extent of absorption (AUC_{0-t}) was similar for both perampanel formulations. The applicant is not applying for an oral suspension.

- **Bioequivalence**

Bioequivalence has been demonstrated between the 2X2mg, 2X3mg, 6X2mg and the equivalent single dose formulations.

Distribution

Perampanel circulates around 96% protein bound to plasma proteins. The blood to plasma ratio ranges between 0.55 and 0.59.

Elimination

Perampanel is primarily eliminated by oxidative metabolism followed by conjugation and faecal and urinary excretion of perampanel metabolites.

A mechanistic approach to drug-drug interactions is predicated on an understanding of the mechanisms/enzymes responsible for the elimination of a drug. For perampanel, uncertainty around the enzymes responsible for its metabolism precludes reassurance that the drug-drug interactions that could lead to increased formation of reactive metabolites or increased exposure to perampanel can be anticipated. This incomplete understanding adds uncertainty around the safety profile of perampanel.

Inconsistent with the impact on perampanel exposure, co-administration with carbamazepine resulted in little reduction in efficacy, while phenytoin showed a pronounced effect. The reason for this inconsistency is not understood.

As the safety and efficacy of perampanel was well documented in the presented studies, the benefit/risk of perampanel is considered to be sufficiently established for adjunctive treatment of partial onset seizures.

The CHMP considers that the continued uncertainty around the safety of perampanel with co-administration of other drugs should be addressed by the Applicant through additional clinical pharmacology studies undertaken as part of the risk management plan.

The studies should include in vitro, in silico (simulations) and if needed in vivo investigations to characterise the enzymes involved in the formation of all identified metabolites (including M5), further elucidate the contribution of pathways other than CYP3A and better inform the SmPC regarding risk of drug-drug interactions. A stepwise approach will be necessary, with the results of in vitro studies

potentially informing the final model used for additional PBPK simulations and the necessity of further in vivo studies (e.g. additional drug-drug interaction studies).

The CHMP endorses the proposed SmPC wording regarding co-administration of strong inhibitors of enzymes other than CYP3A until the results of the undertaken studies are available.

Dose proportionality and time dependencies

Perampanel has shown linear PK over the dose range of 4mg to 12 mg. Doses above 12 mg showed a slightly less than proportional increases in C_{max} with increasing dose in some individual studies but not in the population PK analysis.

Special populations

- **Impaired hepatic function**

Perampanel clearance is reduced in patients with hepatic dysfunction. Caution is advised in the proposed SmPC (Section 4.2) with regard to use in hepatic impairment. At CHMP's request the applicant has included in the SmPC recommended dosing for patients with mild and moderate impairment which should not exceed 8 mg.

- **Impaired renal function**

Use of Perampanel in patients with moderate or severe renal impairment is not supported by the CHMP. This is acknowledged in the SmPC wording (Section 4.2).

- **Gender**

The results from the controlled Phase III studies showed that perampanel CL/F was slightly lower in a typical female subject (0.605 L/h) than in a typical male subject (0.730 L/h), both with a median fat body mass of 17.1 kg and not taking any AEDs found to have a statistically significant effect on perampanel clearance. The CHMP considers that this finding doesn't have any clinical significance therefore it can be concluded that gender has demonstrated no effect on perampanel clearance.

- **Elderly**

Based on the presented data the CHMP concludes that there's no effect of age on the PK of perampanel. Moreover it is considered that no dose adjustment for the elderly is needed.

- **Adolescents**

The pharmacokinetic parameters in the elderly were found to be similar to both those in the younger age groups studied. It seems unlikely therefore that age alone has any clinically significant impact on the PK of perampanel. On these bases, the CHMP considers that no dose adjustment for the adolescents is needed.

Pharmacokinetic interaction studies

Drug-drug interactions were evaluated in individual in vitro studies, studies in healthy volunteers and in a population PK analysis based on the pool of the double-blind, Phase III studies (CPMS-E2007-2011-002 and CPMS-E2007-2011-003).

- **Carbamazepine**

Treatment with the CYP3A4 inducer carbamazepine (300 mg BID) increased the clearance of perampanel 3-fold and decreased C_{max} and AUC(0-inf) values by 26% and 67%, respectively (Study 006). When administered with carbamazepine, the average $T_{1/2}$ of perampanel was 25 hours.

- **Ketoconazole**

The CYP3A4 inhibitor ketoconazole increased the AUC(0-inf) of perampanel by 20% (Study 005). From PBPK simulations it was shown that a higher extent of interaction could result from co-administration of inhibitors with longer half-lives (e.g. itraconazole) or for longer than 10 days, because of the long half-life of perampanel. Appropriate SmPC (Section 4.5) wording highlights these conclusions.

- **Estradiol and Levonorgestrel**

Multiple doses of perampanel at dose levels of 4 and 8 mg did not alter the pharmacokinetics of OC components ethinylestradiol and levonorgestrel.

The administration of perampanel 12 mg reduced levonorgestrel C_{max} and AUC by approximately 40%. At CHMP's request an appropriate warning has been included in the SmPC.

Following 12 mg multiple doses of perampanel ethinylestradiol, C_{max} was lowered by less than 20% whereas perampanel had no effect on AUC(0-24h) of ethinylestradiol.

- **Population PK Findings**

The results of the population PK analysis should be viewed with caution, given the deficiencies noted in the methodology. The CHMP noted, however, that the clinical efficacy of perampanel was not affected by the addition of other anticonvulsants and therefore further analysis and qualification/validation is not requested.

- **Effect of perampanel on other drugs**

Perampanel was found to have no impact on midazolam exposure and a small (15%) increase in C_{max} following 6 mg perampanel QD for 20 days. In a multiple-dose study, 4 mg of perampanel QD did not alter the PK of levodopa.

Pharmacodynamics

Since Peak Saccadic Velocity (PSV) is a very sensitive measure of CNS depression and has the advantage of being beyond voluntary control, this measure has been used to evaluate the sedative effect of perampanel on the CNS and its potential antiepileptic activity.

There would appear to be a dose-related increase reduction in PSV(peak saccadic velocity) values with doses above 2 mg. Doses below 2mg didn't show any difference in PD effects when compared with placebo. The maximum reduction in PSV values occurred around C_{max} . Section 4.4 of the SmPC contains a warning on the sedative effect of perampanel.

Multiple dose administration studies showed that tolerance to this effect seems to appear over time.

These effects are not altered by ethnic factors.

Perampanel in combination with alcohol (blood alcohol level of 80-100mg/100ml) consistently impaired psychomotor performance at all dose levels. In most of the cases the effects of alcohol were additive to those of perampanel, but in some cases a supra-additive effect was noted. This finding is included in section 4.5 of the SmPC.

As noted above, there is a pharmacokinetic interaction between Perampanel and carbamazepine. A PD interaction is also seen and co-administration of carbamazepine with Perampanel caused greater reductions in PSV and increases in VAMS sedation sub-scores.

Administration of 6mg and 12 mg of perampanel for 7 days didn't show any effects on heart rate and QTc intervals (*see safety section*).

2.4.5. Conclusions on clinical pharmacology

From the data gathered above it appears that perampanel at low doses (<4mg) doesn't have significant difference in PD effects when compared with placebo.

Electroencephalographic changes were largest in the 6mg dose group on day 14. No clear dose-response was observed for the lower dose levels.

With doses above 4mg there is a dose-related reduction in PSV (peak saccadic velocity) values.

The maximum reduction in PSV values occurred around C_{max}.

A tolerance to this effect seems to appear over time.

Perampanel exhibits essentially linear PK over the dose range studied (0.25mg to 12 mg).

Caution is advised in the proposed SmPC (Section 4.2) with regard to use in hepatic impairment. At CHMP's request the applicant has included in the SmPC recommended dosing for patients with mild and moderate impairment which should not exceed 8 mg.

Use of Perampanel in patients with moderate or severe renal impairment is not supported by the CHMP. This is acknowledged in the SmPC wording (Section 4.2).

Age and gender alone are not affecting the PK profile of perampanel.

The efficacy of perampanel is decreased when use concomitantly with inducer AEDs. However, no dose recommendation is needed (*see efficacy part*).

While the CHMP acknowledges that the applicant has conducted a comprehensive pharmacology development plan there's still remaining uncertainty around the safety profile of perampanel when co-administered with other drugs. The CHMP considers that the uncertainty can be addressed through additional clinical pharmacology studies undertaken as part of the risk management plan as detailed below:

1. The applicant should perform in vitro study(ies) to investigate the potential contribution of (i) non-CYP enzymes and (ii) CYP isoforms to the metabolism of perampanel. Due date: 31 May 2013.
2. The applicant should perform simulation studies to estimate the fraction of perampanel metabolised by CYP3A and to explore the possible effect of additional metabolic pathways identified in in-vitro studies on the human pharmacokinetics of perampanel and the impact of potential drug-drug interactions with inhibitors and inducers of the identified pathways. The applicant should submit the study protocol(s) for review prior to study start or provide a justification as to why additional in vivo studies are unnecessary. Due date: 30 June 2013.
3. Depending on the outcome of in-vitro and in-silico studies, the applicant should perform in vivo drug-drug interaction study(ies) to verify non-CYP metabolism contributing $\geq 25\%$ to the clearance of perampanel. The applicant should submit the study protocol(s) for review prior to study start or provide a justification as to why additional in vivo studies are unnecessary. Due date: 31 September 2013.

The CHMP endorses the proposed SmPC wording regarding co-administration of strong inhibitors of enzymes other than CYP3A until the results of the requested studies are available.

2.5. Clinical efficacy

In support of this application, the following efficacy studies have been conducted by the applicant:

- 3 controlled phase III studies(304,305 and 306);
 - 3 open-label extension studies(307,207 and 233);
 - 3 phase II studies(206,208 and 231)
- Tabular overview of clinical efficacy studies

Study ID	No. of study centres/ locations	Design	Study Objective	Study Posology	Sbjs by arm.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
PHASE 2 STUDIES									
E2007-A001-206	43; EU and US	RD, DB, PLA-controlled, parallel-group. 3 phases: 4-w baseline, 12-w DB (8-w titration, 4-w maintenance), 2-w transition	To determine the maximal tolerated dose	PLA PRP QD (1 to 4 mg/d, flexible dosing) PRP BID (1 to 4 mg/d, flexible dosing)	51 51 51	12 w	23/28 38.1 y 22/29 41.2 y 22/29 41.2 y	18-70 y Uncontrolled POS receiving 1 or 2 marketed fixed-dose AEDs	Proportion of 50% responders during maintenance period
E2007-G000-208	17; EU	RD, DB, PLA-controlled, parallel-group. 3 phases: 4-w baseline, 16-w DB (12-w titration, 4-w maintenance), 4-w Follow-up	Safety and tolerability of doses up to 12 mg	PLA PRP (2 to 12 mg; flexible dosing) QD at bedtime	10 38	16 w	5/5 18/20 41.7 y	18-70 y Uncontrolled POS receiving 2 or 3 marketed fixed-dose AEDs	Proportion of 50% responders during maintenance period
E2007-J081-231	9; Japan	OL. 2 phases: 4-w observation, 10-w ttt (6-w titration, 4-w maintenance), 4-w follow-up	Safety and tolerability of doses up to 12 mg co-administered with other AEDs	PRP (2 to 12 mg; dosing to MTD)	30	10 w	16/14 35.4 y	20 to < 65 y Uncontrolled POS receiving 1 or 3 marketed fixed-dose AEDs	Seizure frequency, CGIC, PGIC
CONTROLLED PHASE 3 STUDIES									
E2007-G000-304	77; Argentina, Canada, Chile, Mexico, US	RD, DB, PLA-controlled, parallel-group. 3 phases: 6-w pre-randomisation, 19-w DB (6-w titration, 13-w maintenance), 4-w follow-up	Efficacy and safety	PLA PRP 8 mg PRP 12 mg QD at bedtime	121 133 134		54/67 65/68 69/65 36 y	≥ 12 y Uncontrolled POS receiving up to 3 marketed fixed-dose AEDs	Non-EU: % change in frequency of all POS per 28 days during ttt relative to baseline EU: proportion of 50% responders
E2007-G000-305	84; Australia, EU, India, Israel,	RD, DB, PLA-controlled, parallel-group. 3 phases: 6-w	Efficacy and safety	PLA PRP 8 mg	136 129		71/65 65/64	≥ 12 y Uncontrolled POS receiving up	Non-EU: % change in frequency of all POS per 28

	Russia, South Africa, US	pre-randomisation, 19-w DB (6-w titration, 13-w maintenance), 4-w follow-up		PRP 12 mg QD at bedtime	121		50/71 35.5 y	to 3 marketed fixed-dose AEDs	days during ttt relative to baseline EU: proportion of 50% responders
E2007-G000-306	116; Argentina, Australia, Canada, Chile, China, EU, Hong Kong, India, Malaysia, Philippines, Russia, Serbia, South Korea, Taiwan, Thailand, Ukraine	RD, DB, PLA-controlled, parallel-group. 3 phases: 6-w pre-randomisation, 19-w DB (6-w titration, 13-w maintenance), 4-w follow-up	Efficacy and safety	PLA PRP 2 mg PRP 4 mg PRP 8 mg QD at bedtime	185 180 172 169		95/90 85/95 88/84 77/92 33.8 y	≥ 12 y Uncontrolled POS receiving up to 3 marketed fixed-dose AEDs	Non-EU: % change in frequency of all POS per 28 days during ttt relative to baseline EU: proportion of 50% responders
OPEN-LABEL EXTENSION STUDIES									
E2007-G000-307	283	Ongoing, OL 3 phases: 16-w blinded conversion, 256-w maintenance, 4-w follow-up	Safety and tolerability Maintenance of effect	PRP (2 to 12 mg, flexible dosing) QD at bedtime	1186	5 y	598/588 34.4 y	Subjects with POS who completed studies 304, 305, or 306	% change in frequency of all POS per 28 days compared to baseline of preceding study or pre-PRP baseline Proportion of 50% responders
E2007-A001-207	48	Ongoing, OL 3 phases: 12-w titration, 424-w maintenance, 4-w follow-up	Safety and tolerability Maintenance of effect	PRP (2 to 12 mg, flexible dosing) QD at bedtime	138	436w	58/80 40.7 y	Subjects with POS who completed studies 206 or 208	% change in frequency of all POS per 28 days compared to pre-PRP baseline Proportion of 50% responders
E2007-J081-233	9, Japan	Ongoing, OL 112-w ttt, 4-w follow-up	Safety and tolerability Long-term efficacy	PRP (2 to 12 mg, flexible dosing) QD at bedtime	21	116w	11/10	Subjects with partial seizures who completed 231	% change in frequency of all POS per 28 days compared to baseline of study 231 Proportion of 50% responders
AEDs: antiepileptic drugs BID: twice-a-day dosing DB: double-blind MTD: maximum tolerated dose			OL: open-label, ttt: treatment PLA: placebo POS: partial-onset seizures PRP: perampanel			QD: once-a-day dosing RD: randomised w: week y: years			

2.5.1. Dose response studies

Four phase II studies were designed to assess initial tolerability and pharmacokinetic in the target population (203), establish POC and provide information on the dose regimen (206), and evaluate the safety and tolerability of doses up to 12 mg (208,231).

Study 203 included only 18 subjects and was not designed to assess efficacy.

Results from study 206 guided selection of the once-daily dosing regimen used in the Phase III studies, while data from all Phase II studies guided selection of the perampanel dose range investigated in the Phase III studies (2 to 12 mg).

E2007-A001-203

This randomized, double-blind, placebo-controlled, parallel group study was designed to evaluate the tolerability, safety, PK, and PD of repeated doses of perampanel in epileptic patients with partial and generalized seizures. An initial cohort of subjects received perampanel 1 mg QD (six subjects) or placebo QD (three subjects) for 28 days. Once the safety and tolerability of the initial dosage regimen were deemed satisfactory, a second cohort of subjects received perampanel at a dose of 2 mg QD (six subjects) or placebo QD (three subjects) for 28 days.

The pharmacokinetics of perampanel were characterised by rapid absorption followed by multiphasic disposition.

Exposure was higher after 14 days of dosing than after a single dose.

Steady state was achieved after 14 days of dosing.

Perampanel exposure after repeated dosing was lower among patients also taking anti-epileptic drugs known to cause induction of cytochrome P450.

Perampanel had no apparent effect upon levels of the anti-epileptic drugs carbamazepine, phenytoin and valproate.

E2007-A001-206

This was a 22-week, dose-escalation (to a maximum of 4 mg/day), parallel-group study conducted at 43 centers in the EU, Australia and US.

The primary objective of this study was to determine the maximal tolerated dose (MTD) of perampanel given BID or QD in subjects with refractory partial-onset seizures (including secondarily generalized seizures).

The secondary objectives were to evaluate the safety, efficacy, concentration-efficacy relationship, and pharmacokinetics of perampanel and the effects of perampanel on the Profile of Mood States (POMS) test.

The study drug was administered orally QD or BID. The doses were to be separated by approximately 12 hours, in the morning between 7 and 9 AM, and in the evening between 7 and 9 PM. Subjects were encouraged to take the drug with food.

Within groups, subjects were stratified 1:1 according to their concomitant antiepileptic medication(s) (AEDs) into one of 2 categories:

(1) induced (treated with one or a maximum of 2 marketed and approved antiepileptic inducer medications such as carbamazepine, phenytoin, phenobarbital, or primidone)

(2) non-induced (treated with one or a maximum of 2 marketed and approved antiepileptic non-inducer medications such as topiramate, lamotrigine, gabapentin, tiagabine, zonisamide, valproate, oxcarbazepine, pregabalin, or levetiracetam, and none of the drugs in the induced group).

Overall, 4mg doses of perampanel were well tolerated in the BID and QD dosing and also in the induced and non-induced subgroups.

For the primary efficacy endpoint, the median percentage seizure reduction showed approximately 26% improvement in perampanel and 19% improvement in the placebo in the Maintenance Phase

(LOCF). Despite a trend in antiepileptic effect is seen for perampanel, there was not a statistically significant difference compared with the placebo group ($p=0.1894$). The study did not show a significant p -value of <0.05 in the responder rate.

No statistically significant difference was also noted for the secondary efficacy endpoints.

The applicant states that the study was under powered to statistically detect the effect size seen in the trial. This is considered acceptable.

The AE profile and the safety and tolerability results obtained with Study 206 showed that the maximum tolerated dose of perampanel has not been reached in this trial and higher doses could be investigated.

E2007-G000-208

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Explore the Safety and tolerability of Doses of E2007 up to a maximum of 12 mg in Patients with Refractory Partial Seizures

The primary objective of this study was to determine the safety and tolerability of doses up to a maximum of 12 mg per day of perampanel in patients with refractory partial seizures who were taking inducing and non inducing anti-epileptic drugs (AEDs).

Secondary objectives were:

- To investigate the efficacy of perampanel for the treatment of partial seizures;
- To explore the relationship between perampanel plasma concentrations and safety and efficacy measurements.

Exploratory:

- To determine the proportion of responders at the maximum tolerated dose (MTD) in the Maintenance Phase.

The result shows that doses up to 8mg are well tolerated. A small subgroup of subjects tolerated well the 12mg dose.

Since this study was not powered to detect statistical significance in any of the efficacy endpoints, the efficacy results are not discussed.

E2007-J081-231

This was an ascending high-dose; add on study of E2007 in Japanese patients with refractory partial seizures uncontrolled with other antiepileptic drugs.

Primary objective was to explore the safety and tolerability of perampanel up to 12mg co administered with other AEDs.

This study was conducted in Japanese subjects with epilepsy in an open-label manner for safety consideration since this was the first step to find out the maximum dose (maximum tolerated dose: MTD) of perampanel per subject.

The titration was set to be 6 weeks consisting of 5-week up-titration to 12 mg (the maximum dose) and the following 1-week with the maintained dose to confirm the safety, if started from 2 mg and titrate at 2 mg each week up to the maximum 12 mg.

As the period of safety review for a certain period of perampanel administration, maintenance period was 4 weeks in total, combining steady state period plus another 2 weeks. The treatment period was designed to be 10 weeks in total.

Perampanel up to 10 mg was well tolerated by the Japanese volunteers (50% tolerable subjects).

Tolerability for 8mg, 10mg and 12 mg doses was slightly higher in non Japanese subjects.

The analysis of the efficacy variables were descriptive and no formal statistical testing was done.

2.5.2. Main studies

A Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group Study to Evaluate the Efficacy and Safety of E2007 (perampanel) Given as Adjunctive Therapy in Subjects with Refractory Partial Seizures (E2007-G000-304)

Methods

Study Participants

Male or female subjects, greater than or equal to 12 years of age with a diagnosis of refractory partial seizures with or without secondarily generalized seizures.

This study were to include approximately 60-80 sites in the North America (NA), and South America. Approximately 375 subjects were planned for enrollment.

• Inclusion Criteria

Subjects who were to be included in the study were those:

1. Who provided written informed consent signed by the 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 was also obtained.)
2. Who were considered reliable and willing to be available for the study period and able to record seizures and report AEs themselves or had a caregiver who could record seizures and report AEs for them.
3. Male or female and greater than or equal to 12 years of age within the course of the study.
4. Females were either of nonchildbearing potential (defined as having undergone surgical sterilization, or postmenopausal [age 50 and amenorrheic for 12 months]) or of childbearing potential. Females of childbearing potential had a negative serum betahuman chorionic gonadotropin (β -hCG) at Visit 1 and a negative urine pregnancy test prior to randomization at Visit 2. Female subjects of childbearing potential agreed to be abstinent or to use at least 1 medically acceptable method of contraception (e.g., a double-barrier method [e.g., condom + spermicide, condom + diaphragm with spermicide], intrauterine device, or have a vasectomized partner) starting at Visit 1 and throughout the entire study period and for 2 months after the last dose of study drug. Women using hormonal contraceptives also used an additional approved method of contraception (as described previously) starting at Visit 1 and continuing throughout the entire study period and for 2 months after the last dose of study drug. It was not required for male subjects to use contraceptive measures.)
5. Who had a diagnosis of epilepsy with partial seizures with or without secondarily generalized seizures according to the International League Against Epilepsy's Classification of Epileptic Seizures (1981). Diagnosis was established by clinical history and an EEG that was consistent with localization-related epilepsy; normal interictal EEGs were allowed provided that the subject met the other diagnosis criterion (i.e., clinical history).

6. Who had a computed tomography or magnetic resonance imaging within the last 10 years that ruled out a progressive cause of epilepsy.
7. Who had uncontrolled partial seizures despite having been treated with at least two different AEDs within approximately the last 2 years.
8. During the 6-week Prerandomization Phase, subjects must have had five or more partial seizures (with two or more partial seizures per each 3-week period) and no 25-day seizure-free period in the 6-week period, as documented via a valid seizure diary. Only simple partial seizures with motor signs, complex partial seizures, and complex partial seizures with secondary generalization were counted toward this inclusion.
9. Who were currently being treated with stable doses of one, two or a maximum of three approved AEDs. Only one inducer AED (defined as carbamazepine, phenytoin, phenobarbital, or primidone) out of the maximum of three AEDs was allowed.
10. Who were on a stable dose of the same concomitant AED(s) for 1 month (or no less than 21 days) prior to Visit 1; in the case where a new AED regime was initiated for a subject, the dose must have been stable for 2 months (or no less than 49 days) prior to Visit 1.
11. If on a stable dose (other than intermittent rescue use) of benzodiazepines for epilepsy (or for anxiety or sleep disorders), the prescribed dose was stable for 1 month (or no less than 21 days) prior to Visit 1. (Note that the use of intermittent rescue benzodiazepines is defined in exclusion criterion #22 below.) When used in these cases (epilepsy, anxiety or sleep disorders), benzodiazepines were counted as one AED; therefore, only one or a maximum of two additional approved AEDs were allowed.
12. A vagal nerve stimulator was allowed but it must have been implanted \geq 5 months prior to Visit 1. Stimulator parameters could not be changed for 1 month (or no less than 21 days) prior to Visit 1 or thereafter during the study.

- **Exclusion Criteria**

Subjects who were to be excluded from the study were those:

1. Who participated in a study involving administration of an investigational compound or device within 1 month (or no less than 21 days) prior to Visit 1, or within approximately five half-lives of the previous investigational compound, whichever is longer
2. Who were pregnant and/or lactating
3. Who participated in previous perampanel studies
4. With a presence of non motor simple partial seizures only
5. With a presence of primary generalized epilepsies or seizures, such as absences and or myoclonic epilepsies
6. With a presence or previous history of Lennox-Gastaut syndrome
7. With a history of status epilepticus within approximately 12 months prior to Visit 1
8. With seizure clusters where individual seizures could not be counted
9. With a history of psychogenic seizures
10. With evidence of clinically significant disease (e.g., cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could have affected the subject's safety or the study conduct

11. Scheduled and/or confirmed to have epilepsy surgery within 6 months after Visit 1; however those with previously documented "failed" epilepsy surgery were allowed.
12. With evidence of significant active hepatic disease. Stable elevations of liver enzymes, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) due to concomitant medication(s) were allowed if they were less than 3 times the upper limit of normal (ULN).
13. With evidence of significant active hematological disease; white blood cell (WBC) count $\leq 2500/\mu\text{L}$ ($2.50 \text{ 1E}+09/\text{L}$) or an absolute neutrophil count $\leq 1000/\mu\text{L}$ ($1.00 \text{ 1E}+09/\text{L}$)
14. With a clinically significant ECG abnormality, including prolonged QTc defined as $> 450 \text{ msec}$
15. Suffering from psychotic disorder(s) and/or unstable recurrent affective disorder(s) evident by use of antipsychotics or who had a suicide attempt(s) within approximately the last 2 years
16. With a presence of a progressive central nervous system (CNS) disease, including degenerative CNS diseases and progressive tumors
17. With a history of drug or alcohol dependency or abuse within approximately the last 2 years
18. Who had multiple drug allergies or a severe drug reaction to an AED(s), including dermatological (e.g., Stevens-Johnson syndrome), hematological, or organ toxicity reactions.
19. If felbamate was used as a concomitant AED, subjects were on felbamate for at least 2 years, with a stable dose for 2 months (or no less than 49 days) prior to Visit 1. They must not have had a history of WBC count of $\leq 2500/\mu\text{L}$ ($2.50 \text{ 1E}+09/\text{L}$), platelets below $100,000/\text{mm}^3$, liver function tests above 3 times the ULN, or other indication of hepatic or bone marrow dysfunction while receiving felbamate. If subjects received felbamate in the past, it must have been discontinued 2 months (or no less than 49 days) prior to Visit 1.
20. With concomitant use of vigabatrin. Subjects who took vigabatrin in the past were off vigabatrin for approximately 5 months prior to Visit 1 and had documentation showing no evidence of a vigabatrin-associated clinically significant abnormality in a visual perimetry test.
21. With concomitant use of barbiturates (except for seizure control indication) within 1 month (or no less than 21 days) prior to Visit 1
22. With use of intermittent rescue benzodiazepines (i.e., one or two doses over a 24-hour period considered one-time rescue) two or more times in a 1-month period prior to Visit 1
23. With any condition(s) that made the subject, in the opinion of the investigator, unsuitable for the study.

Treatments

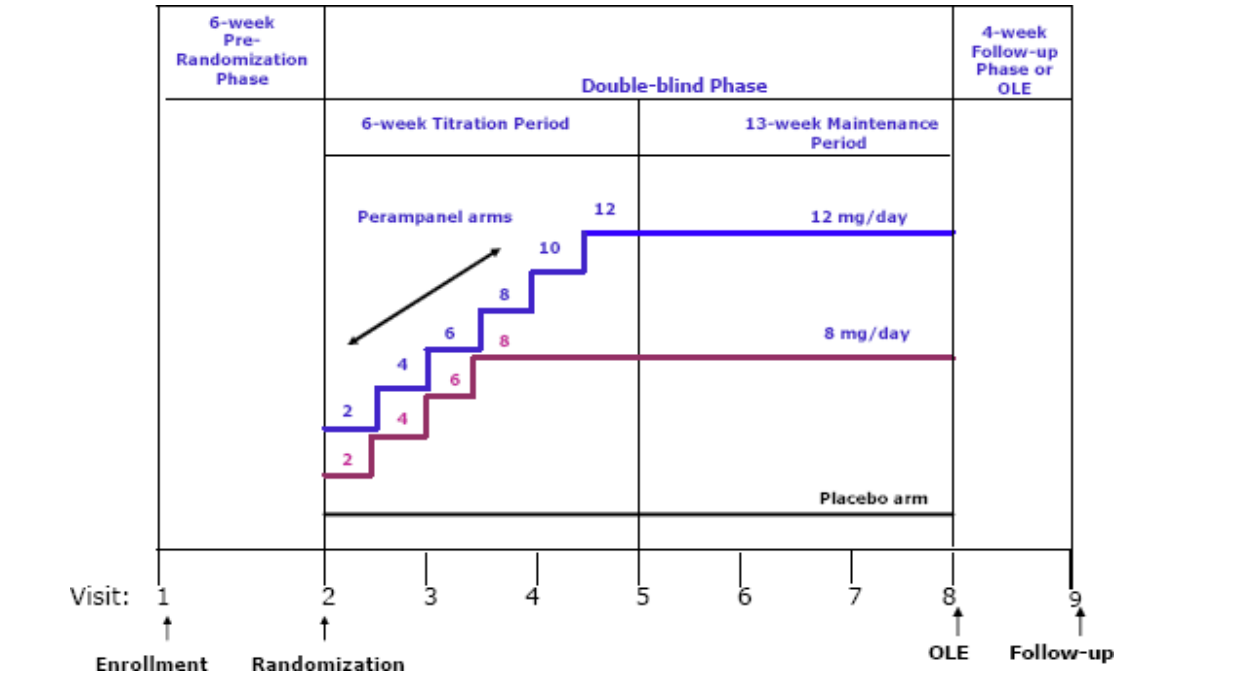
The study consisted of three phases:

- The Pre randomization Phase was 6 weeks in duration.
- The Double-blind Phase was 19 weeks in duration and included two periods: Titration and Maintenance. The Titration Period was 6 weeks in duration and the Maintenance Period was 13 weeks in duration.
- The Follow-up Phase was 4 weeks in duration.

No treatment was to be administered during the Pre-randomization Phase of the study. Once a subject completed this phase, they were randomized to treatment and begin the 6-week Double- Blind Phase

Titration Period (Visit 2 to Visit 5). Throughout the entire Double-blind Phase, all subjects took a total of 6 tablets daily.

During the Titration Period, all subjects started on 6 tablets (1 tablet of 2 mg perampanel plus 5 tablets of placebo or 6 tablets of placebo) and titrated to the appropriate randomized dose (8 mg or 12 mg perampanel, or placebo).



Objectives

• Primary Objectives

- To evaluate the efficacy of two doses of perampanel (8 and 12 mg) in comparison to placebo given as an adjunctive therapy in subjects with refractory partial seizures.

• Secondary Objectives

- To evaluate the safety and tolerability of perampanel vs. placebo in subjects with refractory partial seizures.

• Exploratory Objectives

- To explore potential withdrawal symptoms of perampanel vs. placebo in subjects with refractory partial seizures.
- To explore potential photosensitivity of perampanel vs. placebo in subjects with refractory partial seizures.
- To explore the relationship of DNA sequence variability to exposure, development of AEs, or response to perampanel in subjects with refractory partial seizures.
- To explore the effects of perampanel on partial seizure frequency (in 25% increments), on the frequency of complex partial seizures with secondary generalization, and on Clinical and Patient Global Impressions of Change.

Outcomes/endpoints

- **Primary Efficacy Variable(s)**

The primary efficacy endpoint for EU registration was the 50% responder rate. Responders were defined as subjects who experienced a 50% or greater reduction in seizure frequency per 28 days in the Maintenance Period relative to the Prerandomization Phase.

- **Secondary Efficacy Variable(s)**

- The key secondary efficacy endpoint was the percent change in seizure frequency.
- The other secondary endpoint was the percent change in complex partial plus secondarily generalized seizure frequency per 28 days during treatment relative to baseline.

- **Exploratory Efficacy Variable(s)**

Exploratory efficacy endpoints included:

- The percentage of subjects experiencing decreases/increases (25% increments) in seizure frequency per 28 days; change in the number of seizure-free days per 28 days;
- The percentage of subjects who achieved seizure-free status;
- Clinical and Patient Global Impressions of Change;
- Time to 1st, 3rd, 6th, 9th, and 12th seizures during treatment;
- Time to first 50% response;
- The percent change in the frequency per 28 days of complex partial seizures with secondary generalization; 50% responder rates based on complex partial plus secondarily generalized seizures, and on complex partial seizures with secondary generalization only;
- Change in total and subscale scores for the QOLIE-31-P.

Sample size

A sample size of 375 subjects was estimated.

Based on Phase II studies in subjects with epilepsy, it was assumed that the percent change in seizure frequency per 28 days in the Maintenance Period relative to the Prerandomization Phase would be 10% in the placebo group and 32% in the 8 mg group in the ITT Analysis Set. Therefore, a sample size of 120 subjects in each treatment group in the ITT Analysis Set would have 83% power to detect a treatment difference of 22% in seizure frequency (assuming a common SD of 56%) between placebo and each perampanel group based on the Wilcoxon rank-sum test with a 0.05 two-sided significance level. To account for subjects who might be randomized but not be included in the ITT Analysis Set, the number of subjects randomized was to be approximately 125 per treatment group.

Randomisation

Subjects were assigned randomized to one of the three treatment groups in a 1:1:1 ratio based on a randomization scheme generated using a computer program. The randomization scheme was reviewed and approved by an independent statistician and locked after approval.

Blinding

The double-blind design of these studies 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 treatment groups.

During the Double-blind Phase, the subject and all personnel involved with the conduct and the interpretation of the study, including the investigators, investigational site personnel and Eisai staff, were blinded to the treatment codes. Randomization data were kept strictly confidential, filed securely by the Eisai Scientific and Operational Clinical Support Core Functional Unit, and accessible only to authorized persons per SOPs until the time of unblinding.

Statistical methods

The primary efficacy endpoint for EU registration was the 50% responder rate. For all other purposes, this was the key secondary endpoint. Responders were defined as subjects who experienced a 50% or greater reduction in seizure frequency per 28 days in the Maintenance Period relative to the Pre-randomisation Phase.

Responder rate analysis of subjects who experienced a 50% or greater reduction in seizure frequency during treatment relative to baseline was conducted using the Cochran–Mantel–Haenszel (CMH) test adjusting for pooled countries.

The key secondary efficacy endpoint was the percent change in seizure frequency per 28 days during treatment relative to baseline. In this context, seizure frequency refers to the frequency of all partial seizures. For this analysis, both the baseline seizure frequencies per 28 days and the percent change per 28 days during treatment were rank transformed separately. An analysis of covariance (ANCOVA) was then conducted on the rank-transformed percent change data, with treatment and pooled countries as factors and the ranked baseline seizure frequency per 28 days as a covariate. P values were computed using contrasts between active and placebo treatment groups.

Due to an expected irregular distribution of seizure frequency, median was the primary statistic of interest for comparing the percent change between the treatment groups. The Hodges–Lehmann estimator and 95% confidence interval (CI) for this estimator were displayed for understanding the treatment effect size. The Applicant also presents results using standard parametric log-transformed ANCOVA.

The Applicant defines various analysis populations, including the Safety Analysis Set, the Full Intention to Treat Analysis Set, The ITT analysis set, the ITT analysis Set for Responder Rate, the Per Protocol Analysis set and the modified PP analysis set.

The ITT Analysis Set for Responder Rate is the group of subjects who were randomized to study drug, received study drug, and entered the Maintenance Period (i.e. took at least one dose of study drug during the Maintenance Period and had any seizure frequency data during the Maintenance Period). The Full Intent-to-Treat (ITT) Analysis Set is the group of subjects who were randomised to study drug, received study drug, and had any seizure frequency data during the Double blind Phase.

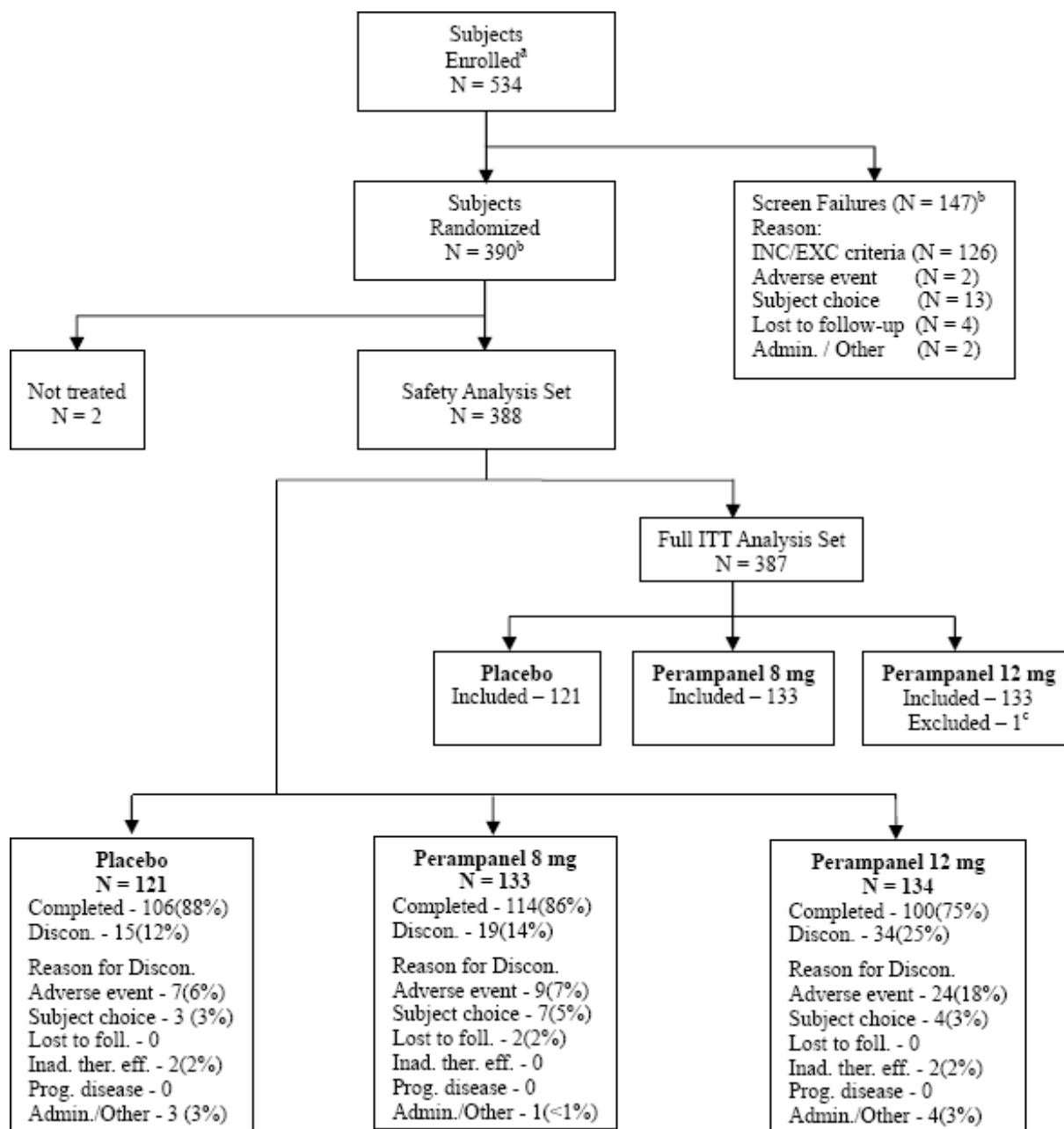
In order to handle missing data, the Applicant used an LOCF approach. A sensitivity analysis including missing data as non-responders (for the EU primary analysis) was also provided.

The sensitivity analysis using missing data as failure is more suitable than the primary analysis and is in line with the CHMP Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1). The LOCF approach is acceptable for the key secondary analysis.

The proposed analysis method for the primary and key secondary variables is acceptable. The ranked ANCOVA is acceptable given that the data are expected a priori to not be normally distributed.

Results

Participant flow



Recruitment

390 subjects were randomized in the study. The study was conducted between 30 Apr 2008 and 11 Nov 2010.

Conduct of the study

- **Protocol amendments**

There was one global amendment (Amendment 01; 20 Mar 2009), which was initiated after 109 subjects had been enrolled in the study.

• **Protocol deviations**

Thirty-seven subjects in the ITT Analysis Set were excluded from the PP Analysis Set, including eight (6.7%) subjects in the placebo group, 20 (15.2%) subjects in the perampanel 8 mg group, and 11 (8.5%) subjects in the perampanel 12 mg group. The most common reasons for exclusion were failure to experience the required minimum number of seizures during the Pre randomization Phase (three, seven, and four subjects, respectively) and not being treated with stable doses of one to three AEDs (three, seven, and four subjects, respectively). (Only one of these subjects had both reasons.)

Eleven subjects in the ITT Analysis Set were excluded from the Modified PP Analysis Set, including two (1.7%) subjects in the placebo group, five (3.8%) subjects in the 8 mg group, and four (3.1%) subjects in the 12 mg group. The most common reason for exclusion was violation of GCP (one, two, and two subjects, respectively). Although a number of deviations from the protocol (e.g., missed visits, visit outside the protocol-specified window) occurred, these deviations were not considered to have affected the evaluation of efficacy or safety. No treatment codes were broken prior to database lock.

No study drug dispensing errors occurred.

Baseline data

Summary of Demography and Baseline Characteristics - Intent-to-Treat Analysis Set

Category	Perampanel				
	Placebo (N=119)	8 mg (N=132)	12 mg (N=130)	Total (N=262)	Combined Total (N=381)
Age (Year)*					
n	119	132	130	262	381
Mean (SD)	35.6 (14.76)	35.7 (14.22)	37.0 (14.73)	36.4 (14.46)	36.1 (14.54)
Median	34.0	35.5	36.5	36.0	36.0
Min, Max	12, 73	12, 68	14, 77	12, 77	12, 77
Age Group, n (%)					
<18	14 (11.8)	15 (11.4)	10 (7.7)	25 (9.5)	39 (10.2)
18-64	100 (84.0)	115 (87.1)	115 (88.5)	230 (87.8)	330 (86.6)
>64	5 (4.2)	2 (1.5)	5 (3.8)	7 (2.7)	12 (3.1)
Sex, n (%)					
Male	54 (45.4)	65 (49.2)	66 (50.8)	131 (50.0)	185 (48.6)
Female	65 (54.6)	67 (50.8)	64 (49.2)	131 (50.0)	196 (51.4)
Race, n (%)					
White	101 (84.9)	114 (86.4)	113 (86.9)	227 (86.6)	328 (86.1)
Black or African American	13 (10.9)	6 (4.5)	8 (6.2)	14 (5.3)	27 (7.1)
Asian	0	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Japanese	0	0	0	0	0
Chinese	0	1 (<1)	1 (<1)	2 (<1)	2 (<1)
American Indian or Alaska Native	0	4 (3.0)	1 (<1)	5 (1.9)	5 (1.3)
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Other	5 (4.2)	6 (4.5)	6 (4.6)	12 (4.6)	17 (4.5)

Numbers analysed

Analyses have been performed on the following analyses sets:

Summary of Analysis Sets - All Randomized Subjects

Analysis Set	Perampanel				
	Placebo (N=122) n (%)	8 mg (N=133) n (%)	12 mg (N=135) n (%)	Total (N=268) n (%)	Combined Total (N=390) n (%)
Safety Analysis Set ^a	121 (99.2)	133 (100)	134 (99.3)	267 (99.6)	388 (99.5)
Intent-to-Treat (ITT) ^b	119 (97.5)	132 (99.2)	130 (96.3)	262 (97.8)	381 (97.7)
Completer Analysis Set ^c	106 (86.9)	114 (85.7)	100 (74.1)	214 (79.9)	320 (82.1)
Per Protocol Analysis Set ^d	111 (91.0)	114 (85.7)	119 (88.1)	233 (86.9)	344 (88.2)
Modified Per Protocol Analysis Set ^e	117 (95.9)	127 (95.5)	126 (93.3)	253 (94.4)	370 (94.9)
Full ITT ^b	121 (99.2)	133 (100)	133 (98.5)	266 (99.3)	387 (99.2)
ITT for Responder Rate ^e	113 (92.6)	121 (91.0)	115 (85.2)	236 (88.1)	349 (89.5)

Source: Appendix 16.2.3.1

Percentages are based on the total number of subjects in the relevant Analysis Set and treatment groups.

a: Includes subjects who signed informed consent, were randomized, took at least 1 dose of the double-blind treatment, and had a post-dose safety assessment.

b: Full ITT includes subjects who signed informed consent, were randomized, took at least 1 dose of double-blind treatment, and had at least 1 day of seizure diary data from the Double-blind Phase. ITT includes Full ITT subjects who had at least 14 days of seizure diary from the Pre-randomization Phase and the Double-blind Phase.

c: Includes subjects in the ITT Analysis Set who completed the Double-blind Phase.

d: Includes ITT subjects with no major protocol deviations/violations and were $\geq 80\%$ compliant with the study treatment. Major protocol deviations/violations were finalized prior to unblinding.

e: Includes subjects who signed informed consent, were randomized, took at least 1 dose of treatment, and had at least 1 day of seizure diary data from the Maintenance Period.

• Primary efficacy results

- 50% responder rate

The percentage of subjects who experienced a decrease in seizure frequency of at least 50% relative to baseline was greater in the 8 mg group (37.6%) and the 12 mg group (36.1%) than in the placebo group (26.4%). The *P* values for the difference from placebo were 0.0760 for 8 mg and 0.0914 for 12 mg. The results for the ITT Analysis Set and the ITT Analysis Set for Responder Rate were consistent with those for the Full ITT Analysis Set.

Table 11.7 Responder Analysis: Full ITT Analysis Set

Analysis Window	Placebo (N=121) n (%)	Perampanel	
		8 mg (N=133) n (%)	12 mg (N=133) n (%)
Responder			
Maintenance-LOCF			
Yes	32 (26.4)	50 (37.6)	48 (36.1)
No	89 (73.6)	83 (62.4)	85 (63.9)
Total	121 (100)	133 (100)	133 (100)
p-value ^a			
Compared with Placebo		0.0760	0.0914

A responder is a subject who experienced a 50% or greater reduction in seizure frequency per 28 days from the Pre-randomization Phase.

ITT = Intent-to-Treat, LOCF = last observation carried forward

a: The p-value is based on non-missing values and is from the Cochran-Mantel-Haenszel (CMH) test adjusted for pooled country.

Subgroup Analyses

A highly significant treatment-by-region interaction ($P=0.0035$) was detected during the standard model examination of the primary efficacy analysis using the rank ANCOVA with Maintenance (LOCF) data and the ITT Analysis Set. The regional difference reflected a strong treatment effect and dose

response in the “North America” region, in contrast to a high placebo response and no dose response or treatment difference in the “Central and South America” region.

Therefore, the impact of region on the results for the Full ITT Analysis Set was assessed. As shown in Table 11.6, the median change for North America was -11.34% in the placebo group, -27.63% in the 8 mg group, and -36.91% in the 12 mg group. For the US sites only, the median change was -9.52%, -25.38%, and -35.22%, respectively. All *P* values for the differences between perampanel and placebo were ≤ 0.0020 (both rank ANCOVA and log transformation-based ANCOVA). For Central and South America, the median change was similar in the three treatment groups due to a much higher response in the placebo group compared with the responses seen in the placebo groups for North America and for the United States.

For North America, the percentage of subjects who experienced a decrease in seizure frequency of at least 50% relative to baseline was greater in the 8 mg (40.5%) and 12 mg (40.0%) groups than in the placebo group (21.9%). For US sites only, the percentage of 50% responders was 37.5%, 43.1%, and 16.7%, respectively. All *P* values for the difference from placebo were ≤ 0.0209 .

The responder rates were similar across treatment groups for Central and South America, and the *P* values for the difference from placebo were > 0.05 for both perampanel doses.

• **Secondary Efficacy Results**

- Percent Change in Seizure Frequency

The median change was -20.95% in the placebo group, -26.34% in the 8 mg group, and -34.49% in the 12 mg group. The *P* values for the difference from placebo were 0.0261 for 8 mg and 0.0158 for 12 mg based on the rank ANCOVA and 0.0044 and 0.0184, respectively, based on the log transformation-based ANCOVA. The median differences from placebo for the ITT Analysis Set (Double-blind Phase and Maintenance-LOCF) were similar to those for the Full ITT Analysis Set (Double-blind Phase).

Table 11.6 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline for the Full ITT Analysis Set: Results by Region

Subgroup Statistic	Perampanel		
	Placebo	8 mg	12 mg
North America			
n	73	74	80
Median	-11.34	-27.63	-36.91
p-value compared with placebo			
Rank ANCOVA		0.0010	0.0005
Log transformation-based ANCOVA		0.0001	0.0005
United States			
n	66	64	72
Median	-9.52	-25.38	-35.22
p-value compared with placebo			
Rank ANCOVA		0.0020	0.0002
Log transformation-based ANCOVA		0.0002	<0.0001
Central and South America			
n	48	59	53
Median	-26.18	-24.88	-20.73
p-value compared with placebo			
Rank ANCOVA		0.5121	0.5151
Log transformation-based ANCOVA		0.7495	0.4856

ANCOVA = analysis of covariance, ITT = Intent-to-Treat
 Source: Listing 16.2.6.2, Tables 14.2.9.1, 14.2.10.1, 14.2.12.2, 14.2.12.3

- Percent Change in Frequency of Complex Partial Plus Secondarily Generalized Seizures

The median percent change was -17.88% in the placebo group, -33.03% in the 8 mg group, and -33.06% in the 12 mg group. The *P* values were 0.0020 for the comparison of 8 mg and placebo, and 0.0081 for the comparison of 12 mg and placebo. The results for the ITT Analysis Set (both Double-blind Phase and Maintenance- LOCF) were consistent with those for the Full ITT Analysis Set (Double-blind Phase).

For North America, the median percent change during the Double-blind Phase relative to baseline was -15.36% in the placebo group, -36.65% in the 8 mg group, and -35.95% in the 12 mg group. For US sites, the median percent change was -11.46%, -34.07%, and -35.95%, respectively. The *P* values for the difference from placebo were ≤ 0.0018 for both perampanel doses. For Central and South America, the median percent change was similar in the three treatment groups, and the *P* values for the difference from placebo were > 0.05 for both doses.

- **Exploratory Efficacy Results**

- Change in the Number of Seizure-free Days

At baseline, the mean number of seizure-free days per 28 days was approximately 16 days in each treatment group for the ITT Analysis Set. In the Double-blind Phase, there were mean increases in the number of seizure-free days of 1.4 days in the placebo group, 2.7 days in the perampanel 8 mg group, and 2.7 days in the perampanel 12 mg group. The *P* values were 0.0353 for the comparison of 8 mg and placebo, and 0.0280 for the comparison of 12 mg and placebo.

- Percentage of Subjects Who Achieved Seizure-free Status

Among the subjects in the ITT Analysis Set with at least 28 days of treatment in the Maintenance Period, 1.8% of those in the placebo group, 10.0% of those in the 8 mg group, and 7.4% of those in the 12 mg group achieved seizure-free status during the last 28 days of treatment. The *P* values for the comparison with placebo were 0.0113 for the 8 mg group and 0.0567 for the 12 mg group. Among the subjects who completed the Maintenance Period, 0%, 2.6%, and 2.0%, respectively, in the placebo, 8, and 12 mg groups achieved seizure-free status. The *P* values for the comparison with placebo were 0.2476 for 8 mg and 0.2344 for 12 mg.

- Responder Rates for Complex Partial Seizures plus Secondarily Generalized Seizures

The responder rates during the Maintenance Period were 28.7% in the placebo group, 40.3% in the perampanel 8 mg group, and 42.4% in the perampanel 12 mg group. The *P* values for the comparison with placebo were 0.0873 for 8 mg and 0.0321 for 12 mg.

- Responder Rates for Secondarily Generalized Seizures

The responder rates during the Maintenance Period were 38.2% in the placebo group, 66.7% in the 8 mg group, and 58.8% in the 12 mg group. The *P* values for the comparison with placebo were 0.0041 for 8 mg and 0.0336 for 12 mg.

- Clinical Global Impression of Change

At the end of treatment, 27.4% of the subjects in the placebo group, 43.2% of those in the perampanel 8 mg group, and 35.7% of those in the perampanel 12 mg group were considered much or very much improved by the investigators; the remaining subjects were rated minimally improved to very much worse. The *P* values for the differences relative to placebo were 0.0122 for 8 mg and 0.2545 for 12 mg.

- Patient Global Impression of Change

At the end of treatment, 38.5% of the subjects in the placebo group, 51.6% of those in the perampanel 8 mg group, and 46.5% of those in the perampanel 12 mg group considered themselves much or very much improved; the remaining subjects considered themselves minimally improved to very much worse. The *P* values for the differences relative to placebo were 0.0533 for 8 mg and 0.2706 for 12 mg. The results for the ITT Analysis Set were consistent with those for the Full ITT Analysis Set.

- Change in total and subscale scores for the QOLIE-31-P

The changes in quality of life were similar in the three treatment groups.

Outcomes and estimation

Based on the full ITT (the group of subjects who were randomized to study drug, received at least one dose of study drug, and had any seizure data during the Double-blind Phase), Analysis Set, the results of the primary efficacy endpoints showed that:

The 50% responder rate during the Maintenance Period was 37.6% in the 8 mg and 36.1% in the 12 mg groups and 26.4% in the placebo group. The *P* values for the difference from placebo were 0.0760 and 0.0914, respectively.

The median percent change in seizure frequency per 28 days during the Double-blind Phase relative to baseline was -26.34% and -34.49% for perampanel 8 mg and 12 mg respectively. The percentage change in seizure frequency for the placebo group was 20.95%.

The *P* values for the difference from placebo for 8 and 12 mg were 0.0044 and 0.0184, respectively, by log transformation-based ANCOVA.

Data from subsets of the Double-blind Phase, and by regional analyses showed that:

The *P* values for the differences from placebo were ≤ 0.0020 for both dose groups (rank ANCOVA and log transformation-based ANCOVA) for North America and for the United States. For the 50% responder rate, the *P* values were ≤ 0.0209 .

The results in subjects with more severe, clinically important seizure types (complex partial seizures and complex partial seizures that secondarily generalized) showed that the median percent change in the frequency of these types of seizures was -33.03% in the 8 mg and -33.06% in the 12 mg groups with *P* values of 0.0020 and 0.0081, respectively. The placebo group response was -17.88%.

For North America and the United States, the *P* values for the difference from placebo were ≤ 0.0018 for both doses. For Central and South America, the median percent change was similar in the three treatment groups, and the *P* values for the difference from placebo were > 0.05 for both doses.

The dose-response analysis focused on the Maintenance Period showed that for all partial seizures and for the more severe seizure types, the median percent change in frequency was greater in the 12 mg group than the 8 mg group.

The exploratory efficacy endpoints showed general improvement associated with perampanel.

When taken as a whole population the responder analysis (50% greater reduction in seizure frequency per 28 days during the maintenance period from pre-randomization phase) of placebo, 8mg and 12mg/day group showed a higher but not statistically significant response for the perampanel groups.

A high response to placebo was recorded from the sites in central and South America (162 of 390 subjects, 41.5%) and no difference between either perampanel group and the placebo group in the median percent change in seizure frequency per 28 days during the Double-blind Phase (*P* = 0.5121

for 8 mg group; $P = 0.5151$ for 12 mg group) or in the responder rate during the Maintenance Period ($P = 0.9335$ for 8 mg group; $P = 0.7925$ for 12 mg group) was found.

As a result, the treatment differences relative to placebo for the 8-mg and 12-mg groups in Study 304 did not achieve statistical significance ($P = 0.0760$ and $P = 0.0914$, respectively).

Ancillary analyses

Several analysis were conducted to explore the influence of demographic and baseline characteristics (age and baseline body weight) and concomitant AED therapy on the efficacy results for the Central and South American region but none of the factor examined fully explains the high placebo response for the Central and South American regional subgroup.

A Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group Study to Evaluate the Efficacy and Safety of E2007 (perampanel) Given as Adjunctive Therapy in Subjects with Refractory Partial Seizures (E2007-G000-305)

Methods

Study Participants

Male or female subjects, greater than or equal to 12 years of age with a diagnosis of refractory partial seizures with or without secondarily generalized seizures.

This study were to include approximately 60-80 sites in the North America (NA), European Union (EU), Asia, Australia, South Africa, and Rest of World (ROW). Approximately 375 subjects were planned for enrollment.

• Inclusion Criteria

Subjects who were to be included in the study were those:

1. Who provided written informed consent signed by the 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 was also obtained.)

- In Germany: Who provided written informed consent signed prior to entering the study or undergoing any study procedures.

2. Who were considered reliable and willing to be available for the study period and able to record seizures and report AEs themselves or had a caregiver who could record seizures and report AEs for them

3. Male or female and greater than or equal to 12 years of age within the course of the study

- In Germany, the Netherlands, France, and India, subjects had to be greater than or equal to 18 years of age (at the time of signing the informed consent).

- In Denmark and Sweden subjects had to be greater than or equal to 18 years of age (within the course of the study)

4. Females were either of non-childbearing potential (defined as having undergone surgical sterilization, or postmenopausal [age 50 and amenorrheic for 12 months]) or of childbearing potential. Females of childbearing potential had a negative serum beta-human chorionic gonadotropin (β -hCG) at Visit 1 and a negative urine pregnancy test prior to randomization at Visit 2. Female subjects of

childbearing potential agreed to be abstinent or to use at least 1 medically acceptable method of contraception (e.g., a double-barrier method [e.g., condom + spermicide, condom + diaphragm with spermicide], intrauterine device, or have a vasectomized partner) starting at Visit 1 and throughout the entire study period and for 2 months after the last dose of study drug. Women using hormonal contraceptives also used an additional approved method of contraception (as described previously) starting at Visit 1 and continuing throughout the entire study period and for 2 months after the last dose of study drug. (It was not required for male subjects to use contraceptive measures.)

5. Who had a diagnosis of epilepsy with partial seizures with or without secondarily generalized seizures according to the International League Against Epilepsy's Classification of Epileptic Seizures (1981). Diagnosis was established by clinical history and an EEG that was consistent with localization-related epilepsy; normal interictal EEGs were allowed provided that the subject met the other diagnosis criterion (i.e., clinical history).

6. Who had a computed tomography or magnetic resonance imaging within the last 10 years that ruled out a progressive cause of epilepsy

7. Who had uncontrolled partial seizures despite having been treated with at least two different AEDs within approximately the last 2 years

- For Germany: Had uncontrolled partial seizures despite having been treated with at least two different AEDs for a minimum of 2 years

8. During the 6-week Prerandomization Phase, subjects must have had five or more partial seizures (with two or more partial seizures per each 3-week period) and no 25-day seizure-free period in the 6-week period, as documented via a valid seizure diary. Only simple partial seizures with motor signs, complex partial seizures, and complex partial seizures with secondary generalization were counted toward this inclusion.

9. Who were currently being treated with stable doses of one, two or a maximum of three approved AEDs. Only one inducer AED (defined as carbamazepine, phenytoin, phenobarbital, or primidone) out of the maximum of three AEDs was allowed.

10. Who were on a stable dose of the same concomitant AED(s) for 1 month (or no less than 21 days) prior to Visit 1; in the case where a new AED regime was initiated for a subject, the dose must have been stable for 2 months (or no less than 49 days) prior to Visit 1.

11. If on a stable dose (other than intermittent rescue use) of benzodiazepines for epilepsy (or for anxiety or sleep disorders), the prescribed dose was stable for 1 month (or no less than 21 days) prior to Visit 1. (Note that the use of intermittent rescue benzodiazepines is defined in exclusion criterion #22 below.) When used in these cases (epilepsy, anxiety or sleep disorders), benzodiazepines were counted as one AED; therefore, only one or a maximum of two additional approved AEDs were allowed.

12. A vagal nerve stimulator was allowed but it must have been implanted \geq 5 months prior to Visit 1. Stimulator parameters could not be changed for 1 month (or no less than 21 days) prior to Visit 1 or thereafter during the study.

- **Exclusion Criteria**

Subjects who were to be excluded from the study were those:

1. Who participated in a study involving administration of an investigational compound or device within 1 month (or no less than 21 days) prior to Visit 1, or within approximately five half-lives of the previous investigational compound, whichever is longer

2. Who were pregnant and/or lactating

3. Who participated in previous perampanel studies
4. With a presence of nonmotor simple partial seizures only
5. With a presence of primary generalized epilepsies or seizures, such as absences and or myoclonic epilepsies
6. With a presence or previous history of Lennox-Gastaut syndrome
7. With a history of status epilepticus within approximately 12 months prior to Visit 1
8. With seizure clusters where individual seizures could not be counted
9. With a history of psychogenic seizures
10. With evidence of clinically significant disease (e.g., cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could have affected the subject's safety or the study conduct
11. Scheduled and/or confirmed to have epilepsy surgery within 6 months after Visit 1; however those with previously documented "failed" epilepsy surgery were allowed.
12. With evidence of significant active hepatic disease. Stable elevations of liver enzymes, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) due to concomitant medication(s) were allowed if they were less than 3 times the upper limit of normal (ULN).
13. With evidence of significant active hematological disease; white blood cell (WBC) count \leq \square 2500/ μ L (2.50 1E+09/L) or an absolute neutrophil count \leq \square 1000/ μ L (1.00 1E+09/L)
14. With a clinically significant ECG abnormality, including prolonged QTc defined as $>$ 450 msec
15. Suffering from psychotic disorder(s) and/or unstable recurrent affective disorder(s) evident by use of antipsychotics or who had a suicide attempt(s) within approximately the last 2 years
16. With a presence of a progressive central nervous system (CNS) disease, including degenerative CNS diseases and progressive tumors
17. With a history of drug or alcohol dependency or abuse within approximately the last 2 years
18. Who had multiple drug allergies or a severe drug reaction to an AED(s), including dermatological (e.g., Stevens-Johnson syndrome), hematological, or organ toxicity reactions
19. If felbamate was used as a concomitant AED, subjects were on felbamate for at least 2 years, with a stable dose for 2 months (or no less than 49 days) prior to Visit 1. They must not have had a history of WBC count of \leq \square 2500/ μ L (2.50 1E+09/L), platelets below 100,000/mm³, liver function tests above 3 times the ULN, or other indication of hepatic or bone marrow dysfunction while receiving felbamate. If subjects received felbamate in the past, it must have been discontinued 2 months (or no less than 49 days) prior to Visit 1.
20. With concomitant use of vigabatrin. Subjects who took vigabatrin in the past were off vigabatrin for approximately 5 months prior to Visit 1 and had documentation showing no evidence of a vigabatrin-associated clinically significant abnormality in a visual perimetry test.
21. With concomitant use of barbiturates (except for seizure control indication) within 1 month (or no less than 21 days) prior to Visit 1
22. With use of intermittent rescue benzodiazepines (i.e., one or two doses over a 24-hour period considered one-time rescue) two or more times in a 1-month period prior to Visit 1

23. With any condition(s) that made the subject, in the opinion of the investigator, unsuitable for the study

24. The following criteria applied to only those countries specified:

- In Germany: Those committed to an institution by official or judicial order.
- In France: Protected people in accordance with French regulation (persons under tutelage or guardianship).

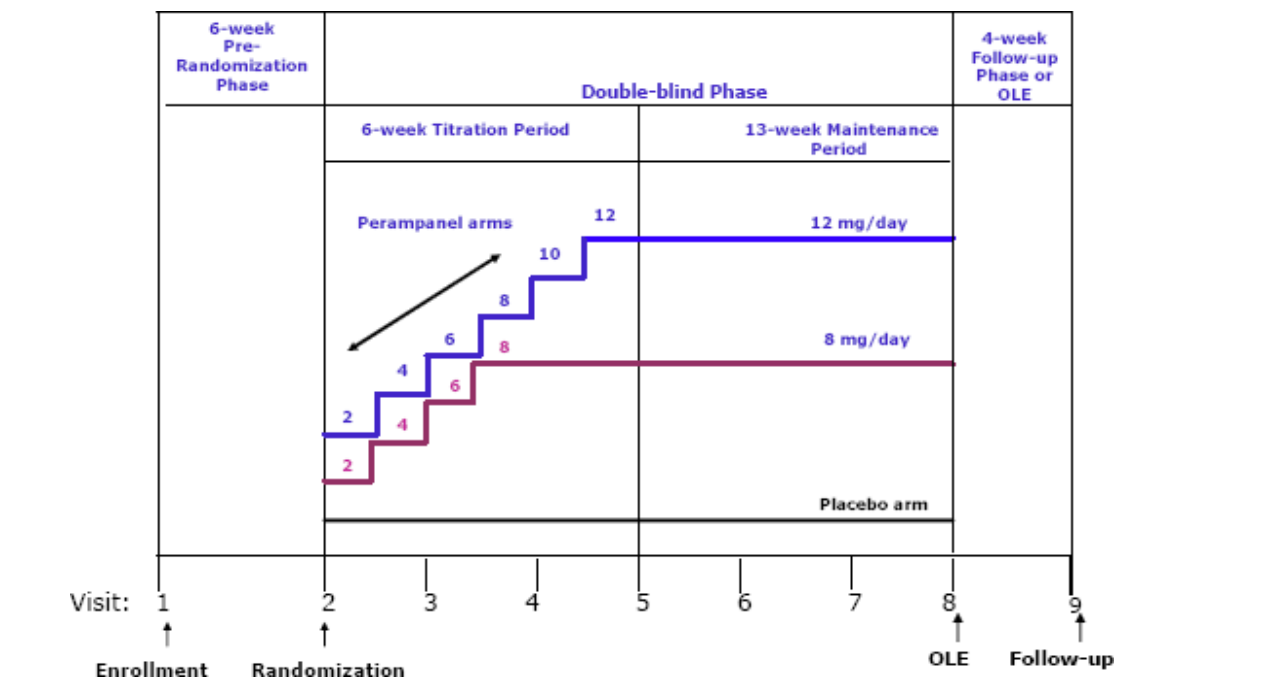
Treatments

The study consisted of three phases:

- The Pre randomization Phase was 6 weeks in duration.
- The Double-blind Phase was 19 weeks in duration and included two periods: Titration and Maintenance. The Titration Period was 6 weeks in duration and the Maintenance Period was 13 weeks in duration.
- The Follow-up Phase was 4 weeks in duration.

No treatment was to be administered during the Pre-randomization Phase of the study. Once a subject completed this phase, they were randomized to treatment and begin the 6-week Double- Blind Phase Titration Period (Visit 2 to Visit 5). Throughout the entire Double-blind Phase, all subjects took a total of 6 tablets daily.

During the Titration Period, all subjects started on 6 tablets (1 tablet of 2 mg perampanel plus 5 tablets of placebo or 6 tablets of placebo) and titrated to the appropriate randomized dose (8 mg or 12 mg perampanel, or placebo).



Objectives

- Primary Objectives

- To evaluate the efficacy of two doses of perampanel (8 and 12 mg) in comparison to placebo given as an adjunctive therapy in subjects with refractory partial seizures.

- **Secondary Objectives**

- To evaluate the safety and tolerability of perampanel vs. placebo in subjects with refractory partial seizures.

- **Exploratory Objectives**

- To explore potential withdrawal symptoms of perampanel vs. placebo in subjects with refractory partial seizures.
- To explore potential photosensitivity of perampanel vs. placebo in subjects with refractory partial seizures.
- To explore the effects of perampanel on partial seizure frequency (in 25% increments), on the frequency of complex partial seizures with secondary generalization, and on Clinical and Patient Global Impressions of Change.

Outcomes/endpoints

- **Primary Efficacy Variable(s)**

The primary efficacy endpoint for EU registration was the 50% responder rate. Responders were defined as subjects who experienced a 50% or greater reduction in seizure frequency per 28 days in the Maintenance Period relative to the Prerandomization Phase.

- **Secondary Efficacy Variable(s)**

- The key secondary efficacy endpoint was the percent change in seizure frequency.
- The other secondary endpoint was the percent change in complex partial plus secondarily generalized seizure frequency per 28 days during treatment relative to baseline.

- **Exploratory Efficacy Variable(s)**

Exploratory efficacy endpoints included:

- The percentage of subjects experiencing decreases/increases (25% increments) in seizure frequency per 28 days; change in the number of seizure-free days per 28 days;
- The percentage of subjects who achieved seizure-free status;
- Clinical and Patient Global Impressions of Change;
- Time to 1st, 3rd, 6th, 9th, and 12th seizures during treatment;
- Time to first 50% response;
- The percent change in the frequency per 28 days of complex partial seizures with secondary generalization; 50% responder rates based on complex partial plus secondarily generalized seizures, and on complex partial seizures with secondary generalization only;
- Change in total and subscale scores for the QOLIE-31-P.

Sample size

A sample size of 375 subjects was estimated.

Based on Phase II studies in subjects with epilepsy, it was assumed that the percent change in seizure frequency per 28 days in the Maintenance Period relative to the Prerandomization Phase would be 10% in the placebo group and 32% in the 8 mg group in the ITT Analysis Set. Therefore, a sample size of 120 subjects in each treatment group in the ITT Analysis Set would have 83% power to detect a treatment difference of 22% in seizure frequency (assuming a common SD of 56%) between placebo and each perampanel group based on the Wilcoxon rank-sum test with a 0.05 two-sided significance level. To account for subjects who might be randomized but not be included in the ITT Analysis Set, the number of subjects randomized was to be approximately 125 per treatment group.

Randomisation

Subjects were assigned randomized to one of the three treatment groups in a 1:1:1 ratio based on a randomization scheme generated using a computer program. The randomization scheme was reviewed and approved by an independent statistician and locked after approval.

Blinding

The double-blind design of these studies 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 treatment groups.

During the Double-blind Phase, the subject and all personnel involved with the conduct and the interpretation of the study, including the investigators, investigational site personnel and Eisai staff, were blinded to the treatment codes. Randomization data were kept strictly confidential, filed securely by the Eisai Scientific and Operational Clinical Support Core Functional Unit, and accessible only to authorized persons per SOPs until the time of unblinding.

Statistical methods

The primary efficacy endpoint for EU registration was the 50% responder rate. For all other purposes, this was the key secondary endpoint. Responders were defined as subjects who experienced a 50% or greater reduction in seizure frequency per 28 days in the Maintenance Period relative to the Pre-randomisation Phase.

Responder rate analysis of subjects who experienced a 50% or greater reduction in seizure frequency during treatment relative to baseline was conducted using the Cochran–Mantel–Haenszel (CMH) test adjusting for pooled countries.

The key secondary efficacy endpoint was the percent change in seizure frequency per 28 days during treatment relative to baseline. In this context, seizure frequency refers to the frequency of all partial seizures. For this analysis, both the baseline seizure frequencies per 28 days and the percent change per 28 days during treatment were rank transformed separately. An analysis of covariance (ANCOVA) was then conducted on the rank-transformed percent change data, with treatment and pooled countries as factors and the ranked baseline seizure frequency per 28 days as a covariate. P values were computed using contrasts between active and placebo treatment groups.

Due to an expected irregular distribution of seizure frequency, median was the primary statistic of interest for comparing the percent change between the treatment groups. The Hodges–Lehmann estimator and 95% confidence interval (CI) for this estimator were displayed for understanding the treatment effect size. The Applicant also presents results using standard parametric log-transformed ANCOVA.

The Applicant defines various analysis populations, including the Safety Analysis Set, the Full Intention to Treat Analysis Set, The ITT analysis set, the ITT analysis Set for Responder Rate, the Per Protocol Analysis set and the modified PP analysis set.

The ITT Analysis Set for Responder Rate is the group of subjects who were randomized to study drug, received study drug, and entered the Maintenance Period (i.e. took at least one dose of study drug during the Maintenance Period and had any seizure frequency data during the Maintenance Period). The Full Intent-to-Treat (ITT) Analysis Set is the group of subjects who were randomised to study drug, received study drug, and had any seizure frequency data during the Double blind Phase.

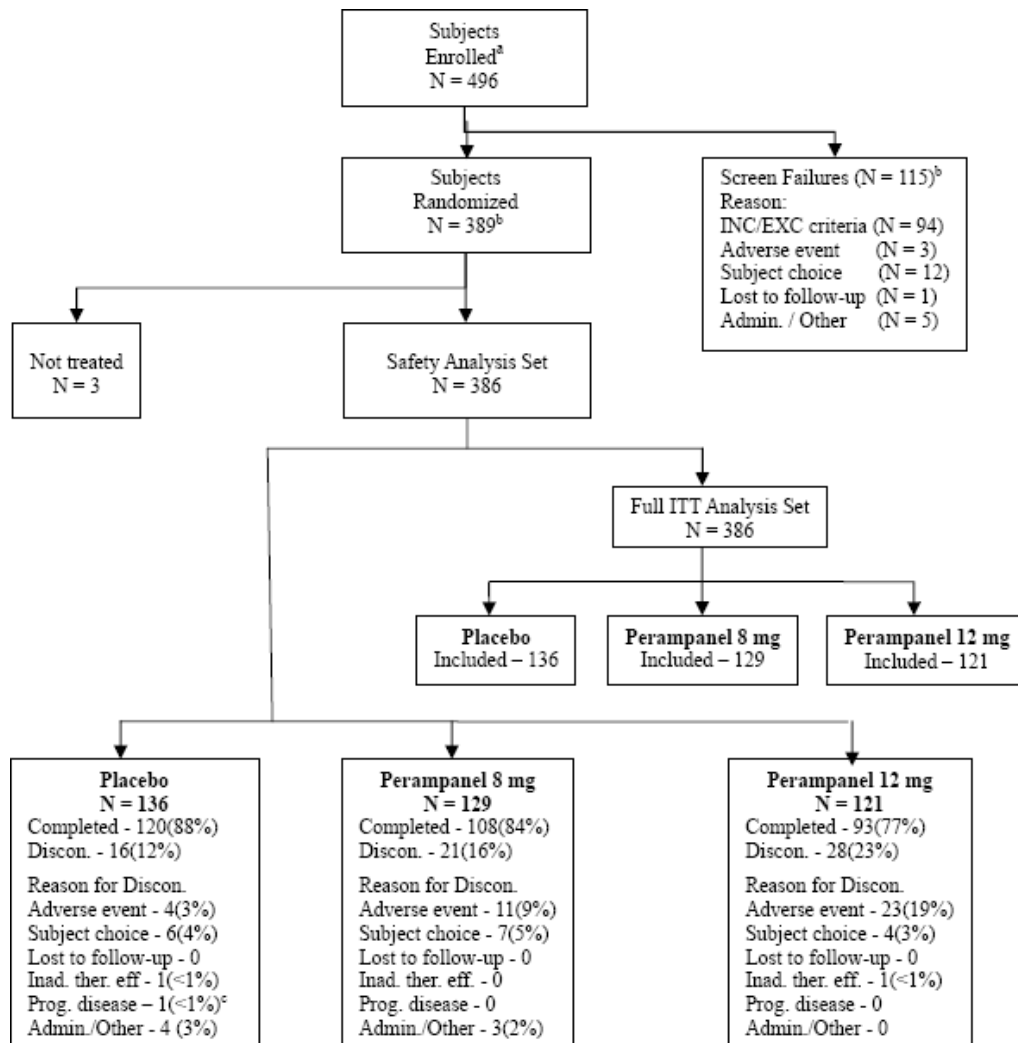
In order to handle missing data, the Applicant used an LOCF approach. A sensitivity analysis including missing data as non-responders (for the EU primary analysis) was also provided.

The sensitivity analysis using missing data as failure is more suitable than the primary analysis and is in line with the CHMP Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1). The LOCF approach is acceptable for the key secondary analysis.

The proposed analysis method for the primary and key secondary variables is acceptable. The ranked ANCOVA is acceptable given that the data are expected a priori to not be normally distributed.

Results

Participant flow



Recruitment

389 subjects were randomized in the study. The study was conducted between 20 May 2008 and 14 Jan 2011.

Conduct of the study

• Protocol amendments

There were two global amendments:

- Amendment 01 (20 Mar 2009), was initiated after 109 subjects had been enrolled in the study Protocol
- Amendment 02 (23 Nov 2010), was initiated after all subjects had been enrolled in the study but before database lock.

There were also seven country specific protocol amendments as follows:

Amendment A – Germany, Denmark, Sweden (09 May 2008)

Amendment B – Germany (05 November 2008).

Amendment C – Netherlands and Switzerland (18 Aug 2008)

Amendment D – France (17 Sep 2008)

Amendment E – France (05 Nov 2008)

Amendment F – India (05 Nov 2008)

Amendment G – South Africa (17 Feb 2009)

• Protocol deviations

Thirty-one subjects in the Full ITT Analysis Set were excluded from the PP Analysis Set, including 11 (8.1%) subjects in the placebo group, 13 (10.1%) subjects in the perampanel 8 mg group, and seven (5.8%) subjects in the perampanel 12 mg group. The most common reasons for exclusion were not being treated with stable doses of one to three AEDs (five, three, and two subjects, respectively) and failure to experience the required minimum number of seizures during the Prerandomization Phase (two, three, and two subjects, respectively). (One of these subjects had both reasons.)

Twelve subjects in the Full ITT Analysis Set were excluded from the Modified PP Analysis Set, including four (2.9%) subjects in the placebo group, five (3.9%) subjects in the 8 mg group, and three (2.5%) subjects in the 12 mg group. The reasons for exclusion were < 80% compliance with study drug (two, two, and one subjects, respectively) and received unblinded drug kit at Visit 7 (two, three, and two subjects, respectively).

Although a number of deviations from the protocol (e.g., missed visits, visit outside the protocol-specified window) occurred, these deviations were not considered to have affected the evaluation of efficacy or safety. No treatment codes were broken prior to database lock.

No study drug dispensing errors occurred.

Baseline data

Summary of Demography and Baseline Characteristics - Full Intent-to-Treat Analysis Set

Category	Perampanel				
	Placebo (N=136)	8 mg (N=129)	12 mg (N=121)	Total (N=250)	Combined Total (N=386)
Age (Year) ^a					
n	136	129	121	250	386
Mean (SD)	34.4 (13.62)	36.7 (14.35)	35.5 (14.12)	36.1 (14.22)	35.5 (14.02)
Median	35.0	37.0	35.0	35.5	35.0
Min, Max	12, 76	12, 72	12, 74	12, 74	12, 76
Age Group, n (%)					
<18	17 (12.5)	17 (13.2)	10 (8.3)	27 (10.8)	44 (11.4)
18-64	118 (86.8)	109 (84.5)	109 (90.1)	218 (87.2)	336 (87.0)
>64	1 (<1)	3 (2.3)	2 (1.7)	5 (2.0)	6 (1.6)
Sex, n (%)					
Male	71 (52.2)	65 (50.4)	50 (41.3)	115 (46.0)	186 (48.2)
Female	65 (47.8)	64 (49.6)	71 (58.7)	135 (54.0)	200 (51.8)
Race, n (%)					
White	115 (84.6)	107 (82.9)	100 (82.6)	207 (82.8)	322 (83.4)
Black or African American	1 (<1)	2 (1.6)	1 (<1)	3 (1.2)	4 (1.0)
Asian	12 (8.8)	14 (10.9)	16 (13.2)	30 (12.0)	42 (10.9)
Japanese	0	0	0	0	0
Chinese	0	0	0	0	0
American Indian or Alaska Native	1 (<1)	0	0	0	1 (<1)
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Other	7 (5.1)	6 (4.7)	4 (3.3)	10 (4.0)	17 (4.4)

Numbers analysed

Analyses have been performed on the following analyses sets:

Summary of Analysis Sets - All Randomized Subjects					
Perampanel					
Analysis Set	Placebo (N=138) n (%)	8 mg (N=130) n (%)	12 mg (N=121) n (%)	Total (N=251) n (%)	Combined Total (N=389) n (%)
Safety Analysis Set ^a	136 (98.6)	129 (99.2)	121 (100)	250 (99.6)	386 (99.2)
Full Intent-to-Treat (ITT) ^b	136 (98.6)	129 (99.2)	121 (100)	250 (99.6)	386 (99.2)
ITT for Responder Rate ^c	125 (90.6)	118 (90.8)	104 (86.0)	222 (88.4)	347 (89.2)
Completer Analysis Set ^d	120 (87.0)	108 (83.1)	93 (76.9)	201 (80.1)	321 (82.5)
Per Protocol Analysis Set ^e	125 (90.6)	116 (89.2)	114 (94.2)	230 (91.6)	355 (91.3)
Per Protocol Analysis Set for Responder Rate ^e	116 (84.1)	108 (83.1)	99 (81.8)	207 (82.5)	323 (83.0)
Modified Per Protocol Analysis Set ^e	132 (95.7)	124 (95.4)	118 (97.5)	242 (96.4)	374 (96.1)
Modified Per Protocol Analysis Set for Responder Rate ^e	122 (88.4)	114 (87.7)	102 (84.3)	216 (86.1)	338 (86.9)
ITT with at Least 14 Days of Seizure Data during Treatment	135 (97.8)	126 (96.9)	118 (97.5)	244 (97.2)	379 (97.4)

Source: Listing 16.2.3.1

Percentages are based on the total number of subjects in the relevant Analysis Set and treatment groups.

a: Includes subjects who signed informed consent, were randomized, took at least 1 dose of the double-blind treatment, and had a post-dose safety assessment.

b: Includes subjects who signed informed consent, were randomized, took at least 1 dose of double-blind treatment, and had at least 1 day of seizure diary data from the Double-blind Phase.

c: Includes subjects who signed informed consent, were randomized, took at least 1 dose of treatment, and had at least 1 day of seizure diary data from the Maintenance Period.

d: Includes subjects in the ITT Analysis Set who completed the Double-blind Phase.

e: Includes subjects in the corresponding ITT Analysis Set who did not have any major protocol deviations/violations and were >=80% compliant with the study treatment during the Double-blind Phase. Major protocol deviations/violations for each Analysis Set were defined in the Statistical Analysis Plan.

• Primary efficacy results

- 50% responder rate

Full ITT Analysis Set. The percentage of subjects who experienced a decrease in seizure frequency of at least 50% relative to baseline was greater in the 8 mg (33.3%) and 12 mg groups (33.9%) than in the placebo group (14.7%). The *P* values for the difference from placebo were 0.0018 for 8 mg and 0.0006 for 12 mg. Similar results were noted for the ITT Analysis Set for Responder Rate and the ITT Analysis Set with at Least 14 Days of Seizure Data.

The results for the Per-Protocol Analysis Set for Responder Rate and the Completer Analysis Set were consistent with those for the Full ITT Analysis Set.

Table 11.6 Responder Analysis: Full ITT Analysis Set

Perampanel					
Analysis Window	Placebo (N=136) n (%)	8 mg (N=129) n (%)	12 mg (N=121) n (%)		
Responder					
Maintenance-LOCF					
Yes	20 (14.7)	43 (33.3)	41 (33.9)		
No	116 (85.3)	86 (66.7)	80 (66.1)		
Total	136 (100)	129 (100)	121 (100)		
p-value ^a					
Compared with Placebo		0.0018	0.0006		

A responder is a subject who experienced a 50% or greater reduction in seizure frequency per 28 days from the Pre-randomization Phase.

ITT = Intent-to-Treat; LOCF = last observation carried forward.

a: The p-value is based on non-missing values and is from the Cochran-Mantel-Haenszel (CMH) test adjusted for pooled country.

Subgroup Analyses

The responder rates for subgroups of the ITT Analysis Set for Responder Rate. Many of the subgroups were small. These results will be integrated with the results from the other Phase 3 studies in the final submission to evaluate possible effects on seizure outcomes. No inferential analyses of these subgroup results were performed.

• Secondary Efficacy Results

- Percent Change in Seizure Frequency

The median change was -9.72% in the placebo group, -30.52% in the 8 mg group, and -17.57% in the 12 mg group. The *P* values for the difference from placebo were 0.0008 for 8 mg and 0.0105 for 12 mg based on the rank ANCOVA. Similar results were noted when examining percent change in seizure frequency per 28 days for the ITT Analysis Set with at Least 14 Days of Seizure Data.

Table 11.5 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline: Full ITT Analysis Set

Parameter Statistic	Perampanel		
	Placebo (N=136)	8 mg (N=129)	12 mg (N=121)
Double-blind Phase			
Pre-randomization Seizure Frequency			
N	136	129	121
Mean (SD)	32.03 (52.717)	37.59 (80.940)	42.29 (94.788)
Median	11.79	13.02	13.69
Min, Max	3.4, 358.4	3.3, 652.2	1.4, 598.4
Percent Change from Pre-randomization			
N	136	129	121
Mean (SD)	1.01 (66.587)	-21.43 (48.258)	1.08 (129.422)
Median	-9.72	-30.52	-17.57
Min, Max	-91.8, 404.3	-94.0, 234.3	-100.0, 858.3
Median Difference to Placebo		-19.10	-13.69
(95% Confidence Interval) ^a		(-29.169, -8.447)	(-25.198, -2.257)
p-value ^b Compared with Placebo		0.0008	0.0105
p-value ^c Compared with Placebo		0.0013	0.0253

ANCOVA = analysis of covariance; ITT = Intent-to-Treat; Max = maximum, Min = minimum

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 rank ANCOVA for percent change from Pre-randomization of seizure frequency per 28 days with treatment and pooled country as factors, and Pre-randomization seizure frequency per 28 days as covariate. The Pre-randomization and post randomization efficacy measurements are rank transformed separately.

c: The p-values are obtained from an ANCOVA model. The model has log-seizure frequency ratio as the response with treatment and pooled country as factors and centralized pre-randomization log-transformed seizure frequency per 28 days as covariate.

- Percent Change in Frequency of Complex Partial Plus Secondarily Generalized Seizures

The median percent change was -8.05% in the placebo group, -32.72% in the 8 mg group, and -21.89% in the 12 mg group. The *P* values were 0.0007 for the comparison of 8 mg and placebo, and 0.0045 for the comparison of 12 mg and Placebo.

Dose-response Analysis of Seizure Frequency

The summary data for the reduction of partial seizure frequency did not suggest a difference in efficacy between doses of 8 mg and 12 mg in this study. The median percent change in the frequency of all partial seizures was greater in the 8 mg group (-32.37%) than in the 12

mg group (-24.91%) When examining the secondary analysis of complex partial seizures and complex partial seizures with secondary generalization, the median percent change in the frequency of all partial seizures was similar in the 8 mg (-33.33%) and 12 mg groups (-29.67%).

- **Exploratory Efficacy Results**

- Change in the Number of Seizure-free Days

Maintenance Period, there were mean increases in the number of seizure-free days of 1.1 days in the placebo group, 2.4 days in the perampanel 8 mg group, and 1.9 days in the perampanel 12 mg group. The *P* values were 0.0289 for the comparison of 8 mg and placebo, and 0.1547 for the comparison of 12 mg and placebo.

- Percentage of Subjects Who Achieved Seizure-free Status

Among the subjects in the ITT Analysis Set for Responder Rate with at least 28 days of treatment in the Maintenance Period, 3.2% of those in the placebo group, 9.5% of those in the 8 mg group, and 10.4% of those in the 12 mg group achieved seizure-free status during the last 28 days of treatment. The *P* values for the comparison with placebo were 0.0610 for the 8 mg group and 0.0482 for the 12 mg group. Among the subjects who completed the Maintenance Period, 1.7%, 2.8%, and 6.5%, respectively, in the placebo, 8 mg, and 12 mg groups achieved seizure-free status. The *P* values for the comparison with placebo were 0.6697 for 8 mg and 0.0818 for 12 mg.

- Responder Rates for Complex Partial Seizures plus Secondarily Generalized Seizures

The responder rates during the Maintenance Period (LOCF) were 17.4% in the placebo group, 37.0% in the perampanel 8 mg group, and 37.5% in the perampanel 12 mg group. The *P* values for the comparison with placebo were 0.0037 for 8 mg and 0.0025 for 12 mg.

- Responder Rates for Secondarily Generalized Seizures

The responder rates during the Maintenance Period (LOCF) were 25.6% in the placebo group, 48.8% in the 8 mg group, and 48.6% in the 12 mg group. The *P* values for the comparison with placebo were 0.0174 for 8 mg and 0.0528 for 12 mg

- Clinical Global Impression of Change

At the end of treatment, 17.2% of the subjects in the placebo group, 28.8% of those in the perampanel 8 mg group, and 27.3% of those in the perampanel 12 mg group were considered much or very much improved by the investigators; the remaining subjects were rated minimally improved to very much worse. The *P* values for the differences relative to placebo were 0.0367 for 8 mg and 0.0491 for 12 mg

- Patient Global Impression of Change

At the end of treatment, 21.8% of the subjects in the placebo group, 36.7% of those in the perampanel 8 mg group, and 30.6% of those in the perampanel 12 mg group considered themselves much or very much improved; the remaining subjects considered themselves minimally improved to very much worse. The *P* values for the differences relative to placebo were 0.0207 for 8 mg and 0.0885 for 12 mg.

- Change in total and subscale scores for the QOLIE-31-P

The changes in quality of life were similar in the three treatment groups.

Outcomes and estimation

Based on the Full ITT Analysis Set, the results of both primary efficacy endpoints showed:

The median percent change in seizure frequency per 28 days during the Double-blind Phase relative to baseline was -30.52% with perampanel 8 mg, -17.57% with Perampanel 12mg and -9.72% with placebo. The *P* values for the difference from placebo for 8 and 12 mg were 0.0008 and 0.0105, respectively, by rank ANCOVA and 0.0013 and 0.0253, respectively, by log transformation-based ANCOVA.

The 50% responder rate during the Maintenance Period was (33.3%) for the 8mg, (33.9%) for the 12mg and (14.7%) for the placebo groups.

The *P* values for the difference from placebo were 0.0018 and 0.0006, respectively.

Data from subsets of the Double-blind Phase showed that the results of the primary efficacy endpoints based on other analysis sets were consistent with those based on the Full ITT Analysis Set.

Results in subjects with more severe, clinically important seizure types (complex partial seizures and complex partial seizures that secondarily generalized) showed that the median percent change in the frequency of these types of seizures was larger in both the 8 mg (-32.72%) and 12 mg (-21.89%) groups than the placebo group (-8.05%), with *P* values of 0.0007 and 0.0045, respectively.

The dose-response analysis focused on the Maintenance Period didn't show any difference in efficacy between doses of 8mg and 12 mg.

The median percent change in the frequency of all partial seizures was greater in the 8 mg group (-32.37%) than in the 12 mg group (-24.91%).

The exploratory efficacy endpoints showed general improvement associated with perampanel.

- The percentages of subjects who achieved seizure-free status during the last 28 days of treatment was more than twice as large in the perampanel groups as in the placebo group.
- The mean increase in the number of seizure-free days per 28 days during the Maintenance Period was nearly twice as large in the perampanel groups (2.4 days in the 8 mg group and 1.9 days in the 12 mg group) as in the placebo group (1.1 days).
- The investigators rated approximately 28% of the subjects in the perampanel groups much or very much improved at the end of the study, compared with less than 18% of those in the placebo group.
- More than 30% of the subjects who received perampanel rated themselves much or very much improved at the end of the study, compared with less than 22% of those who received placebo.

The efficacy results of study 305 showed that perampanel 8mg and 12mg are effective versus placebo (*P* values 0.0018 and 0.0006 respectively). These results are comparable with those obtained in study 304 when central and south American populations were excluded.

The 50% responder rate during the maintenance period showed no significant difference between the 8mg (33.3%) and 12mg (33.9%) groups. In addition, the number of TEAEs that resulted in discontinuation of study or study drug occurred with double frequency in the 12mg group (19.0%) than the 8mg group (9.3%) and were mainly central nervous system disorders. The need of dose reduction or interruption also occurred with a higher frequency in the 12mg group (28.1%) than the 8mg Group (20.9%) and again related to the central nervous system.

A Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group Study to Evaluate the Efficacy and Safety of E2007 (perampanel) Given as Adjunctive Therapy in Subjects with Refractory Partial Seizures (E2007-G000-306)

Methods

Study Participants

Male or female subjects, greater than or equal to 12 years of age with a diagnosis of refractory partial seizures with or without secondarily generalized seizures.

This study was to include approximately 100 to 120 sites in Asia, Australia, Europe, and Russia. Approximately 680 subjects were planned for enrollment.

• Inclusion Criteria

Subjects who were to be included in the study were those:

1. Who provided written informed consent signed by the 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 was also obtained.)

- In Germany: Who provided written informed consent signed prior to entering the study or undergoing any study procedures.

2. Who were considered reliable and willing to be available for the study period and able to record seizures and report AEs themselves or had a caregiver who could record seizures and report AEs for them

3. Male or female and greater than or equal to 12 years of age within the course of the study

- For sites in Germany, Bulgaria, Portugal, Lithuania, India, and China, subjects must have been greater than or equal to 18 years of age at the time of signing the informed consent.

4. Females were either of non-childbearing potential (defined as having undergone surgical sterilization, or postmenopausal [age 50 and amenorrheic for 12 months]) or of childbearing potential. Females of childbearing potential had a negative serum beta-human chorionic gonadotropin (β -hCG) at Visit 1 and a negative urine pregnancy test prior to randomization at Visit 2. Female subjects of childbearing potential agreed to be abstinent or to use at least 1 medically acceptable method of contraception (e.g., a double-barrier method [e.g., condom + spermicide, condom + diaphragm with spermicide], intrauterine device, or have a vasectomized partner) starting at Visit 1 and throughout the entire study period and for 2 months after the last dose of study drug. Women using hormonal contraceptives also used an additional approved method of contraception (as described previously) starting at Visit 1 and continuing throughout the entire study period and for 2 months after the last dose of study drug. (It was not required for male subjects to use contraceptive measures.)

5. Who had a diagnosis of epilepsy with partial seizures with or without secondarily generalized seizures according to the International League Against Epilepsy's Classification of Epileptic Seizures (1981). Diagnosis was established by clinical history and an EEG that was consistent with localization-related epilepsy; normal interictal EEGs were allowed provided that the subject met the other diagnosis criterion (i.e., clinical history).

6. Who had a computed tomography or magnetic resonance imaging within the last 10 years that ruled out a progressive cause of epilepsy

7. Who had uncontrolled partial seizures despite having been treated with at least two different AEDs within approximately the last 2 years

- For Germany: Had uncontrolled partial seizures despite having been treated with at least two different AEDs for a minimum of 2 years

8. During the 6-week Prerandomization Phase, subjects must have had five or more partial seizures (with two or more partial seizures per each 3-week period) and no 25-day seizure-free period in the 6-week period, as documented via a valid seizure diary. Only simple partial seizures with motor signs, complex partial seizures, and complex partial seizures with secondary generalization were counted toward this inclusion.

9. Who were currently being treated with stable doses of one, two or a maximum of three approved AEDs. Only one inducer AED (defined as carbamazepine, phenytoin, phenobarbital, or primidone) out of the maximum of three AEDs was allowed.

- For Lithuania: Were currently being treated with stable doses of two or a maximum of three approved AEDs

10. Who were on a stable dose of the same concomitant AED(s) for 1 month (or no less than 21 days) prior to Visit 1; in the case where a new AED regime was initiated for a subject, the dose must have been stable for 2 months (or no less than 49 days) prior to Visit 1.

11. If on a stable dose (other than intermittent rescue use) of benzodiazepines for epilepsy (or for anxiety or sleep disorders), the prescribed dose was stable for 1 month (or no less than 21 days) prior to Visit 1. (Note that the use of intermittent rescue benzodiazepines is defined in exclusion criterion #22 below.) When used in these cases (epilepsy, anxiety or sleep disorders), benzodiazepines were counted as one AED; therefore, only one or a maximum of two additional approved AEDs were allowed.

12. A vagal nerve stimulator was allowed but it must have been implanted \geq 5 months prior to Visit 1. Stimulator parameters could not be changed for 1 month (or no less than 21 days) prior to Visit 1 or thereafter during the study.

• **Exclusion Criteria**

Subjects who were to be excluded from the study were those:

1. Who participated in a study involving administration of an investigational compound or device within 1 month (or no less than 21 days) prior to Visit 1, or within approximately five half-lives of the previous investigational compound, whichever is longer

2. Who were pregnant and/or lactating

3. Who participated in previous perampanel studies

4. With a presence of nonmotor simple partial seizures only

5. With a presence of primary generalized epilepsies or seizures, such as absences and or myoclonic epilepsies

6. With a presence or previous history of Lennox-Gastaut syndrome

7. With a history of status epilepticus within approximately 12 months prior to Visit 1

8. With seizure clusters where individual seizures could not be counted

9. With a history of psychogenic seizures
10. With evidence of clinically significant disease (e.g., cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could have affected the subject's safety or the study conduct
11. Scheduled and/or confirmed to have epilepsy surgery within 6 months after Visit 1; however those with previously documented "failed" epilepsy surgery were allowed.
12. With evidence of significant active hepatic disease. Stable elevations of liver enzymes, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) due to concomitant medication(s) were allowed if they were less than 3 times the upper limit of normal (ULN).
13. With evidence of significant active hematological disease; white blood cell (WBC) count \leq \square 2500/ μ L (2.50 1E+09/L) or an absolute neutrophil count \leq \square 1000/ μ L (1.00 1E+09/L)
14. With a clinically significant ECG abnormality, including prolonged QTc defined as $>$ 450 msec
15. Suffering from psychotic disorder(s) and/or unstable recurrent affective disorder(s) evident by use of antipsychotics or who had a suicide attempt(s) within approximately the last 2 years
16. With a presence of a progressive central nervous system (CNS) disease, including degenerative CNS diseases and progressive tumors
17. With a history of drug or alcohol dependency or abuse within approximately the last 2 years
18. Who had multiple drug allergies or a severe drug reaction to an AED(s), including dermatological (e.g., Stevens-Johnson syndrome), hematological, or organ toxicity reactions
19. If felbamate was used as a concomitant AED, subjects were on felbamate for at least 2 years, with a stable dose for 2 months (or no less than 49 days) prior to Visit 1. They must not have had a history of WBC count of \leq \square 2500/ μ L (2.50 1E+09/L), platelets below 100,000/mm³, liver function tests above 3 times the ULN, or other indication of hepatic or bone marrow dysfunction while receiving felbamate. If subjects received felbamate in the past, it must have been discontinued 2 months (or no less than 49 days) prior to Visit 1.
20. With concomitant use of vigabatrin. Subjects who took vigabatrin in the past were off vigabatrin for approximately 5 months prior to Visit 1 and had documentation showing no evidence of a vigabatrin-associated clinically significant abnormality in a visual perimetry test.
21. With concomitant use of barbiturates (except for seizure control indication) within 1 month (or no less than 21 days) prior to Visit 1
22. With use of intermittent rescue benzodiazepines (i.e., one or two doses over a 24-hour period considered one-time rescue) two or more times in a 1-month period prior to Visit 1
23. With any condition(s) that made the subject, in the opinion of the investigator, unsuitable for the study
24. The following criteria applied to only those countries specified:
 - In Germany: Those committed to an institution by official or judicial order.

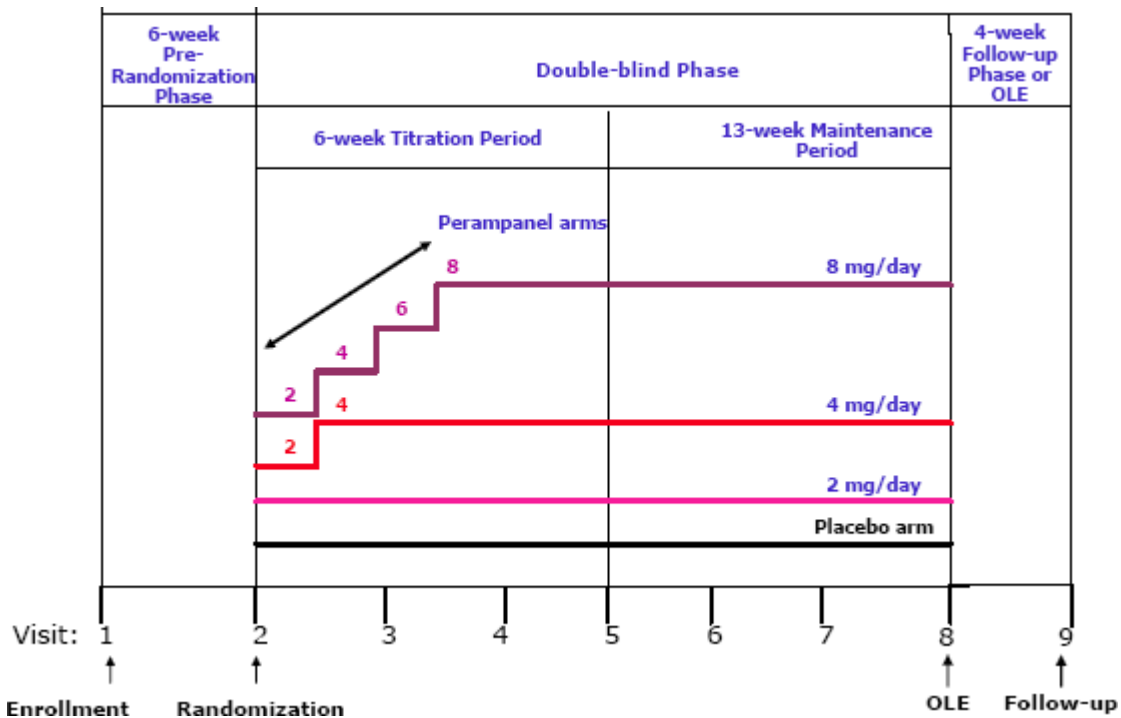
Treatments

The study consisted of three phases:

- The Pre randomization Phase was 6 weeks in duration.
- The Double-blind Phase was 19 weeks in duration and included two periods: Titration and Maintenance. The Titration Period was 6 weeks in duration and the Maintenance Period was 13 weeks in duration.
- The Follow-up Phase was 4 weeks in duration.

No treatment was to be administered during the Pre-randomization Phase of the study. Once a subject completed this phase, they were randomized to treatment and begin the 6-week Double- Blind Phase Titration Period (Visit 2 to Visit 5). Throughout the entire Double-blind Phase, all subjects took a total of 6 tablets daily.

During the Titration Period, all subjects started on 6 tablets (1 tablet of 2 mg perampanel plus 5 tablets of placebo or 6 tablets of placebo) and titrated to the appropriate randomized dose (2 mg, 4 mg or 8mg perampanel, or placebo).



Objectives

• Primary Objectives

- To evaluate the efficacy of three doses of perampanel (2, 4 and 8 mg) in comparison to placebo given as an adjunctive therapy in subjects with refractory partial seizures.

• Secondary Objectives

- To evaluate the safety and tolerability of perampanel vs. placebo in subjects with refractory partial seizures.

- **Exploratory Objectives**

- To explore potential withdrawal symptoms of perampanel vs. placebo in subjects with refractory partial seizures.
- To explore potential photosensitivity of perampanel vs. placebo in subjects with refractory partial seizures.
- To explore the effects of perampanel on partial seizure frequency (in 25% increments), on the frequency of complex partial seizures with secondary generalization, and on Clinical and Patient Global Impressions of Change.

Outcomes/endpoints

- **Primary Efficacy Variable(s)**

The primary efficacy endpoint for EU registration was the 50% responder rate. Responders were defined as subjects who experienced a 50% or greater reduction in seizure frequency per 28 days in the Maintenance Period relative to the Prerandomization Phase.

- **Secondary Efficacy Variable(s)**

- The key secondary efficacy endpoint was the percent change in seizure frequency.
- The other secondary endpoint was the percent change in complex partial plus secondarily generalized seizure frequency per 28 days during treatment relative to baseline.

- **Exploratory Efficacy Variable(s)**

Exploratory efficacy endpoints included:

- The percentage of subjects experiencing decreases/increases (25% increments) in seizure frequency per 28 days; change in the number of seizure-free days per 28 days;
- The percentage of subjects who achieved seizure-free status;
- Clinical and Patient Global Impressions of Change;
- Time to 1st, 3rd, 6th, 9th, and 12th seizures during treatment;
- Time to first 50% response;
- The percent change in the frequency per 28 days of complex partial seizures with secondary generalization; 50% responder rates based on complex partial plus secondarily generalized seizures, and on complex partial seizures with secondary generalization only;
- Change in total and subscale scores for the QOLIE-31-P.

Sample size

A sample size of 680 subjects was estimated.

Based on Phase 2 studies in subjects with epilepsy, it was assumed that the percent change in seizure frequency per 28 days in the Maintenance Period relative to the Prerandomization Phase would be 10% in the placebo group, 32% in the 8 mg group, and 26% in the 4 mg group in the ITT Analysis Set. Therefore, a sample size of 162 subjects in each treatment group in the ITT Analysis Set would have 92% power to detect a treatment difference of 22% in seizure frequency (assuming a common SD of 56%) between placebo and the 8 mg group based on the Wilcoxon rank-sum test with a 0.05 two-

sided significance level. The same sample size of 162 subjects in each treatment group corresponds to 71% power to detect a treatment difference of 16% in seizure frequency (assuming a common SD of 56%) between placebo and the 4 mg group based on the Wilcoxon rank-sum test with a 0.05 two-sided significance level. To account for subjects who might be randomized but not be included in the ITT Analysis Set, the number of subjects randomized was to be approximately 170 per treatment group.

Randomisation

Subjects were assigned randomized to one of the four treatment groups in a 1:1:1:1 ratio based on a randomization scheme generated using a computer program. The randomization scheme was reviewed and approved by an independent statistician and locked after approval.

Blinding

The double-blind design of these studies 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 treatment groups.

During the Double-blind Phase, the subject and all personnel involved with the conduct and the interpretation of the study, including the investigators, investigational site personnel and Eisai staff, were blinded to the treatment codes. Randomization data were kept strictly confidential, filed securely by the Eisai Scientific and Operational Clinical Support Core Functional Unit, and accessible only to authorized persons per SOPs until the time of unblinding.

Statistical methods

The primary efficacy endpoint for EU registration was the 50% responder rate. For all other purposes, this was the key secondary endpoint. Responders were defined as subjects who experienced a 50% or greater reduction in seizure frequency per 28 days in the Maintenance Period relative to the Pre-randomisation Phase.

Responder rate analysis of subjects who experienced a 50% or greater reduction in seizure frequency during treatment relative to baseline was conducted using the Cochran–Mantel–Haenszel (CMH) test adjusting for pooled countries.

The key secondary efficacy endpoint was the percent change in seizure frequency per 28 days during treatment relative to baseline. In this context, seizure frequency refers to the frequency of all partial seizures. For this analysis, both the baseline seizure frequencies per 28 days and the percent change per 28 days during treatment were rank transformed separately. An analysis of covariance (ANCOVA) was then conducted on the rank-transformed percent change data, with treatment and pooled countries as factors and the ranked baseline seizure frequency per 28 days as a covariate. P values were computed using contrasts between active and placebo treatment groups.

Due to an expected irregular distribution of seizure frequency, median was the primary statistic of interest for comparing the percent change between the treatment groups. The Hodges–Lehmann estimator and 95% confidence interval (CI) for this estimator were displayed for understanding the treatment effect size. The Applicant also presents results using standard parametric log-transformed ANCOVA.

The Applicant defines various analysis populations, including the Safety Analysis Set, the Full Intention to Treat Analysis Set, The ITT analysis set, the ITT analysis Set for Responder Rate, the Per Protocol Analysis set and the modified PP analysis set.

The ITT Analysis Set for Responder Rate is the group of subjects who were randomized to study drug, received study drug, and entered the Maintenance Period (i.e. took at least one dose of study drug during the Maintenance Period and had any seizure frequency data during the Maintenance Period). The Full Intent-to-Treat (ITT) Analysis Set is the group of subjects who were randomised to study drug, received study drug, and had any seizure frequency data during the Double blind Phase.

In order to handle missing data, the Applicant used an LOCF approach. A sensitivity analysis including missing data as non-responders (for the EU primary analysis) was also provided.

The sensitivity analysis using missing data as failure is more suitable than the primary analysis and is in line with the CHMP Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1). The LOCF approach is acceptable for the key secondary analysis.

The proposed analysis method for the primary and key secondary variables is acceptable. The ranked ANCOVA is acceptable given that the data are expected a priori to not be normally distributed.

Results

Participant flow

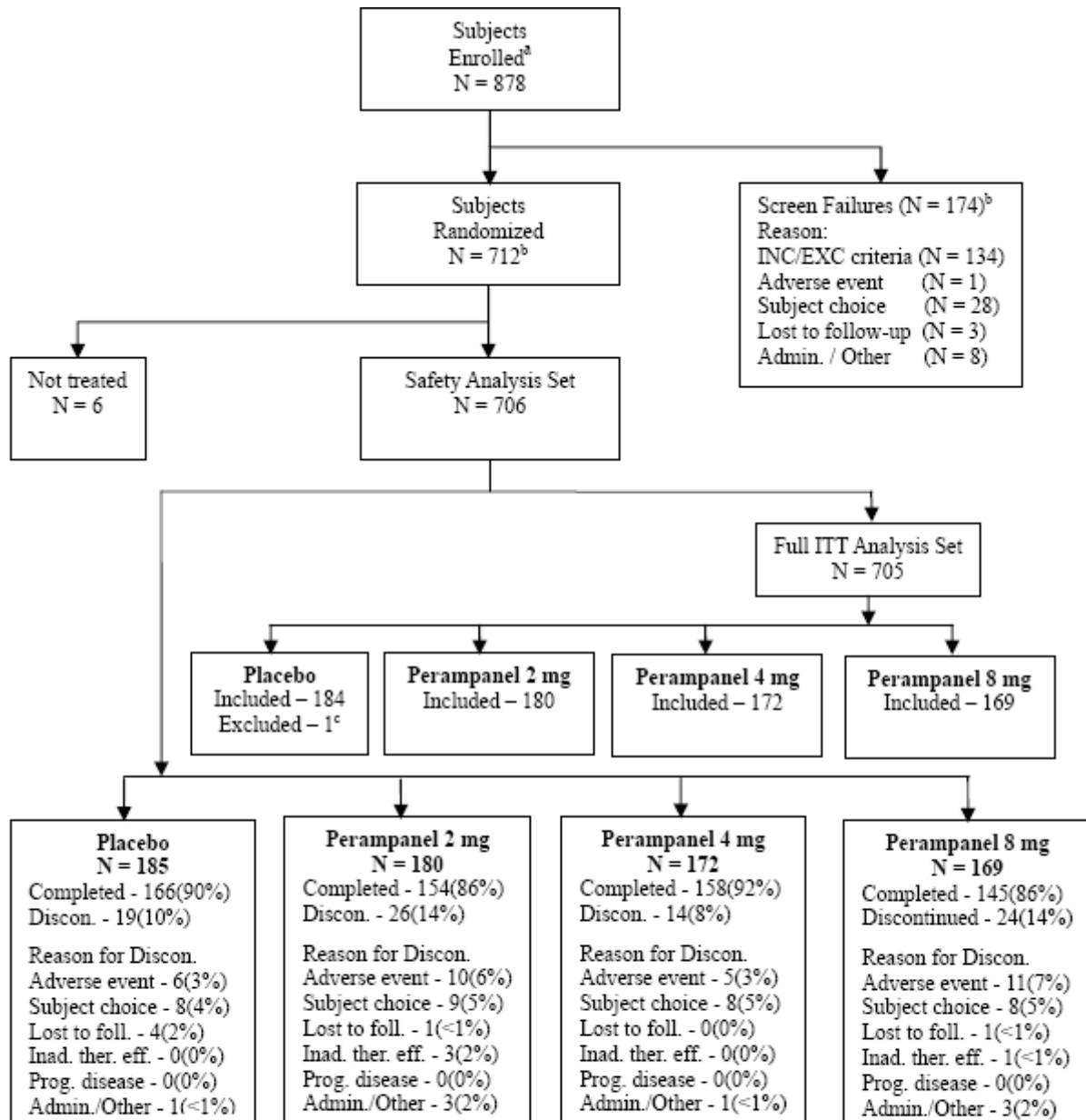


Figure 10.1 Subject Disposition

Admin. = administrative, Discon. = discontinued/discontinuation, Foll. = follow-up, Inad. ther. eff. = inadequate therapeutic effect, INC/EXC = inclusion/exclusion, ITT = intent-to-treat, Prog. disease = progressive disease.

a: Subjects who signed informed consent forms

b: Includes eight subjects who were screen failures and were inappropriately randomized to a treatment group

c: Subject 43056003 was treated for 1 day and did not complete a seizure diary that day.

Source: [Table 14.1.1](#), [Table 14.1.2.1](#), [Table 14.1.4](#)

Recruitment

706 subjects were randomized in the study. The study was conducted between 04 Aug 2008 and 21 Jul 2010.

Conduct of the study

• Protocol amendments

There was one global amendment (Amendment 01; 20 Mar 2009), which was initiated after 146 subjects had been enrolled in the study.

There were also seven country specific protocol amendments that were initiated primarily to address differences in local regulations:

Amendment A – Germany; (09 May 2008)

Amendment B – Germany; (05 Nov 2008)

Amendment C – Bulgaria; (17 Sep 2008)

Amendment D – Portugal; (15 Dec 2008)

Amendment E – Lithuania; (05 Nov 2008)

Amendment F – India; (20 Nov 2008)

Amendment G – China; (19 Jan 2009)

• Protocol deviations

Forty-three subjects in the ITT Analysis Set were excluded from the PP Analysis Set, including 14 (7.7%) subjects in the placebo group, eight (4.5%) subjects in the perampanel 2 mg group, eight (4.8%) subjects in the perampanel 4 mg group, and 13 (7.8%) subjects in the perampanel 8 mg group. The most common reasons for exclusion were failure to experience the required minimum number of seizures during the Prerandomization Phase (three, five, one, and eight subjects, respectively) and not being treated with stable doses of one to three AEDs (six, two, three, and three subjects, respectively).

Eleven subjects in the ITT Analysis Set were excluded from the Modified PP Analysis Set, including five (2.7%) subjects in the placebo group, one (0.6%) subject in the 2 mg group, three (1.8%) subjects in the 4 mg group, and two (1.2%) subjects in the 8 mg group. The most common reason for exclusion was interruption or discontinuation of all baseline AEDs (three, one, one, and one subjects, respectively).

Although a number of deviations from the protocol (e.g., missed visits, visit outside the protocol-specified window) occurred, these deviations were not considered to have affected the evaluation of efficacy or safety. No treatment codes were broken prior to database lock.

Incorrect study drug kits were dispensed to the following subjects, who received the incorrect treatment for part of the study.

- Subject 18016013 in the placebo group received perampanel 2 mg for 2 weeks during the Titration Period.
- Subject 26046004 in the placebo group received perampanel 2 mg for 1 week and 4 mg for 1 week (first 2 weeks of the Titration Period).
- Subject 48026001 in the perampanel 2 mg group received 4 mg for the last week of the Titration Period.
- Subject 44036001 in the perampanel 4 mg group received 2 mg for more than 5 weeks during the Maintenance Period.

- Subject 26046005 in the perampanel 4 mg group received placebo for the first 2 weeks of the Titration Period.
- Subject 15026021 in the perampanel 8 mg group received placebo for the first 2 weeks of the Titration Period.

Baseline data

Summary of Demography and Baseline Characteristics - Intent-to-Treat Analysis Set

Category	Perampanel					Combined Total (N=693)
	Placebo (N=182)	2 mg (N=177)	4 mg (N=168)	8 mg (N=166)	Total (N=511)	
Age (Year)*						
n	182	177	168	166	511	693
Mean (SD)	33.1 (12.42)	33.6 (13.45)	33.3 (12.13)	34.8 (12.81)	33.9 (12.81)	33.7 (12.70)
Median	31.0	32.0	32.0	33.0	32.0	32.0
Min, Max	12, 66	13, 72	12, 68	12, 69	12, 72	12, 72
Age Group, n (%)						
<18	14 (7.7)	21 (11.9)	13 (7.7)	12 (7.2)	46 (9.0)	60 (8.7)
18-64	166 (91.2)	153 (86.4)	154 (91.7)	150 (90.4)	457 (89.4)	623 (89.9)
>64	2 (1.1)	3 (1.7)	1 (<1)	4 (2.4)	8 (1.6)	10 (1.4)
Sex, n (%)						
Male	95 (52.2)	83 (46.9)	85 (50.6)	77 (46.4)	245 (47.9)	340 (49.1)
Female	87 (47.8)	94 (53.1)	83 (49.4)	89 (53.6)	266 (52.1)	353 (50.9)
Race, n (%)						
White	119 (65.4)	116 (65.5)	103 (61.3)	115 (69.3)	334 (65.4)	453 (65.4)
Black or African American	0	0	0	0	0	0
Asian	32 (17.6)	35 (19.8)	35 (20.8)	27 (16.3)	97 (19.0)	129 (18.6)
Japanese	0	0	0	0	0	0
Chinese	30 (16.5)	25 (14.1)	29 (17.3)	24 (14.5)	78 (15.3)	108 (15.6)
American Indian or Alaska Native	0	0	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0
Other	1 (<1)	1 (<1)	1 (<1)	0	2 (<1)	3 (<1)

Source: [Appendix 16.2.4.1](#)

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

a: Age at Informed Consent.

b: BMI represents subject's Body Mass Index (kg/m²). The units used are kg/m².

SD = standard deviation.

Numbers analysed

Analyses have been performed on the following analyses sets:

Summary of Analysis Sets - All Randomized Subjects

Analysis Set	Perampanel					
	Placebo (N=187) n (%)	2 mg (N=180) n (%)	4 mg (N=174) n (%)	8 mg (N=171) n (%)	Total (N=525) n (%)	Combined Total (N=712) n (%)
Safety Analysis Set ^a	185 (98.9)	180 (100)	172 (98.9)	169 (98.8)	521 (99.2)	706 (99.2)
Intent-to-Treat (ITT) ^b	182 (97.3)	177 (98.3)	168 (96.6)	166 (97.1)	511 (97.3)	693 (97.3)
Completer Analysis Set ^c	166 (88.8)	154 (85.6)	158 (90.8)	145 (84.8)	457 (87.0)	623 (87.5)
Per Protocol Analysis Set ^d	168 (89.8)	169 (93.9)	160 (92.0)	153 (89.5)	482 (91.8)	650 (91.3)
Modified Per Protocol Analysis Set ^e	177 (94.7)	176 (97.8)	165 (94.8)	164 (95.9)	505 (96.2)	682 (95.8)
Full ITT ^f	184 (98.4)	180 (100)	172 (98.9)	169 (98.8)	521 (99.2)	705 (99.0)
ITT for Responder Rate ^f	174 (93.0)	169 (93.9)	163 (93.7)	156 (91.2)	488 (93.0)	662 (93.0)

Source: Appendix 16.2.3.1

Percentages are based on the total number of subjects in the relevant Analysis Set and treatment groups.

a: Includes subjects who signed informed consent, were randomized, took at least 1 dose of the double-blind treatment, and had a post-dose safety assessment.

b: Includes subjects who signed informed consent, were randomized, took at least 1 dose of double-blind treatment, and had at least 14 days of seizure diary data from the Pre-randomization Phase and at least 14 days of seizure diary data from the Double-blind Phase.

c: Includes subjects in the ITT Analysis Set who completed the Double-blind Phase.

d: Includes subjects in the ITT Analysis Set who did not have any major protocol deviations/violations and were $\geq 75\%$ compliant with the study treatment during the Double-blind Phase. Major protocol deviations/violations for the Per Protocol Analysis Set were defined in the Statistical Analysis Plan.

e: Includes subjects who signed informed consent, were randomized, took at least 1 dose of double-blind treatment, and had at least 1 day of seizure diary data from the Double-blind Phase.

f: Includes subjects who signed informed consent, were randomized, took at least 1 dose of treatment, and had at least 1 day of seizure diary data from the Maintenance Period.

• Primary efficacy results

- 50% responder rate

Full ITT Analysis Set. (Maintenance- LOCF). The percentage of subjects who experienced a decrease in seizure frequency of at least 50% relative to baseline was 17.9% in the placebo group, 20.6% in the 2 mg group, 28.5% in the 4 mg group, and 34.9% in the 8 mg group. The *P* values for the difference from placebo were 0.4863, 0.0132, and 0.0003, respectively.

The results for the ITT Analysis Set and the ITT Analysis Set for Responder Rate were consistent with those for the Full ITT Analysis Set.

Table 11.6 Responder Analysis: Full ITT Analysis Set

Analysis Window	Perampanel			
	Placebo (N=184) n (%)	2 mg (N=180) n (%)	4 mg (N=172) n (%)	8 mg (N=169) n (%)
Responder				
Maintenance-LOCF				
Yes	33 (17.9)	37 (20.6)	49 (28.5)	59 (34.9)
No	151 (82.1)	143 (79.4)	123 (71.5)	110 (65.1)
Total	184 (100)	180 (100)	172 (100)	169 (100)
p-value ^a				
Compared with Placebo		0.4863	0.0132	0.0003

A responder is a subject who experienced a 50% or greater reduction in seizure frequency per 28 days from the Pre-randomization Phase. ITT = Intent-to-Treat, LOCF = last observation carried forward.

a: The p-value is based on non-missing values and is from the Cochran-Mantel-Haenszel (CMH) test adjusted for pooled country.

Source: Listing 16.2.6.2, Table 14.2.2.3.5

Subgroup Analyses

The responder rates for subgroups of the ITT Analysis Set for Responder Rate. Many of the subgroups were small. These results will be integrated with the results from the other Phase III studies in the

Final submission to evaluate possible effects on seizure outcomes. No inferential analyses of these subgroup results were performed.

• **Secondary Efficacy Results**

- Percent Change in Seizure Frequency

Full ITT Analysis Set. The median change was -10.69% in the placebo group, -13.63% in the 2 mg group, -23.33% in the 4 mg group, and -30.80% in the 8 mg group. The *P* values for the difference from placebo were 0.4197 for 2 mg, 0.0026 for 4 mg, and < 0.0001 for 8 mg based on the rank ANCOVA and 0.2542, 0.0037, and < 0.0001, respectively, based on the log transformation-based ANCOVA. The median differences from placebo for the ITT Analysis Set (Double-blind Phase and Maintenance-LOCF) were similar to those for the Full ITT Analysis Set (Double-blind Phase).

Table 11.5 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline: Full ITT Analysis Set

Analysis Window Parameter Statistic	Perampanel			
	Placebo (N=184)	2 mg (N=180)	4 mg (N=172)	8 mg (N=169)
Double-blind Phase				
Pre-randomization Seizure Frequency				
n	184	180	172	169
Mean (SD)	23.94 (50.541)	31.20 (55.420)	62.56 (354.872)	32.61 (73.127)
Median	9.33	10.12	10.02	10.93
Min, Max	3.3, 569.1	3.2, 429.6	2.9, 4503.9	3.4, 723.2
Percent Change from Pre-randomization				
n	184	180	172	169
Mean (SD)	0.82 (67.438)	-7.25 (58.392)	-14.33 (66.977)	-20.86 (60.937)
Median	-10.69	-13.63	-23.33	-30.80
Min, Max	-100.0, 420.6	-100.0, 346.3	-100.0, 416.0	-100.0, 390.6
Median Difference to Placebo (95% Confidence Interval) ^a		-4.36 (-14.091, 5.227)	-13.71 (-23.306, -4.500)	-20.13 (-29.656, -10.425)
p-value ^b Compared with Placebo		0.4197	0.0026	<0.0001
p-value ^c Compared with Placebo		0.2542	0.0037	<0.0001

ANCOVA = analysis of covariance, ITT = Intent-to-Treat, Max = maximum, Min = minimum

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 rank ANCOVA for percent change from Pre-randomization of seizure frequency per 28 days with treatment and pooled country as factors, and Pre-randomization seizure frequency per 28 days as covariate. The Pre-randomization and post randomization efficacy measurements are rank transformed separately.

c: The p-value is obtained from an ANCOVA model. The model has log-seizure frequency ratio as the response with treatment and pooled country as factors and centralized pre-randomization log-transformed seizure frequency per 28 days as covariate.

- Percent Change in Frequency of Complex Partial Plus Secondarily Generalized Seizures

Full ITT Analysis Set. The median percent change was -17.63% in the placebo group, -20.50% in the 2 mg group, -31.18% in the 4 mg group, and -38.69% in the 8 mg group. The *P* values for the comparison with placebo were 0.6506 for 2 mg, 0.0070 for 4 mg and 0.0005 for 8 mg. The results for the ITT Analysis Set (both Double-blind Phase and Maintenance-LOCF) were consistent with those for the Full ITT Analysis Set (Double-blind Phase).

Dose-response Analysis of Seizure Frequency

The dose-response analysis focused on the Maintenance Period (Full ITT Analysis Set; LOCF) when the doses of perampanel became more stable. The median percent change in the frequency of all partial seizures was -15.25% in the 2 mg group, -28.08% in the 4 mg group, and -33.04% in the 8 mg group (Table 14.2.1.1.6.1), and the dose-response trend test on ranks using linear contrast was positive

($P < 0.0001$). The secondary analysis of complex partial plus secondarily generalized seizures had similar results. The results for the ITT Analysis Set were consistent with those for the Full ITT Analysis Set.

- **Exploratory Efficacy Results**

- Change in the Number of Seizure-free Days

At baseline, the mean number of seizure-free days per 28 days was approximately 17 days in each treatment group for the ITT Analysis Set. In the Double-blind Phase, there were mean increases in the number of seizure-free days of 0.8 days in the placebo group, 1.5 days in the perampanel 2 mg group, 1.8 days in the perampanel 4 mg group, and 2.1 days in the perampanel 8 mg group. The P values for the comparison with placebo were 0.0965 for 2 mg, 0.0153 for 4 mg, and 0.0006 for 8 mg.

- Percentage of Subjects Who Achieved Seizure-free Status

Among the subjects in the ITT Analysis Set with at least 28 days of treatment in the Maintenance Period, 7.0% of those in the placebo group, 9.1% of those in the 2 mg group, 9.3% of those in the 4 mg group, and 11.3% of those in the 8 mg group achieved seizure-free status during the last 28 days of treatment. The P values for the comparison with placebo were 0.5487, 0.5478, and 0.2416, respectively, for the perampanel groups. Among those who completed the Maintenance Period, the percentages of subjects who achieved seizure-free status were 1.2% in the placebo group, 1.9% in the 2 mg group, 4.4% in the 4 mg group, and 4.8% in the 8 mg group. The P values for the comparison with placebo were 0.6745, 0.0972, and 0.0875, respectively, for the perampanel groups.

- Responder Rates for Complex Partial Seizures plus Secondarily Generalized Seizures

The responder rates during the Maintenance Period (LOCF) were 24.0% in the placebo group, 27.4% in the 2 mg group, 35.9% in the 4 mg group, and 39.1% in the 8 mg group. The P values for the comparison with placebo were 0.4583 for 2 mg, 0.0183 for 4 mg, and 0.0048 for 8 mg.

- Responder Rates for Secondarily Generalized Seizures

The responder rates during the Maintenance Period (LOCF) were 45.6% in the placebo group, 44.8% in the 2 mg group, 50.0% in the 4 mg group, and 61.7% in the 8 mg group. The P values for the comparison with placebo were 0.5373 for 2 mg, 0.7062 for 4 mg, and 0.2708 for 8 mg.

- Clinical Global Impression of Change

At the end of treatment, 15.9% of the subjects in the placebo group, 21.3% of those in the 2 mg group, 28.1% of those in the 4 mg group, and 30.4% of those in the 8 mg group were considered much or very much improved by the investigators; the remaining subjects were rated minimally improved to very much worse. The P values for the differences relative to placebo were 0.2093 for 2 mg, 0.0063 for 4 mg, and 0.0013 for 8 mg. The results for the ITT Analysis Set were consistent with those for the Full ITT Analysis Set.

- Patient Global Impression of Change

At the end of treatment, 23.1% of the subjects in the placebo group, 24.3% of those in the 2 mg group, 32.1% of those in the 4 mg group, and 32.3% of those in the 8 mg group considered themselves much or very much improved; the remaining subjects considered themselves minimally improved to very much worse. The P values for the differences relative to placebo were 0.8039 for 2 mg, 0.0618 for 4 mg, and 0.0529 for 8 mg. The results for the ITT Analysis Set were consistent with those for the Full ITT Analysis Set.

- Change in total and subscale scores for the QOLIE-31-P

The changes in quality of life were similar in all four treatment groups.

Outcomes and estimation

The Full ITT Analysis Set, the results of both primary efficacy endpoints showed that:

The median percent change in seizure frequency per 28 days during the Double-blind Phase relative to baseline was -23.33% for the 4 mg and -30.80% for the 8 mg perampanel when placebo was -10.69%. The median percent change with perampanel 2 mg (-13.63%) was similar to that with placebo. The *P* values for the difference from placebo for 2, 4, and 8 mg were 0.4197, 0.0026, and < 0.0001, respectively, by rank ANCOVA and 0.2542, 0.0037, and < 0.0001, respectively, by log transformation-based ANCOVA.

The 50% responder rate during the Maintenance Period, when doses became more stable, was higher in both the 4 mg (28.5%) and 8 mg (34.9%) groups than the placebo group (17.9%). The responder rate in the 2 mg group (20.6%) was similar to that in the placebo group. The *P* values for the difference from placebo were 0.4863 for 2 mg, 0.0132 for 4 mg, and 0.0003 for 8 mg.

The results in subjects with more severe, clinically important seizure types (complex partial seizures and complex partial seizures that secondarily generalized) showed that the median percent change in the frequency of these types of seizures was larger in both the 4 mg (-31.18%) and 8 mg (-38.69%) groups than the placebo group (-17.63%). The median percent change in the 2 mg group (-20.50%) was similar to that in the placebo group. The *P* values for the difference from placebo were 0.6506 for 2 mg, 0.0070 for 4 mg, and 0.0005 for 8 mg.

The dose-response analysis focused on the Maintenance Period showed that there were positive dose-response trend tests on ranks using linear contrast (*P*<0.0001 for all seizures and *P*=0.0003 for more severe types).

Ancillary analyses

The findings of the primary efficacy analyses were supported by sensitivity analyses using different analysis populations and data from subsets of the Double-blind Phase.

Summary of main studies

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

Table 2. Summary of Efficacy for trial 304

Title: A double-blind, placebo-controlled, dose-escalation, parallel-group study to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures		
Study identifier	E2007-G000-304	
Design	Double-blind, randomized, placebo-controlled, no active comparator group. 3 phases: pre-randomisation (6 weeks), double-blind (6-week titration phase followed by 13-week maintenance period), and follow-up phase (4 weeks)	
	Duration of main phase:	13-week maintenance period
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Superiority compared to placebo	
Treatments groups	placebo	Comparator, 19 weeks, 121 subjects

	Perampanel 8 mg		Treatment, 19 weeks, 133 subjects	
	Perampanel 12 mg		Treatment, 19 weeks, 134 subjects	
Endpoints and definitions	Primary endpoint	50% Responder rate	50% or greater reduction in seizure frequency during treatment relative to baseline. Responder rate was analysed for the maintenance period.	
	Secondary endpoint	Percent change in seizure frequency per 28 days	Per 28 days during treatment relative to baseline. The percent change in seizure frequency was analysed over the maintenance period and the entire double-blind phase (titration + maintenance period).	
	Secondary other specify endpoint			
Database lock	11 Nov 2010			
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	Full Intent to treat Analysis set: group of subject who were randomised to study drug, received study drug, and had any seizure frequency data during the double-blind phase Analysis at the end of the 13- week maintenance period			
Descriptive statistics and estimate variability	Treatment group	Placebo	Perampanel 8 mg	Perampanel 12 mg
	Number of subject	121	133	134
	50 % responder rate	26.4 %	37.6 %	36.1 %
	variability statistic			
Effect estimate per comparison	Comparison with placebo		Perampanel 8 mg	Perampanel 12 mg
	Difference to placebo		11.2%	9.7%
	variability statistic			
	P-value		0.0760	0.0914
Notes				
Analysis description	Secondary analysis			
Analysis population and time point description	Full Intent to treat Analysis set: group of subject who were randomised to study drug, received study drug, and had any seizure frequency data during the double-blind phase Analysis for the entire double-blind phase			
Descriptive statistics and estimate variability	Treatment group	Placebo	Perampanel 8 mg	Perampanel 12 mg
	Number of subject	121	133	134
	Percent change in seizure frequency (median)	- 20.95	- 26.34	- 34.49
	variability statistic			
Effect estimate per comparison	Percent change in seizure frequency	Comparison with placebo	Perampanel 8 mg	Perampanel 12 mg
		Median difference to placebo	- 13.53	- 14.20
		95 % CI	- 26.172, - 1.944	- 25.030, - 2.729
		P-value	0.0261	0.0184
Notes				

Table 3. Summary of Efficacy for trial 305

Title: A double-blind, placebo-controlled, dose-escalation, parallel-group study to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures				
Study identifier	E2007-G000-305			
Design	Double-blind, randomized, placebo-controlled, no active comparator group. 3 phases: pre-randomisation (6 weeks), double-blind (6-week titration phase followed by 13-week maintenance period), and follow-up phase (4 weeks)			
	Duration of main phase:	13-week maintenance period		
	Duration of Run-in phase:	not applicable		
	Duration of Extension phase:	not applicable		
Hypothesis	Superiority compared to placebo			
Treatments groups	placebo	Comparator, 19 weeks, 136 subjects		
	Perampanel 8 mg	Treatment, 19 weeks, 129 subjects		
	Perampanel 12 mg	Treatment, 19 weeks, 121 subjects		
Endpoints and definitions	Primary endpoint	50 % Responder rate	50% or greater reduction in seizure frequency during treatment relative to baseline. Responder rate was analysed for the maintenance period.	
	Secondary endpoint	Percent change in seizure frequency per 28 days	Per 28 days during treatment relative to baseline. The percent change in seizure frequency was analysed over the maintenance period and the entire double-blind phase (titration + maintenance period).	
	Secondary other specify endpoint			
Database lock	14 Jan 2011			
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	Full Intent to treat Analysis set: group of subject who were randomised to study drug, received study drug, and had any seizure frequency data during the double-blind phase Analysis at the end of the 13- week maintenance period			
Descriptive statistics and estimate variability	Treatment group	Placebo	Perampanel 8 mg	Perampanel 12 mg
	Number of subject	136	129	121
	50 % responder rate	14.7 %	33.3 %	33.9 %
	variability statistic			
Effect estimate per comparison	Comparison with placebo		Perampanel 8 mg	Perampanel 12 mg
	Difference to placebo		18.6%	19.2%
	variability statistic			
	P-value		0.0018	0.0006
Notes				
Analysis description	Secondary analysis			
Analysis population and time point description	Full Intent to treat Analysis set: group of subject who were randomised to study drug, received study drug, and had any seizure frequency data during the double-blind phase Analysis for the entire double-blind phase			
Descriptive statistics and estimate variability	Treatment group	Placebo	Perampanel 8 mg	Perampanel 12 mg
	Number of subject	136	129	121
	Percent change in seizure frequency (median)	- 9.72	- 30.52	- 17.57

	variability statistic			
Effect estimate per comparison	Percent change in seizure frequency	Comparison with placebo	Perampanel 8 mg	Perampanel 12 mg
		Median difference to placebo	- 19.10	- 13.69
		95 % CI	- 29.169, - 8.447	- 25.198, - 2.257
		P-value	0.0008	0.0105
Notes				

Table 4. Summary of Efficacy for trial 306

Title: A double-blind, placebo-controlled, dose-escalation, parallel-group study to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures					
Study identifier	E2007-G000-306				
Design	Double-blind, randomized, placebo-controlled, no active comparator group. 3 phases: pre-randomisation (6 weeks), double-blind (6-week titration phase followed by 13-week maintenance period), and follow-up phase (4 weeks)				
	Duration of main phase:	13-week maintenance period			
	Duration of Run-in phase:	not applicable			
	Duration of Extension phase:	not applicable			
Hypothesis	Superiority compared to placebo				
Treatments groups	placebo	Comparator, 19 weeks, 184 subjects			
	Perampanel 2 mg	Treatment, 19 weeks, 180 subjects			
	Perampanel 4 mg	Treatment, 19 weeks, 172 subjects			
	Perampanel 8 mg	Treatment, 19 weeks, 169 subjects			
Endpoints and definitions	Primary endpoint	50% Responder rate	50% or greater reduction in seizure frequency during treatment relative to baseline. Responder rate was analysed for the maintenance period.		
	Secondary endpoint	Percent change in seizure frequency per 28 days	Per 28 days during treatment relative to baseline. The percent change in seizure frequency was analysed over the maintenance period and the entire double-blind phase (titration + maintenance period).		
	Secondary other specify endpoint				
Database lock	21 Jul 2010				
Results and Analysis					
Analysis description	Primary Analysis				
Analysis population and time point description	Full Intent to treat Analysis set: group of subject who were randomised to study drug, received study drug, and had any seizure frequency data during the double-blind phase Analysis at the end of the 13- week maintenance period				
Descriptive statistics and estimate variability	Treatment group	placebo	Perampanel 2 mg	Perampanel 4 mg	Perampanel 8 mg
	Number of subject	184	180	172	169
	50 % responder rate	17.9 %	20.6 %	28.5 %	34.9 %
	variability statistic				
Effect estimate per comparison	Comparison with placebo		Perampanel 2 mg	Perampanel 4 mg	Perampanel 8 mg
	Difference to placebo		2.7%	10.6%	17.0%
	variability statistic				

	P-value	0.4863	0.0132	0.0003	
Notes					
Analysis description	Secondary analysis				
Analysis population and time point description	Full Intent to treat Analysis set: group of subject who were randomised to study drug, received study drug, and had any seizure frequency data during the double-blind phase Analysis for the entire double-blind phase				
Descriptive statistics and estimate variability	Treatment group	placebo	Perampanel 2 mg	Perampanel 4 mg	Perampanel 8 mg
	Number of subject	184	180	172	169
	Percent change in seizure frequency (median) variability statistic	- 10.69	- 13.63	- 23.33	- 30.80
Effect estimate per comparison	Comparison with placebo		Perampanel 2 mg	Perampanel 4 mg	Perampanel 8 mg
	Median difference to placebo		- 4.63	- 13.71	- 20.13
	95 % CI		- 14.091, - 5.227	- 23.306, - 4.500	- 29.656, - 10.425
	P-value		0.4197	0.0026	< 0.001
Notes					

Analysis performed across trials (pooled analyses and meta-analysis)

Demographic data were similar across the 3 Phase III studies.

The doses of 2 mg and 4 mg were included in one study (306), 12 mg in two studies (304 and 305) and 8 mg in the 3 Phase III studies.

No difference was observed between placebo and the 2 mg dose of perampanel in study 306.

The 50% responder rates in study 306 were 17.9% in placebo group and 28.5% in the 4 mg group. The treatment difference relative to placebo rate was statistically significant (10.6%, $p=0.0132$).

The dose of 8 mg was the only dose included in all 3 Phase III studies. In study 304, 305 and 306, 50% responder rates during the maintenance period were respectively 37.6%, 33.3%, and 34.9%, and the differences to placebo rates were respectively, 11.2% ($p=0.0760$), 18.6% ($p=0.0018$), and 17.0% ($p=0.0003$).

The dose of 12 mg was included in two studies (304 and 305). The 50% responder rates during the maintenance period were respectively 36.1%, and 33.9% and differences to placebo rates were respectively 9.7% ($p=0.0914$), and 19.2% ($p=0.006$).

Difference was statistically significant in study 304 for the two dose groups (8 and 12 mg) when patients from Central and South American centres were excluded (respectively 18.6% and 18.1% in North America centres).

No difference on 50% responder rate analysis was observed between the doses 8 mg and 12 mg across studies.

In Study 306, median percent change in seizure frequency per 28 days in Double-blind period was - 23.33% in 4 mg group. Median difference to placebo was statistically significant (-13.71%, $p=0.0026$).

In Studies 304, 305, and 306, median percent changes in seizure frequency in 8 mg group were respectively -26.34%, -30.52% and -30.80%. Median differences to placebo were respectively -13.53 (p=0.0261), -19.10 (p=0.0008) and -20.13 (p<0.001).

In Studies 304, and 305, median percent changes in seizure frequency in 12 mg group were respectively -34.49% and -17.57%. Median differences to placebo were respectively -14.20 (p=0.0184), and -13.69 (p<0.0105).

A numerical advantage was observed for the perampanel 8 mg dose as compared to 12 mg dose.

Pooled data of studies 304 and 305 indicated that responder rates in patients without concomitant carbamazepine, oxcarbazepine or phenytoin drugs (i.e. perampanel non-inducer subgroup) in studies 304 and 305 were 15.0% in placebo group, 50% in 8 mg group and 54.3% in 12 mg group. Differences to placebo rate were respectively 35% and 39.3%. Responder rates in patients with concomitant carbamazepine, oxcarbazepine or phenytoin drugs were 20.6% in placebo group, 30.9% in 8 mg group, and 32.9% in 12 mg group. Differences to placebo rate were respectively 10.3% and 12.3%. Effect is higher when perampanel is not associated with inducer carbamazepine, oxcarbazepine, and phenytoin.

These results were consistent in study 306 with a responder rates in placebo, 4 mg and 8 mg groups respectively of 19.4%, 34.8% and 39.6% in perampanel non-inducer subgroup (with difference to placebo rate of 15.4% and 20.2%) compared to 18.1%, 26.2% and 34.2% in perampanel inducer subgroup (with difference to placebo rate of 8.1% and 15.5%).

Differences with placebo were much higher when perampanel was not concomitantly used with the inducer drugs carbamazepine, oxcarbazepine or phenytoin. In the 4 mg group, the effect is 2 fold higher in non-inducer subgroup than in inducer subgroup. In the 8 mg and 12 mg dose groups, the effect is between 2 and 3 fold higher. This difference is clinically relevant and was more discussed in the D121 response document.

Regarding descriptive efficacy results, the 50% responder rates in the 4 mg, 8 mg and 12 mg groups were respectively 23.0%, 31.5%, and 30.0% when perampanel was associated with inducer AEDs, and were 33.3%, 46.5% and 50.0% when perampanel was not associated with inducer AEDs. These results confirm the high response of the treatment when perampanel is not concomitantly used with carbamazepine, oxcarbazepine, or phenytoin. However, no additional benefit was observed with the 12 mg as compared to the 8 mg dose in patients with inducer AEDs and most of these patients (36%) received the last dose of 8 mg. Perampanel dose does not need systematic increased to 12 mg when associated with inducer AEDs. No specific dose recommendations are needed when perampanel is concomitantly used with inducer AEDs.

There is good statistical evidence of efficacy across the trials, although Study 304 just fails to reach statistical significance. Several analysis were conducted to explore the influence of demographic and baseline characteristics (age and baseline body weight) and concomitant AED therapy on the efficacy results for the Central and South American region but none of the factors examined fully explained the high placebo response for the Central and South American regional subgroup. The data showed that there is a substantial treatment by region relationship and that the drug was less effective in South America. This is mainly driven by the much higher placebo response rate in South America and the high concomitantly use of AEDs inducers in patients in Central and South America and by no means suggest a change in the point estimate for the Fycompa group.

The drug when compared to placebo demonstrated efficacy in North America (where it reached statistical significance), a patient population which is likely to be more similar to the EU than South and Central America. The North America results were also consistent with the other 2 trials. It is therefore

reasonable to conclude that efficacy has been demonstrated and the lack of significance of Study 304 is not a concern.

In general, the results seen using the missing = failure analysis are consistent with the last observation carried forward analysis, with no significance for the 2 mg dose in 306 but highly significant results for 4mg and 8mg doses.

The results are still borderline non-significant for Study 304 and borderline significant for Study 305. This robustness is important given the borderline nature of the results, and there are no concerns regarding uncertainty around the estimated treatment effect.

The Applicant also provided the key secondary results which show a similar picture, but with significance of the 8 and 12 mg doses across all trials. The results of the parametric log-transformed ANCOVA are also all significant, with smaller p-values, as expected.

It is noted that none of the trials actually used the posology requested in the SmPC. However it is noted that:

- titration was used in all studies;
- efficacy has been demonstrated for doses up to 8 mg with good evidence of a dose response effect; however the separation between the 8 and 12 mg is less clear in terms of dose response. Since the 12 mg dose seems to be associated with an increase number of AEs and has not demonstrated any higher efficacy than the 8mg dose, concern was raised on the practical benefit this dose can provide.

• **Justification for the 12 mg dose**

Efficacy results from pivotal studies did not show more benefit of the 12 mg dose as compared to the 8 mg dose in the overall population. The 12 mg dose is associated with more treatment adverse events than the 8 mg dose, with a dose-dependent relationship on undesirable effects, and more serious adverse events than 8 mg (8.2% vs 5.6%).

Benefit of 12 mg dose is observed in patients previously treated with 8 mg dose, who tolerated the 8 mg dose, and whom response to treatment was not completely satisfactory with 8 mg. Benefit of 12 mg dose is observed in open long-term studies. Over 90% of study patients were titrated to the 10- or 12- mg doses, and achieved benefits greater than those provided by the 8 mg dose (with an increase of the 50% responder rate from 38.5% to 48.3%). The dose increase during the open-label long term studies shows that perampanel could be well tolerated in some patients who previously tolerated 8 mg dose.

Of the subjects randomized on the 12mg dose arms of the studies 304 and 305 the percent of patients who received the highest dose of 12 mg was greater when perampanel was concomitantly used with carbamazepine, oxcarbazepine, or phenytoin (18%) than when it was not (11%). This finding leads to the conclusion that perampanel could be a useful option for the patients with co-administered inducers AEDs.

Data pooled from the Phase III studies and OLE study 307 were assessed in order to estimate whether the 12 mg dose can provide higher benefit when compared the 8mg dose. The results of this analysis showed an improved efficacy for the subjects who were randomised to and completed the double-blind maintenance period (studies 304, 305 and 306) on 8 mg and received 12 mg as their last dose in the blinded conversion period (study 307). The 50% responder rates increased from 37.8% to 43.5%.

Seizure frequency decreased from -32.42% to -43.27% from the double-blind maintenance period. The analysis of the pooled safety results, however, confirms the dose-related increased risk of certain AEs such as: gait disturbances, dysarthria, weight increase, fatigue, irritability, somnolence, dizziness, and

euphoric mood. This is confirmed by the results of exploratory PK/PD analysis which showed the increase of the above AEs with increase in perampanel exposure.

The CHMP concluded that the use of the 12 mg dose is beneficial in a sub-group of patients. An usual posology of 4-8 mg perampanel per day is recommended, and 12 mg for patients who tolerate the dose of 8 mg, and when the clinical response is considered insufficient based on individual benefit- risk assessment. Section 4.2 of the SmPC reflects this conclusion.

Clinical studies in special populations

Perampanel didn't show any difference in efficacy to placebo when assessed in patient affected by neuropathic pain, Parkinson's disease and migraine. No significant differences based on gender or age.

- **In adolescent**

143 adolescents with a mean age of 14.8 years (12-17 years) were included in the Phase III studies. 58.7% were male.

The responder rate in placebo and perampanel 2 mg, 4 mg, 8 mg and 12 mg were respectively 22.2%, 4.8%, 23.1%, 40.9%, and 45.0%. Clinically significant difference was observed between placebo group and perampanel 8 mg (18.7%) and perampanel 12 mg (22.8%) groups. Of note, the 50% responder rate in 2 mg group (4.8%) was lower than in placebo group (22.2%) and no difference between placebo and 4 mg group was observed (0.9%).

The median percent change in seizure frequency per 28 days in double-blind phase (titration + maintenance period) was -17.97% in placebo group, + 12.77% in perampanel 2 mg group, -23.91% in 4 mg group, - 34.84% in 8 mg group and -19.91% in 12 mg group. The median difference to placebo was -14.65% in perampanel 4 mg, -23.60% in 8 mg group and -19.91% in 12 mg group. Of note, the percent of seizure in 2 mg group increased from baseline.

These data suggested efficacy of perampanel 8 mg and 12 mg in adolescents and no difference in effect between these two doses.

As recommended (CHMP/EWP/556/98 Rev.2/Corr), one randomised, double-blind, placebo-controlled study of adjunctive therapy with perampanel on cognition, growth, safety, tolerability, and PK in adolescents (12 to <18 years of age) should be performed. This study is ongoing (Study 235). 13 patients were enrolled as of 1 Mar 2011 cut-off date.

- **In elderly \geq 65 years**

A total of 28 elderly (> 64 years old) were included across the 3 phase III studies (28/1480, 1.9%). This small number of subjects didn't allow evaluating differences between treatment groups for this age group.

The incidence and prevalence of epilepsy increase substantially after 65 years of age. Efficacy and safety of AEDs in newly diagnosed elderly patients may be different from those in younger adults. A distinction should be made between elderly patients, who may have suffered from epilepsy for years and those who developed epilepsy recently due to an underlying disease, as responses are different, as stated by the Note for Guidance (CHMP/EWP/556/98 Rev.2/Corr). However, different efficacy is not expected.

- **In pregnant women**

Experimental data on reproductive toxicity are overall reassuring, no effects were observed in rats and rabbits even if animal exposure was limited due to effects on CNS. In addition, since transplacental transfer was demonstrated to be limited, no effects on foetus are expected. Therefore, there is no need to include a recommendation in the SmPC for contraception in women of childbearing potential.

Studies in lactating rats have shown excretion of perampanel and/or its metabolites in milk. There is very limited clinical experience. Because of these elements, the proposed SmPC recommendation "Fycompa is not recommended during pregnancy" is considered as appropriate.

- **Race**

Two studies were conducted in healthy Japanese male volunteers, including an ascending single-dose study (Study 010) and an ascending multiple-dose study (Study 026).

The population PK analysis for data from the controlled Phase III studies included 576 Caucasians, 14 Blacks, 97 non-Chinese Asians, and 62 Chinese subjects.

The efficacy for the Whites group was comparable with the rest of the overall study population.

- **Impaired renal function**

Since renal clearance is a very minor pathway of perampanel elimination, a prospective clinical study examining the effect of renal impairment on perampanel PK has not been conducted.

The concentrations of perampanel metabolites in plasma are very low compared to unchanged drug (Studies 007 and 017). Perampanel metabolites are primarily eliminated by faecal excretion.

The population PK analysis for data from the controlled Phase III study (CPMS-E2007- 2011-003) showed that clearance of perampanel was not significantly affected by baseline creatinine clearance.

The SmPC therefore does not recommend dose adjustment in patients with mild renal impairment. Use of perampanel in patients with moderate or severe renal impairment is not supported by the CHMP. This is acknowledged in the SmPC wording (Section 4.2).

- **Impaired hepatic function**

Because perampanel is eliminated primarily by oxidative metabolism, the effect of hepatic impairment on perampanel PK was evaluated in a prospective study:

Study-015 (PK in adults with hepatic impairments vs. healthy adults)

This open-label, one treatment, parallel, four group study evaluated the effect of hepatic impairment on the PK of perampanel in adults with mild or moderate hepatic impairment (Child-Pugh A or B, respectively) vs. adults with normal hepatic function, (six in each group). The study population included 24 subjects. Each subject received a single 1 mg dose of perampanel after food on Day 1.

PK Results showed that plasma concentrations of unbound perampanel were higher in hepatically impaired subjects compared to matched healthy controls.

For Child-Pugh A subjects, compared with their respective control groups, the unbound concentration at 2 h was 1.26-fold higher, the half-life was 2.4-fold longer, and the unbound AUC (0-inf) was 1.8-fold higher. For Child-Pugh B subjects, compared with their respective control groups, the unbound concentration at 2 h was 1.18-fold higher, the half-life was 2.1-fold longer, and the unbound AUC (0-inf) was 3.3-fold higher.

Perampanel is primarily eliminated by oxidative metabolism followed by glucuronidation and fecal and urinary excretion of its metabolites. It is therefore to be expected that its clearance should be reduced in patients with hepatic dysfunction.

A dose recommendation is included in section 4.2 of the SmPC and caution is advised in the SmPC with regard to use in hepatic impairment.

Supportive studies

Three Open-label Extension Studies have been conducted to assess long term safety and maintenance of efficacy of perampanel (*E2007-G000-307*, *E2007-A001-207* and *E2007-J081-233*).

During the Maintenance Period, subjects continued treatment with the perampanel (or placebo) 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; however, according to the investigators' clinical judgment, subjects experiencing intolerable AEs could have their dose down-titrated.

E2007-G000-307

Subjects who completed the Double-blind Phase could enter the Open label extension (OLE) study (307).

Subjects who did not elect to enrol in the OLE study or who withdrew prematurely during the Double-blind Phase entered the 4-week Follow-up Phase. Study medication was discontinued at the start of this phase (i.e., no downward titration of study drug was required).

Among subjects who received at least 40 weeks of perampanel treatment at a dose of 12 mg, the median percent change in seizure frequency per 28 days from Pre-perampanel Baseline was -44.93% for Weeks 1 to 13, -49.94% for Weeks 14 – 26, and -51.25% for Weeks 27-39.

E2007-A001-207

The magnitude of the median percent change in total seizure frequency for the entire OLE study for subjects who received at least 1 year, 2 years, 3 years, and 4 years of open-label treatment was -45.0%, -53.2%, -52.6%, and -48.4%, respectively, while the 50% responder rates for these subgroups of subjects were 47.2%, 53.0%, 51.9%, and 50.0%, respectively.

Among the subjects who received placebo in the core DB study, improvement was seen following the start of the open-label perampanel treatment.

E2007-J081-233

The median (minimum, maximum) of percent change in total seizure frequency was -44.60 (-100.0, 58.2) % for Maintenance LOCF of Study 231 (21 subjects), -37.71 (-100.0, 15.3) % for LOCF of the OLE study (21 subjects) and -49.40 (-100.0, 5.0) % for Weeks 40-52 (17 subjects).

The responder rate of total seizure frequency was 47.6% (10/21 subjects) for Maintenance LOCF of Study 231, 38.1% (8/21 subjects) for LOCF of the OLE study and 47.1% (8/17 subjects) for Weeks 40-52.

Regarding CGIC for the end of treatment until Week 52, investigators evaluated 9.5% (2/21 subjects) as very much improved, 4.8% (1/21 subject) as much improved, and 52.4% (11/21 subjects) as minimally improved.

Regarding PGIC for the end of treatment until Week 52, 14.3% (3/21 subjects) of subjects evaluated as very much improved, 14.3% (3/21 subjects) as much improved and 42.9% (9/21 subjects) as minimally improved.

- **Conclusion**

The data collected so far from the studies mentioned above showed that among subjects who received prior double-blind treatment with placebo, both the median percent reduction in total seizure frequency and the responder rate increased to a level similar to that for subjects receiving previous double-blind treatment with perampanel by the end of the Conversion Period of the OLE study.

The data presented shows that improvement in seizure frequency seems to be maintained during long-term open-label treatment up to 4 years (Study 207).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The three Phase III studies of perampanel as adjunctive therapy for the treatment of partial-onset seizures, with or without secondarily generalized seizures, were similar in design. Studies 306, 305, and 304 were randomized, double-blind, placebo-controlled, parallel-group, multicenter investigations of the efficacy, safety, and tolerability of fixed doses of perampanel given as adjunctive therapy (one to three concomitant AEDs) in subjects aged 12 years and older (18 years for sites in some countries).

The controlled Phase III studies differed in the fixed doses of perampanel evaluated.

Studies 305 and 304 compared daily perampanel doses of 8 mg and 12 mg once daily to placebo. The doses evaluated in these studies were those expected to show efficacy based upon results of earlier Phase 2 studies.

These trials were multicentre, double-blind, randomised, parallel-group trials, using a placebo control and two doses of Fycompa (8 and 12 mg). Subjects with refractory partial seizures were randomized to one of the three treatment groups in a 1:1:1 ratio.

In Study 306, perampanel doses of 2 mg, 4 mg, and 8 mg once daily were compared to placebo. This study was specifically designed to detect the minimally effective dose of perampanel as adjunctive therapy in the target population and establish the dose response relationship for doses up to 8 mg. As such, the target sample size for this Phase III study (~170/group) was larger than that for the other Phase III studies (~125/group).

Doses of 2, 4 and 8 mg were used in a 1:1:1:1 randomisation.

Each of the Phase III studies consisted of three phases: Pre-randomization Phase, including a Screening visit and a 6-week prospective Baseline Period; Double-blind Phase, consisting of a 6-week Titration Period and a 13-week Maintenance Period; and Follow-up Phase of 4 weeks duration for subjects who withdrew prematurely or did not elect to enter the OLE study.

Subjects who completed the Double-blind Phase could enter the OLE study (307) and received treatment with open-label perampanel.

Subjects who did not elect to enrol in the OLE study or who withdrew prematurely during the Double-blind Phase entered the 4-week Follow-up Phase. Study medication was discontinued at the start of this phase (i.e., no downward titration of study drug was required).

Efficacy data and additional analyses

- **Primary and secondary efficacy endpoints**

The 50% responder rate was considered the Primary efficacy endpoint for EU registration in all 3 studies as recommended by the CHMP guidance (CPMP/EWP/566/98, Rev.2 Corr, 2010).

The results of these essentially similar phase III studies were consistent for the primary efficacy endpoint and showed superior efficacy when compared with placebo for doses of 4 mg to 12 mg.

Consistent statistical significant efficacy results were found between studies 305 and 306 in terms of a 50% or greater reduction in seizure frequency per 28 days during the maintenance period relative to the pre-randomization phase.

Study 304 showed efficacy of 8mg and 12 mg when compared with placebo for the primary endpoint but discrepancies were noted for the responder rate during maintenance period. The p values didn't show any statistically significant difference when compared with placebo. As discussed in more details above, these discrepancies were due to regional differences and the high response to placebo in this population group.

When only data from North American Sites were evaluated for this study, the responder rates during the maintenance period for the 8mg and 12mg perampanel groups were statistically significantly higher than those for the placebo group (P values of 0.0209 and 0.0169, respectively). The magnitude of the perampanel treatment effect seen in Study 304 for the North American sites is consistent with Studies 305 and 306.

Lack of difference in effect size between 8mg and 12mg doses was also consistent in studies 304 and 305.

Percent change in complex partial plus secondarily generalised seizures. All the three studies showed statistically significant difference when compare with placebo.

- **Exploratory efficacy endpoints**

50% reduction in frequency of complex partial plus secondarily generalised seizures.

Statistically significant difference was noted for the 4mg, 8mg and 12 mg doses when compared with placebo in studies 305 and 306. Study 304 showed statistically significant difference for the 12 mg dose when compared with placebo. No difference was noted for the 8mg dose.

Change in frequency and responder rate for secondarily generalised seizures.

A higher response to placebo was noted in study 306 (median percent reduction -35.77%) compared to study 304 (-14.19%) and study 305 (-6.71%). The placebo response in overall partial onset seizures in Study 306 was -10.69%, comparable to that observed in Study 305 (-9.72%) and Study 304 at North American sites (9.52%). The applicant examined racial subgroups, regions, age, and sex and found only a regional interaction (i.e., Central and South America). The much reduced sample size for the subgroup with secondarily generalized seizures (approximately 40% of total study population) could have potentially contributed to the high variability of the data. The response provided was considered acceptable.

Percent of subjects who achieved seizures free status.

Seizures free status was more than double higher in the 4mg, 8 mg and 12 mg group when compared with placebo.

Global assessment (CGIC and PGIC)

Higher improvement was recorded for the 4mg, 8mg and 12 mg doses in study 306; the 8mg and 12mg doses in study 305 and for the 8 mg dose in study 304. An analysis of the Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC) results based on

geographic location was performed in Study 304. For the Central/South American population, both CGIC and PGIC results showed a high placebo response, as seen for the primary endpoint. This is consistent with the primary efficacy analysis on the primary and key secondary endpoints, with the high placebo response rate driving down the effect size.

- **Open-label studies:**

The data gathered from the open-label studies above shows that among subjects who received prior double-blind treatment with placebo, both the median percent reduction in total seizure frequency and the responder rate increased to a level similar to that for subjects receiving previous double-blind treatment with perampanel by the end of the conversion period of the OLE study.

- **Subpopulations:**

Age

Of the 1478 full ITT Analysis set only 1.9% (28) was >65 years of age, this small number of subjects didn't allow evaluating differences between treatment groups for this age group.

Results for the <18 years of age subgroup analysis indicated that for the median percent change in seizure frequency per 28 days for perampanel doses of 4, 8 and 12 mg was generally consistent among the <18 and 18 to <65 years old groups.

143 adolescents were included in Phase III studies with a mean age of 14.8 years (12-17 years). Data appears consistent with those of adults.

Sex

Efficacy results were consistent in males and females.

Race

75.4% of the population was white. 19.6% Asian or Pacific Islander; 2.1% Blacks or African Americans and 3.0% of other races. The principal subgroup analysis of efficacy based on race was done between whites and Asian or Pacific islanders since these were the biggest groups.

The efficacy for the Whites group was comparable with the rest of the overall study population.

For the Asian and Pacific Islanders the primary and secondary endpoints were higher for the 8mg and 12mg groups but not different from placebo in the 2mg and 4mg groups.

Geographic region

There are no data for perampanel doses of 2mg and 4mg in the subgroup population of North America or Central and South America.

For the North American subgroup doses of 8mg and 12 mg were evaluated.

For the Asian-Pacific subgroup, no clinically relevant differences in efficacy responses to perampanel 4mg (or 2mg) and placebo were noted.

Consistent results for the secondary endpoints were noted between North American, European and Asian-Pacific subgroups for the 8mg and 12 mg doses. The responder's rate in the perampanel 8 and 12 mg groups were lower in the European subgroup than in the North American or Asian-Pacific subgroups.

As discussed before, a high response to placebo in the Central/South American groups was recorded (study 304).

Efficacy data in patients with concomitant perampanel inducer AEDs

In post-hoc subgroup analysis with pooled data from studies 304 and 305, results on the 50 % responder rate are different between the patients with concomitant perampanel inducers (carbamazepine, oxcarbazepine, and phenytoin) and patients without concomitant perampanel inducers. Indeed, difference to placebo on the 50% responder rates in perampanel 8 mg and 12 mg groups were higher in patients without concomitant carbamazepine, oxcarbazepine or phenytoin drugs (respectively, 35% and 39.3%) compared to patients with concomitant carbamazepine, oxcarbazepine or phenytoin drugs (10.3% and 12.3%). Results in patients with concomitant carbamazepine, or oxcarbazepine drugs (and without phenytoin) were 16.4% and 17.1%. These results showed that the induction effects of carbamazepine, oxcarbazepine and especially phenytoin on perampanel exposure described in PK analyses have an effect on perampanel response as it could be expected.

At the CHMP's request the applicant presented the percent change from prerandomization to the Doubleblind Phase in responder rate and seizure frequency rate by the last treatment dose for subjects who were receiving perampanel inducers or non-inducers at baseline. A total of 610 patients received perampanel concomitantly with carbamazepine, oxcarbazepine, or phenytoin at baseline in studies 304, 305 and 306. Most patients (36%) received the last dose of 8 mg, 18% received 12 mg and 3% received 10 mg.

A total of 427 patients received perampanel without concomitantly inducer AEDs. Most patients (36%) received the last dose of 8 mg, 20 % received 4 mg, 11 % received 12 mg and 9 % received 6 mg.

These results point out the higher percent of patients who received the last dose of 12 mg dose when perampanel is concomitantly used with inducer AEDs than when it is not (18% versus 11%). The last dose of 12 mg seems to be easily reached or maintained when perampanel is associated with inducer AEDs.

The percent of patients who received the last dose 8 mg dose is the same (36%) with or without inducer AEDs.

Regarding descriptive efficacy results, the 50% responder rates in the 4 mg, 8 mg and 12 mg groups were respectively 23.0%, 31.5%, and 30.0% when perampanel was associated with inducer AEDs, and were 33.3%, 46.5% and 50.0% when perampanel was not associated with inducer AEDs. These results confirm the high response of the treatment when perampanel is not concomitantly used with carbamazepine, oxcarbazepine, or phenytoin. No additional benefit was observed with the 12 mg as compared to the 8 mg dose in patients with inducer AEDs and most of these patients received the last dose of 8 mg. Perampanel dose does not need systematic increase to 12 mg when associated with inducer AEDs. No specific dose recommendations are needed when perampanel is concomitantly used with inducer AEDs.

2.5.4. Conclusions on the clinical efficacy

The development plan has been conducted in line with the recommendations laid down in CHMP/EWP/566/98 Rev.2/Corr "Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders".

The results of the 3 phase III pivotal studies were consistent for the primary efficacy endpoint and showed superior efficacy when compared with placebo for doses of 4 mg to 12 mg.

Although Study 304 just failed to reach significance, the applicant has provided a thorough justification for the results seen, and additionally provided evidence that the drug is effective in the EU population.

The sensitivity analyses and the different analysis populations suggest the results are robust. The secondary endpoints provide a similar picture, and there are no uncertainties around the benefits.

However, no obvious difference in efficacy between the 8mg and 12 mg dose was noted.

The number of adverse events seems to be dose-related with the highest frequency in the 12mg groups and mainly relate to the central nervous system.

The recommended dose range should be 4-8 mg and the dose of 12 mg should be recommended only for patients who tolerate the dose of 8 mg, and when the clinical response is considered insufficient based on individual benefit- risk assessment.

No specific dose recommendations are needed when perampanel is concomitantly used with inducer AEDs.

The data presented shows that improvement in seizure frequency is maintained during long-term open-label treatment up to 4 years.

2.6. Clinical safety

Patient exposure

As of the cut-off date for this submission (01 Dec 2010), 1639 subjects with epilepsy had received perampanel in double-blind Phase II and III studies and open-label extensions (OLEs).

A total of 1147 subjects had received perampanel for > 6 months, 703 subjects had received perampanel for > 1 year, and 95 subjects had received perampanel for > 2 years. For the 132 subjects who were < 18 years old, perampanel had been taken for > 6 months, > 1 year, and > 2 years by 99, 66, and 5 subjects, respectively.

In both the clinical studies in subjects with epilepsy and the clinical studies in other populations, safety was evaluated using the following parameters: AEs, clinical laboratory tests, vital signs and body weight.

All of the epilepsy studies and most of the studies in other populations also included ECGs as a safety measurement. The Phase III epilepsy studies also evaluated photosensitivity and potential withdrawal symptoms.

- **Phase II studies**

In the Phase 2 studies, no deaths or serious adverse events of concern were reported.

Doses up to 4mg didn't show any statistically significant difference in AEs when compared with placebo. The occurrence of all treatment-emergent AEs was similar in the perampanel and placebo groups, with the majority of the events mild or moderate in severity ([Study 206](#)).

When in [Study 208](#) the dose increased up to 12mg, a higher percentage of subjects in the perampanel group had TEAEs that were possibly related to treatment (55.3% vs 40.0% with placebo), and a higher percentage of subjects in the perampanel group had TEAEs that were probably related to treatment (47.4% vs 0% with placebo). The percentages of subjects having severe TEAEs were 13.2% (5/38) in the perampanel group and 0% (0/10) in the placebo group.

The most common AEs were central nervous system disorders (perampanel group: 71.1% vs. placebo group: 20.0%). These include dizziness, somnolence, headache and fatigue.

The percentage of reported infections and infestations was higher in the perampanel group (26.3%) than the placebo one (10.0%). Rhinitis was reported only in the perampanel group (10.5%).

Eye disorders (dyplopia, blurred vision) have been reported only in the perampanel groups (15.8%). These AEs are presented as common adverse reactions in section 4.8 of the SPC.

The perampanel group had higher incidence of probably related AEs (47.4% vs 0%).

The percentages of subjects having severe AEs were 13.2% (5/38) in the perampanel group and 0% (0/10) in the placebo group. However, the sample size is quite small (placebo: 10 vs. Perampanel: 38) to draw a final conclusion.

In Study 231 frequently observed (incidence $\geq 10\%$) adverse events were dizziness at 53.3% (16/30 subjects), somnolence at 46.7% (14/30 subjects), nasopharyngitis at 16.7% (5/30 subjects), contusion at 13.3% (4/30 subjects), and headache, upper respiratory tract inflammation, and irritability at 10.0% (3/30 subjects each).

Frequently observed (incidence $\geq 10\%$) adverse drug reactions were dizziness at 53.3% (16/30 subjects), somnolence at 46.7% (14/30 subjects), and headache and irritability at 10.0% (3/30 subjects each).

None of death or other serious adverse events was observed. Four adverse events that resulted in discontinuation of therapy were observed in 2 patients, consisting of somnolence and asthenia in 1 subject and epileptic aura and face oedema in 1 subject.

Conclusion

The type of drug related adverse events was consistent throughout the studies and involved mainly the central nervous system (dizziness, somnolence, headache, irritability and fatigue).

Doses up to 4mg didn't show any statistical significant difference in AEs when compared with placebo.

The appearance of AEs seems to be dose-related.

• **Phase III studies**

In double blind phase 3 studies in epilepsy the mean duration of exposure was limited to 16 weeks for the higher dose group and 17 weeks for other dose groups. Number of patients exposed more than 20 weeks was very limited.

The mean age of the patients included in double blind phase III studies in patients with partial onset seizures was 34.9 years. 143 adolescent patients were included in these studies. Of them 98 received perampanel and 45 were in the placebo arm.

Safety data on use of perampanel in elderly (over 65 years old) were very limited in the clinical program in Epilepsy (only 31 patients >65 included). This is clearly stated in the SmPC (Section 4.2).

1639 patients with epilepsy received perampanel during double blind phase III studies and open label extension studies, for a total exposure of 12,280.1 subjects-months. Doses used in these studies were 2 mg, 4 mg, 8 mg and 12 mg.

No post-randomisation deaths of SUDEP events were reported during the Phase III studies.

In Study 304 TEAEs occurred more frequently in the perampanel 12 mg group (91.8%), than the 8mg group (88.0%) and placebo (82.6%) and mainly related to the central nervous system (dizziness, somnolence, irritability, headache, fall, and ataxia).

The rate of SAEs was also slightly higher for the 12 mg (6.7%) and 8mg (6.0%) when compared with placebo (5%), although there was no particular difference between these dose groups with respect to the frequency of adverse events. However, discontinuation rate due to TEAEs was notably higher in the 12mg group (19.4%) when compared with the 8mg (6.8%) and placebo (6.6%).

A dose-related increase was noted in 7 of the most frequent TEAEs that occurred with perampanel (dizziness, ataxia, aggression, anxiety, vertigo, irritability, and fall) which resulted in discontinuation.

A higher rate of central nervous system disorder was also responsible for dose reduction or interruption in 31.1 % of subjects in the 12mg dose, 21.1% of subjects in the 8mg dose and 5.0% of subject in the placebo group.

Increases (> 7%) in weight occurred in 8.3% of the subjects in the placebo group, 21.2% of those in the 8 mg group, and 17.3% of those in the 12 mg group.

The above findings demonstrate a dose-related increase in number of AEs in and mainly related to the central nervous system.

In Study 305 perampanel groups had an increased number of AEs when compared with placebo and the group of subjects receiving the 12 mg dose had a higher incidence of TEAEs compared to the group receiving 8mg dose, in particular for the ones concerning the central nervous system. Weight increase was also noted in the perampanel groups and in particular with the 12 mg dose.

The risk of weight increase is presented as a common adverse reaction in section 4.8 of the SPC.

In Study 306 the most frequently ($\geq 10\%$) reported TEAEs were dizziness and somnolence in the 2mg group, dizziness and headache in the 4mg group and dizziness, somnolence and headache in the 8 mg group. No TEAE was reported by $\geq 10\%$ of the subjects in the placebo group.

Dizziness, fatigue, somnolence and gait disturbance occurred in the perampanel groups in a rate that was more than twice the rate in the placebo group.

Discontinuation due to TEAEs occurred more frequently in the perampanel groups and appeared to be dose-related. The main reasons for discontinuation were central nervous system side effects (convulsion, fatigue, and vertigo).

Conclusion

The safety results from the Phase III studies suggest that there is a dose-related increase in adverse events. These events are consistent throughout the studies and mainly relate to the central nervous system (dizziness, ataxia, aggression, anxiety, vertigo, irritability, and fall).

No double-blind study has assessed the doses of 6 mg and 10 mg, whereas the recommended dose according to the SmPC is between 4 and 12 mg/day.

• **Open-label Extension Studies**

The list of adverse events gathered up to the cut-off date of the on-going open-label studies confirms the dose-related increase in certain type of AEs already noticed in the Phase II and III studies (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, and increased appetite).

No obvious changes in vital sign and ECGs were noted. The most common laboratory abnormality was an increase in hepatobiliary parameters (AST, ALT, alkaline phosphatase, GGT and total bilirubin).

In Study 207 there seems to be an increase number of cardiovascular AEs (10.1%) with doses between 8 and 12 mg. which includes atrio-ventricular block first degree (2.9%), palpitations (2.9%), atrial fibrillation (1.4%), cardiac arrest (1.4%) and conduction disorders (1.4%).

The higher number of cardiovascular side effects in study 207 could be a consequence of longer exposure time. Since the incidence of these types of adverse events is not consistent with the safety reports of the other studies, this explanation can be considered acceptable. In addition no new concern arises from the safety review of fatal cases and related narrative provided by the applicant at the CHMP's request.

Adverse events

Treatment emergent adverse events (TEAEs) occurred in 77% of the patients under perampanel during double blind phase III studies in Epilepsy versus 66.5 % for the patients included in the placebo group. They were more frequent in the 12 mg/day arm (89%) compared to other perampanel arms (81.2 % of the 8mg/day arm, 64.5% for the 4 mg/day arm and 61.7% for the 2 mg/day arm). In the pool of all treated subjects with partial-onset seizures, 87.3 % of the patients under perampanel experienced TEAEs.

• Neurological disorders

The most common TEAEs reported during double blind phase III studies in epilepsy, but also in the second pool (including all treated patients with partial onset seizures) were:

- dizziness (reported incidences in the pool of double blind phase 3 studies: 9 % for the placebo group versus 28 % of the patients under perampanel but this rate increases to 42.7% for patients randomized to the 12 mg/day arm)
- somnolence (reported incidences in the pool of double blind phase 3 studies: 7.2% for the placebo group versus 14.5 % for the perampanel group)

Even if somnolence seems more frequent during the first weeks of treatment, somnolence and dizziness will probably preclude the treatment compliance. In addition, somnolence (but also vertigo and blurred vision that have been commonly reported with perampanel during double blind studies) may also affect the patient ability to drive.

• Psychiatric disorders

15.3 % of the patients exposed to perampanel during the double blind phase III studies in epilepsy experienced psychiatric disorders, with the following most frequently reported TEAEs: insomnia, anxiety and aggression.

Eight cases of psychotic disorders and 2 cases of acute psychosis have been reported in perampanel treated patients (among all subjects with partial onset seizures) versus respectively 1 and 0 for patients included in the placebo arm. In addition, 3 cases of paranoia (versus none for the placebo arm), 4 cases of delirium (versus 1 for the placebo group) have also been reported. As patients suffering from "psychotic disorders" were excluded from participating to double blind studies in epilepsy (studies 304, 305 and 306), the CHMP has found appropriate to include in the SmPC a warning related to the use of perampanel in patients with history of psychotic disorders.

• Drug abuse, drug dependence and withdrawal

To address the issues of drug abuse and dependency, two clinical studies were conducted in recreational poly-drug users. The exploratory study (Study 023) provided a basis for selection of doses for the definitive abuse liability study (Study 024) which examined the effects of doses up to 36 mg.

Because sedative effects have been observed in clinical trials with perampanel, alprazolam was selected as the primary comparator. Because perampanel inhibits glutamatergic neurotransmission, ketamine was selected as the second positive control. The findings suggest that there is an elevation in several measures of Drug Liking relative to placebo, indicating that perampanel does have some level of abuse potential. However, this abuse potential is lower than one of ketamine. Specifically, perampanel produced elevations in scores indicative of positive subjective effects that were lower than those produced by ketamine, had a slower onset of effect, and produced negative effects that were persistent. Perampanel did produce positive effects that were comparable to alprazolam, both in magnitude of effect, onset of action, and duration of effect. Perampanel produced negative effects that were higher than alprazolam, and which lasted longer. Further, on the drug identification questionnaire, perampanel was most often identified as a benzodiazepine. This would suggest that the abuse potential of perampanel is no greater than benzodiazepines, and probably less based on the profile of negative effects.

Furthermore, adverse effects related to abuse reported in clinical trials are similar to those observed for benzodiazepines (somnolence, dizziness and euphoric mood). Two cases of dependence were reported and symptoms of withdrawal were described.

Perampanel has an abuse and dependence potential which seems similar to alprazolam. Nevertheless, patients with epilepsy are not expected to be at particularly high risk for recreational abuse of the drug and this is expected to limit the availability of perampanel to inappropriate populations of diverters and abusers.

Drug abuse is clearly identified in the risk management plan as an "important potential risk". Routine pharmacovigilance seems to be sufficient to monitor this effect. In addition a warning has been included in the SmPC section 4.4 as a routine risk minimisation measure.

- **Falls**

14.2% of the patients exposed to perampanel during the double blind studies in epilepsy experienced injury, poisoning and procedural complications. Incidences of TEAEs in this SOC were higher in the 12 mg/day arm compared to other perampanel arms and placebo. In this SOC the most reported TEAEs was fall. A possible link between reported cases of falls and the high incidence of somnolence and dizziness in patients included in perampanel arms during studies in epilepsy cannot be ruled out. No clear relationship between perampanel dose and occurrence of fall has been established.

- **Other TEAEs of interest: weight increase, rash, hypersensitivity**

Cases of weight increase have been reported with perampanel. Those cases do not seem to be correlated with cases of increased appetite, also reported in patients exposed to perampanel.

Additional information has also been requested for the following TEAEs: rash, and hypersensitivity.

Based on the available data, there are a numbers of adverse events that seems to be drug-related, which are: 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, and increased appetite.

Safety data on the 10mg dose was provided for the Phase II study 231 in Japanese volunteers and found to be better tolerated than the 12 mg dose.

Based on these results, the Tolerability and Safety Evaluation Committee proposed that the recommended dose for use in future Japanese clinical studies is 8 mg and the maximum dose is 10 mg, at which 50% subjects were tolerable. The Tolerability and Safety Evaluation Committee proposed that a dose of 12 mg was allowable for subjects on concomitant inducers.

Serious adverse event/deaths/other significant events

There were 5 deaths in the epilepsy studies of which 4 were considered not related to the study drug. The death of subject 15206004 in study 307 was classified by the sponsor as a SUDEP.

Only two deaths were considered possibly related to the study drug (subject 112-002 in study 204 and subject 0407-0015 in study 205). Both studies were conducted in Parkinson Disease patients. In both cases the cause of death had a cardiovascular origin.

Cardiovascular events (cardiopulmonary failure, cardiac failure, and circulatory collapse) were assessed further and from the data provided in response to CHMP's request no increase in cardiovascular events associated with the use of perampanel has been identified.

In addition, the open-label study 207 showed an increased number of cardiovascular AEs (10.1%) with doses between 8 and 12 mg which include atrioventricular block first degree (2.9%), palpitations (2.9%), atrial fibrillation (1.4%), cardiac arrest (1.4%) and conduction disorders (1.4%).

Safety data collected from Phase III studies have demonstrated that TEAEs occurred more frequently in the perampanel 12 mg group (89.0%), than the 8mg group (81.2%) and placebo (66.5%) and are mainly related to the central nervous system (dizziness, somnolence, irritability, headache, fall, and ataxia).

The rate of SAEs was also slightly higher for the 12 mg (8.2%) and 8mg (5.6%) when compared with placebo (5.0%).

Discontinuation rate due to TEAEs was notably higher in the 12mg group (19.2%) when compared with the 8mg (7.7%) and placebo (4.5%).

A dose-related increase was noted in 7 of the most frequent TEAEs that occurred with perampanel (dizziness, ataxia, aggression, anxiety, vertigo, irritability, and fall) which resulted in discontinuation of treatment.

Laboratory findings

No evidence of an adverse effect of perampanel either on the hepatobiliary function or on the renal function emerge from the data provided.

At CHMP's request additional information was provided by the applicant for cases of anemia, leucopenia, neutropenia, thrombocytopenia, and hyponatremia. The Committee has found no reasons for concern in regard to the additional data provided.

Safety in special populations

No notable differences based on age, race, sex or hepatic insufficiency were noted. In the PK studies, there did not appear to be any differences with regard to extrinsic factors. It is therefore unlikely that there should be any PD or safety differences noted between treatment groups based on intrinsic or extrinsic factors.

- **Elderly patients**

A very low number of elderly was included in epilepsy studies. However, in a population pharmacokinetic analysis of patients with partial-onset seizures ranging in age from 12 to 74 years no significant effect of age on perampanel clearance was found. Analysis of safety information in 905 perampanel-treated elderly subjects (in double-blind studies conducted in Parkinson's disease and

neuropathic pain indications) revealed no age-related differences in adverse events. In combination with the lack of age-related difference in perampanel exposure, the results indicate that dose-adjustment in the elderly is not required.

- **Adolescent patients**

143 adolescent patients were included in double blind phase III studies in patients with partial onset seizures. Incidence rates of fatigue and irritability were lower in adolescents than adults who received perampanel. Across treatment groups, the percentages of subjects with TEAEs in all subgroups were generally similar with placebo, 2 mg/d, and 4 mg/d and larger with higher doses of perampanel. Aggression was the most frequently reported psychiatric disorders in adolescent patients and with a higher incidence compared to adult patients (8.2% in the total perampanel group and 15.0% in the 12 mg/day group versus 1.2% in the total perampanel group and 2.2 % in the 12 mg/day group in adult patients).

Nevertheless aggression is a frequent listed AE in section 4.8 of the SmPC and a specific warning is added in SmPC section 4.4.

Regarding the degree of severity, it is noteworthy that results provided in the safety review carried out by the applicant at the CHMP's request showed that around 16% of all cases of aggressiveness were considered serious (5 cases on the 30 reported cases among the double-blind, placebo-controlled studies and 13 cases on the 86 cases in all treated epilepsy population). Thus it is mentioned in the SmPC section 4.4 that, besides the majority of reported cases of aggressiveness were mild to moderate, severe cases were reported which lead to discontinuation of treatment.

Most of reported events recovered either spontaneously or with dose adjustment. Thus it is recommended for prescribers to respect the dose escalation (see SmPC section 4.2) and to consider the dose reduction in case of signs of aggressiveness.

Safety related to drug-drug interactions and other interactions

No clinically significant differences were observed when perampanel was administered with levodopa or midazolam.

The combined effects of perampanel on ethinylestradiol and levonorgestrel suggest that 12 mg QD of perampanel induced metabolism of levonorgestrel, but the induction did not appear to be CYP3A4-dependent.

From the Phase III PK population PK analysis, the following findings were identified:

There was no significant effect of perampanel on the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, or zonisamide.

Perampanel had a statistically significantly effect on the clearance of carbamazepine, clobazam, lamotrigine, and valproic acid, but the magnitude of these effects was < 10% at the highest perampanel dose evaluated (12 mg QD).

The analysis of oxcarbazepine concentrations showed a 26% decrease in clearance in the presence of perampanel.

Treatment with the CYP3A4 inducer carbamazepine (300 mg BID) increased the clearance of perampanel 3-fold and decreased C_{max} and AUC (0-inf) values by 26% and 67%, respectively (Study 006).

In agreement with this finding, the Phase III population PK analysis showed that oxcarbazepine and phenytoin as well as carbamazepine increase perampanel clearance.

Phenobarbital, at the doses used for subjects in this pooled analysis, had no clinically important effects on perampanel clearance.

The CYP3A4 inhibitor ketoconazole increased the AUC (0-inf) of perampanel by 20%.

Population PK Findings. The following coadministered drugs (number of subjects) were evaluated: carbamazepine (n=379), clobazam (n=114), clonazepam (n=81), lamotrigine (n=356), levetiracetam (n=330), phenytoin (n=90), phenobarbital (n=54), oxcarbazepine (n=200), topiramate (n=226), valproic acid (n=349), and zonisamide (n=93). Three known CYP3A4-inducer AEDs increased perampanel CL/F. Carbamazepine treatment increased perampanel CL/F by 167%. Oxcarbazepine treatment increased perampanel CL/F by 84.1%. Phenytoin treatment, at a median phenytoin concentration of 16204 ng/mL, increased perampanel CL/F by 94.2%. Coadministration of perampanel with topiramate also slightly increased perampanel CL/F by 22.8

CYP3A4 inducers (carbamazepine, oxcarbazepine and phenytoin) can significantly increase the clearance of perampanel, resulting in lower exposure of perampanel.

Perampanel showed a statistically significant effect on the clearance of carbamazepine, clobazam, lamotrigine and valproic acid. This was tested at the highest dose of perampanel (12mg) and was <10%.

- **Immunological events**

No specific concern seems to emerge from the few TEAEs reported in the SOC immune system disorders. However, the applicant has been requested to provide additional data on hypersensitivity reaction since 2 cases of hypersensitivity have been reported in patients exposed to perampanel (versus 1 patient included in the placebo arm) during double blind studies in epilepsy, and 3 cases have been reported with perampanel in the second pool of studies (among all treated patients with partial onset seizures). The assessment of the additional data did not raise any reason for concern.

Discontinuation due to adverse events

- **Epilepsy subjects**

The most common cause for discontinuation was dizziness which appeared to be more frequent in the 8mg and 12 mg groups compared with placebo and the lower doses. Convulsion led to discontinuation in similar percentages of subjects in all treatment groups.

Other reasons for discontinuation were psychiatric disorders (aggression and anger), nervous system disorders (dizziness, convulsions, somnolence, ataxia and dysarthria), fatigue, irritability, blurred vision and vertigo. All except fatigue showed a dose-related trend.

- **All treated subjects with partial onset seizures**

The most common adverse event that led to discontinuation was dizziness. The incidence of TEAE leading to discontinuation was higher in the perampanel groups than the placebo.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The safety evaluation plan is based on data from the three completed double-blind, placebo controlled, randomised Phase III studies in subjects 12 years or older (304, 305, 306); five Phase II studies (203, 231, 206, 208, 235) and three on going, open-label extension studies (307, 207, 233) all carried out in epilepsy patients.

The total exposure to perampanel in the epilepsy studies was 19,280.1 subject-months. A total of 1147 subjects had received perampanel for more than 6 months, 703 subjects had received perampanel for more than 1 year, and 95 subjects had received perampanel for more than 2 years. For the 132 subjects who were younger than 18 years old, the total exposure to perampanel as of the cut-off date was 1589.0 subject-months, and perampanel had been taken for more than 6 months, more than 1 year, and 2 years by 99, 66, and 5 subjects, respectively.

In total 4 dosages were evaluated: 2, 4, 8 and 12 mg.

No serious toxicity has been identified. Perampanel did not cause any clinically significant changes in laboratory values, blood pressure, heart rate, ECGs, or photosensitivity.

On the whole, 77% of the patients exposed to perampanel during double blind phase III studies in epilepsy experienced TEAEs (versus 65 % for the placebo arm). This incidence increases to 89 % in the 12 mg/day arm.

Based on the available data, there are a number of adverse events that are likely to be drug-related, which are: 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, and increased appetite.

A dose-related increase was noted in 7 of the most frequent AEs that occurred with perampanel (dizziness, ataxia, aggression, anxiety, vertigo, irritability, and fall) which resulted in discontinuation.

A high incidence of TEAEs belonging to the SOC psychiatric disorders has been noticed, mostly insomnia and anxiety. Psychotic disorders have also been reported.

10% of the patients randomized to the perampanel 12 mg/day dose experienced fall during double blind studies in epilepsy versus 3.4 % for the placebo group. A possible link between reported cases of falls and the high incidence of somnolence and dizziness in patients included in perampanel arms during studies in epilepsy cannot be ruled out. A warning in the SmPC to alert prescribers and patients or care givers of this risk of falls has been added in the SmPC.

There were five deaths in the epilepsy studies of which 4 were considered not related to the study drug. The death of subject 15206004 in study 307 was classified by the sponsor as a SUDEP.

In addition, the open-label study 207 showed an increased number of cardiovascular AEs (10.1%) with doses between 8 and 12 mg. which include atrioventricular block first degree (2.9%), palpitations (2.9%), atrial fibrillation (1.4%), cardiac arrest (1.4%) and conduction disorders (1.4%).

The higher number of cardiovascular side effects in study 207 could be a consequence of longer exposure time. Since the incidence of these types of adverse events is not consistent with the safety reports of the other studies, this explanation can be considered acceptable. In addition no new concern arises from the safety review of fatal cases and related narrative provided by the applicant at CHMP's request.

The rate of SAEs in the pivotal trails was also slightly higher for the 12 mg (8.2%) and 8mg (5.6%) when compared with placebo (5.0 %).

Discontinuation rate due to TEAEs in Phase III trials was notably higher in the 12mg group (19.2%) when compared with the 8mg (7.7%) and placebo (4.5%).

Perampanel shows a risk for abuse potential which is considered to be low.

Perampanel has an abuse and dependence potential which is considered to be low and seems similar to alprazolam. Patients with epilepsy are not expected to be at particularly high risk for recreational abuse of the drug, and this is expected to limit the availability of perampanel to inappropriate populations of diverters and abusers.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

2.6.2. Conclusions on the clinical safety

The safety evaluation plan is based on data from the three completed double-blind, placebo controlled, randomised Phase 3 studies in subjects 12 years or older (304, 305, 306); five Phase 2 studies (203, 231, 206, 208, 235) and three on going, open-label extension studies (307, 207, 233).

From the above data, no serious toxicity has been identified. Perampanel does not seem to cause any clinically significant changes in laboratory values, blood pressure, heart rate, ECGs, or photosensitivity.

Given that perampanel is a first in class medicine with a limited safety database and a long term use the CHMP considered the conduct of a post authorisation safety study as a source of additional safety data on identified safety risks and missing safety information appropriate. Such study will be undertaken by the applicant as part of the pharmacovigilance activities.

Despite a slightly higher incidence of AEs in patients treated with the 12mg dose the CHMP has concluded that the 12 mg dose of perampanel could be a useful option for those patients refractory to the standard dose range. An appropriate dose titration based on response and side effects is necessary and this is detailed in section 4.2 of the SPC.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan

Table 5. Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important Identified Risks		
Dizziness	<ul style="list-style-type: none"> Routine pharmacovigilance <u>Post-marketing observational safety study:</u> "Post Marketing Observational 	<ul style="list-style-type: none"> Warning in Section 4.4 and information in Section 4.7, Perampanel may cause dizziness and somnolence and therefore may influence the ability to drive or use machines (see

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
	<p>Safety Study to Evaluate the Long-Term Safety and Tolerability of Fycompa (Perampanel) as Add-on Therapy in Epilepsy Patients”</p>	<p>Section 4.7)</p> <ul style="list-style-type: none"> Additional information in Section 4.7 that perampanel may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. Patients are advised not to drive a vehicle, operate complex machinery or engage in other potentially hazardous activities until it is known whether perampanel affects their ability to perform these tasks (see Section 4.4 and Section 4.5). Information in Section 4.8, Undesirable Effects of the SmPC that all controlled and uncontrolled trials in patients with partial-onset seizures, 1,639 subjects have received perampanel of whom 1,174 have been treated for 6 months and 703 for longer than 12 months. <p>Adverse reactions leading to discontinuation: In controlled Phase 3 clinical trials, the rate of discontinuation as a result of an adverse reaction was 1.7%, 4.2% and 13.7% in patients randomised to receive perampanel at the recommended doses of 4 mg, 8 mg and 12 mg/day, respectively, and 1.4% in patients randomised to receive placebo. The adverse reactions most commonly ($\geq 1\%$ in the total perampanel group and greater than placebo) leading to discontinuation were dizziness and somnolence.</p> <p>In clinical trials, dizziness was reported as a very common adverse reaction.</p> <ul style="list-style-type: none"> Communicated in the PIL.
Somnolence	<ul style="list-style-type: none"> Routine pharmacovigilance <u>Post-marketing observational safety study</u> 	<p>Warning in Section 4.4 and information in Section 4.7, Effects on Ability to Drive and Use Machines, of the SmPC that perampanel may cause dizziness and somnolence and therefore may influence the ability to drive or use machines (see Section 4.7)</p> <ul style="list-style-type: none"> Additional information in Section 4.7 that perampanel may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. Patients are advised not to drive a vehicle, operate complex machinery or engage in other potentially hazardous activities until it

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		<p>is known whether perampanel affects their ability to perform these tasks (see Section 4.4 and Section 4.5).</p> <ul style="list-style-type: none"> Information in Section 4.8, Undesirable Effects, of the SmPC that all controlled and uncontrolled trials in patients with partial-onset seizures, 1,639 subjects have received perampanel of whom 1,174 have been treated for 6 months and 703 for longer than 12 months. <p>Adverse reactions leading to discontinuation: In controlled Phase 3 clinical trials, the rate of discontinuation as a result of an adverse reaction was 1.7%, 4.2% and 13.7% in patients randomised to receive perampanel at the recommended doses of 4 mg, 8 mg and 12 mg/day, respectively, and 1.4% in patients randomised to receive placebo. The adverse reactions most commonly ($\geq 1\%$ in the total perampanel group and greater than placebo) leading to discontinuation were dizziness and somnolence.</p> <ul style="list-style-type: none"> Communicated in the PIL.
Aggression	<ul style="list-style-type: none"> Routine pharmacovigilance <u>Post-marketing observational safety study</u> 	<ul style="list-style-type: none"> Warning in Section 4.4 that cases of aggression have been reported and are dose related since they were more frequently reported with higher dose. Most of these events were either mild or moderate in severity and recovered either spontaneously or with dose adjustment. However, in some cases reports of aggression were severe which led to discontinuation of treatment. Therefore the dose escalation should be followed (see Section 4.2) and a dose reduction should be considered in case of persistence of aggressive symptoms <p>Information in Section 4.8, Undesirable effects, of the SmPC that in clinical trials aggression was reported as a common adverse reaction.</p> <ul style="list-style-type: none"> Communicated in the PIL.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Balance disorder, ataxia, and falls (particularly in the elderly)	<ul style="list-style-type: none"> • Routine pharmacovigilance • <u>Post-marketing observational safety study</u> 	<ul style="list-style-type: none"> • Warning in Section 4.4 of the SmPC that there appears to be an increased risk of falls; the underlying reason is. • Information in Section 4.8, Undesirable Effects, of the SmPC that balance disorder, ataxia, and fall were reported as common adverse reactions. • Communicated in the PIL.
Interaction with levonorgestrel-containing contraceptives, and unintended pregnancy exposures	<ul style="list-style-type: none"> • Routine pharmacovigilance • <u>Post-marketing observational safety study</u> 	<ul style="list-style-type: none"> • Warning in Section 4.4 of the SmPC that perampanel at doses of 12 mg/day perampanel may decrease the effectiveness of progestative-containing hormonal contraceptive; in this circumstance additional non-hormonal forms of contraception are recommended. • Information in Section 4.5, Interaction with other medicinal products and other forms of interaction, of the SmPC that In healthy women receiving 12 mg (but not 4 or 8 mg/day) for 21 days concomitantly with a combined oral contraceptive, perampanel was shown to decrease the levonorgestrel exposure (mean C_{max} and AUC values were each decreased by 40%). Ethinylestradiol AUC was not affected by perampanel 12 mg whereas C_{max} was decreased by 18%. Therefore, the possibility of decreased efficacy of progestative-containing oral contraceptives should be considered for women needing perampanel 12 mg/day and an additional reliable method (intra-uterine device [IUD], condom) is to be used (see Section 4.4). • Communicated in the PIL.
Weight gain	<ul style="list-style-type: none"> • Routine pharmacovigilance • <u>Post-marketing observational safety study</u> 	<p>This is addressed in the SmPC:</p> <p>Section 4.8, Undesirable effects: In clinical trials, weight increased was reported as a common adverse reaction.</p> <p>This is communicated in the PIL</p>
Blurred Vision	<ul style="list-style-type: none"> • Routine pharmacovigilance • <u>Post-marketing observational safety study</u> 	<p>This is addressed in the SmPC:</p> <p>Section 4.8, Undesirable effects: In clinical trials, vision blurred was reported as a common adverse reaction.</p> <p>This is communicated in the PIL</p>

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important Potential Risks		
Suicidality	<ul style="list-style-type: none"> • Routine pharmacovigilance • Implementation of standard Eisai suicidality assessments as per the FDA (US) guidance for all perampanel clinical studies. • <u>Post-marketing observational safety study</u> 	<ul style="list-style-type: none"> • Warnings in Section 4.4 of the SmPC that suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for perampanel. Therefore patients should be monitored for signs of suicidal ideation and behaviors and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge. • Communicated in the PIL.
Drug abuse, misuse, dependency and withdrawal	<ul style="list-style-type: none"> • Routine pharmacovigilance • <u>Post-marketing observational safety study</u> 	<p>Warnings in Section 4.4 of the SmPC that caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of perampanel abuse.</p> <p>This is communicated in the PIL.</p>
Off-label usage	<ul style="list-style-type: none"> • Routine pharmacovigilance • <u>Post-marketing observational safety study</u> 	<p>The SmPC and PIL provide clear information and guidance on the approved indication for the targeted population.</p>
Skin photosensitivity	<ul style="list-style-type: none"> • Routine pharmacovigilance • <u>Post-marketing observational safety study</u> 	<p>Current experience has not identified any issues to be noted in the SmPC or PIL.</p>
Important Missing Information		
Use in patients <12 years of age	<ul style="list-style-type: none"> • Routine pharmacovigilance • <u>Pediatric Study E2007-G000-232</u>: "Open-label Study to Evaluate PK, Safety and Tolerability of Perampanel in Pediatric Subjects 2 to 11 years With Epilepsy" 	<ul style="list-style-type: none"> • Statement in Section 4.2 Posology and method of administration of the SmPC indicating that the safety and efficacy of perampanel in children below 12 years of age have not been established yet. No data are available. • Communicated in the PIL.
Impact on cognition and growth in the pediatric population.	<ul style="list-style-type: none"> • Routine pharmacovigilance 	<ul style="list-style-type: none"> • Statement in Section 4.2 Posology and method of administration of the SmPC indicating that the safety and

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
	<ul style="list-style-type: none"> • <u>Adolescent Study E2007-G000-235</u>: "Randomized, Double-blind, Placebo-controlled, Parallel-group Study With OLE to Evaluate the Effect on Cognition, Growth, Safety, Tolerability, and PK When Administered as Adjunctive Therapy in Adolescents (12 to less than 18 years of age) With Inadequately Controlled Partial-onset Seizures" 	<p>efficacy of perampanel in children below 12 years of age have not been established yet. No data are available.</p> <ul style="list-style-type: none"> • Communicated in the PIL.
<p>Long term safety in adolescents and adults</p>	<ul style="list-style-type: none"> • Routine Pharmacovigilance • <u>Extension Study E2007-A001-207</u>: "Open-label Extension Phase of the Double-blind, Placebo-controlled, Dose-escalation, Parallel-group Study of E2007 (Perampanel) as an Adjunctive Therapy in Patients With Refractory Partial Seizures" • <u>Adolescent Study E2007-G000-235</u> • <u>Extension Study E2007-G000-307</u>: "An Open-Label Extension Phase of the Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group Studies to Evaluate the Efficacy and Safety of E2007 (perampanel) Given as Adjunctive Therapy in Subjects with Refractory Partial Seizures" • <u>Post-marketing observational safety study</u> 	<p>Current experience has not identified any issues to be noted in the SmPC or PIL.</p>

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Use in human pregnancy and lactation	<ul style="list-style-type: none"> • Routine pharmacovigilance • Pregnancy registry • <u>Post-marketing observational safety study</u> 	<p>• Statements in Section 4.6, Fertility, pregnancy and lactation of the SmPC indicating that:</p> <p><u>Women of childbearing potential and contraception in males and females</u> Perampanel is not recommended in women of childbearing potential not using contraception unless clearly necessary.</p> <p><u>Pregnancy</u> There are limited amounts of data (less than 300 pregnancy outcomes) from the use of perampanel in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats at maternally toxic doses. Perampanel is not recommended during pregnancy.</p> <p><u>Breastfeeding</u> It is not known whether perampanel is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from perampanel therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.</p> <p><u>Fertility</u> In the fertility study in rats, prolonged and irregular estrous cycles were observed at high-dose (30 mg/kg) in females; however, these changes did not affect the fertility and early embryonic development. There were no effects on male fertility (see Section 5.3). The effect of perampanel on human fertility has not been established.</p> <p>This is communicated in the PIL.</p>
Long term effects of perampanel binding to elastin, melanin and hepatic cells	Routine pharmacovigilance	Current experience has not identified any issues to be noted in the SmPC or PIL.
Use in patients with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction or any evidence of	Routine pharmacovigilance <ul style="list-style-type: none"> • <u>Post-marketing observational safety study</u> 	Current experience has not identified any issues to be noted in the SmPC or PIL.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
risk factors for QT prolongation		
Use in patients with a history of psychotic disorder or suicidal behaviour in the previous 2 years	Routine pharmacovigilance • <u>Post-marketing observational safety study</u>	Current experience has not identified any issues to be noted in the SmPC or PIL.
Use in patients with hepatic insufficiency whether related to concomitant medications or underlying liver disease	Routine pharmacovigilance	<ul style="list-style-type: none"> Information in Section 4.2 of the SmPC, Posology and method of administration: Hepatic impairment Dose increases in patients with mild and moderate hepatic impairment should be based on clinical response and tolerability. For patients with mild or moderate hepatic impairment, dosing can be initiated at 2 mg. Patients should be up-titrated using 2 mg doses no faster than every 2 weeks based on tolerability and effectiveness. Perampanel dosing for patients with mild and moderate impairment should not exceed 8 mg. <p>Use in patients with severe hepatic impairment is not recommended.</p> <p>Additional information in Section 5.2 Pharmacokinetic properties</p> <p>Special populations</p> <p>Hepatic impairment</p> <p>The pharmacokinetics of perampanel following a single 1 mg dose were evaluated in 12 subjects with mild and moderate hepatic impairment (Child-Pugh A and B, respectively) compared with 12 healthy, demographically matched subjects. The mean apparent clearance of unbound perampanel in mildly impaired subjects was 188 ml/min vs. 338 ml/min in matched controls, and in moderately impaired subjects was 120 ml/min vs. 392 ml/min in matched controls. The t_{1/2} was longer in mildly impaired (306 h vs. 125 h) and moderately impaired (295 h vs. 139 h) subjects compared to matched healthy subjects.</p> <p>This is communicated in the PIL.</p>
Use in patients with a history of drug or alcohol dependency	Routine pharmacovigilance • <u>Post-marketing observational safety study</u>	<ul style="list-style-type: none"> Information in Section 4.4 of the SmPC, Special warnings and precautions for use: Abuse potential

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		<p>Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of perampanel abuse.</p> <p>Section 4.5 Interaction with other medicinal products and other forms of interaction</p> <p><u>Alcohol</u> The effects of perampanel on tasks involving alertness and vigilance such as driving ability were additive or supra-additive to the effects of alcohol itself, as found in a pharmacodynamic interaction study in healthy subjects. Multiple dosing of perampanel 12 mg/day increased levels of anger, confusion, and depression as assessed using the Profile of Mood State 5-point rating scale (see Section 5.1). These effects may also be seen when perampanel is used in combination with other central nervous system (CNS) depressants.</p> <p>Additional information in Section 5.1 Pharmacodynamic properties Psychomotor performance. Single and multiple doses of 8 mg and 12 mg impaired psychomotor performance in healthy volunteers in a dose-related manner. The effects of perampanel on complex tasks such as driving ability were additive or supra-additive to the impairment effects of alcohol. Psychomotor performance testing returned to baseline within 2 weeks of cessation of perampanel dosing.</p> <p>Alertness and mood. Levels of alertness (arousal) decreased in a dose-related manner in healthy subjects dosed with perampanel from 4 to 12 mg/day. Mood deteriorated following dosing of 12 mg/day only; the changes in mood were small and reflected a general lowering of alertness. Multiple dosing of perampanel 12 mg/day also enhanced the effects of alcohol on vigilance and alertness, and increased levels of anger, confusion and depression as assessed using the Profile of Mood State 5-point rating scale.</p>
Use in patients who are taking vigabatrin	Routine pharmacovigilance <ul style="list-style-type: none"> • <u>Post-marketing observational</u> 	Current experience has not identified any issues to be noted in the SmPC or PIL.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
	<u>safety study</u>	
Use in patients with clinically significant renal or respiratory disease	Routine pharmacovigilance	<ul style="list-style-type: none"> • Information in Section 4.2 of the SmPC, Posology and method of administration: <p>Renal impairment Dose adjustment is not required in patients with mild renal impairment. Use in patients with moderate or severe renal impairment or patients undergoing haemodialysis is not recommended.</p> <p>Additional information in Section 5.2 Pharmacokinetic properties Renal impairment The pharmacokinetics of perampanel have not been formally evaluated in patients with renal impairment. Perampanel is eliminated almost exclusively by metabolism followed by rapid excretion of metabolites; only trace amounts of perampanel metabolites are observed in plasma. In a population pharmacokinetic analysis of patients with partial-onset seizures having creatinine clearances ranging from 39 to 160 mL/min and receiving perampanel up to 12 mg/day in placebo-controlled clinical trials, perampanel clearance was not influenced by creatinine clearance.</p> <p>This is communicated in the PIL.</p> <p>Current experience has not identified any issues to be noted in the SmPC or PIL regarding the use in patients with respiratory disease</p>

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
<p>Use in the elderly with epilepsy, with particular monitoring of dizziness, balance disorders and falls</p>	<p>Routine pharmacovigilance</p> <ul style="list-style-type: none"> • <u>Post-marketing observational safety study</u> 	<ul style="list-style-type: none"> • Information in Section 4.2 of the SmPC, Posology and method of administration: Elderly (65 years of age and above) Clinical studies of perampanel in epilepsy did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Analysis of safety information in 905 perampanel-treated elderly subjects (in double-blind studies conducted in non-epilepsy indications) revealed no age-related differences in the safety profile. In combination with the lack of age-related difference in perampanel exposure, the results indicate that dose-adjustment in the elderly is not required. Perampanel should be used with caution in elderly taking into account the drug interaction potential in polymedicated patients (see Section 4.4). <p>Additionally Section 4.4 Special warnings and precautions for use notes the following:</p> <p><u>Falls</u> There appears to be an increased risk of falls, particularly in the elderly; the underlying reason is unclear..</p> <p>This is communicated in the PIL.</p>
<p>Idiosyncratic reactions related to reactive intermediates</p>	<p>Routine pharmacovigilance</p>	<p>Current experience has not identified any issues to be noted in the SmPC or PIL.</p>

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Non CYP3A drug-drug interactions	<p><u>Routine pharmacovigilance Post Approval experiments will be conducted</u></p> <ul style="list-style-type: none"> • Potential contribution of non-CYP metabolism study • Potential contribution of CYP isoforms in vitro study • In silico simulations and modelling of potential drug interactions • In vivo studies (if necessary) 	<p>Information in Section 4.5, Interaction with other medicinal products and other forms of interaction:</p> <p>Effect of cytochrome P450 inducers on perampanel pharmacokinetics Strong inducers of cytochrome P450, such as rifampicin and hypericum, are expected to decrease perampanel concentrations. Felbamate has been shown to decrease the concentrations of some drugs and may also reduce perampanel concentrations.</p> <p><u>Effect of cytochrome P450 inhibitors on perampanel pharmacokinetics</u> In healthy subjects, the CYP3A4 inhibitor ketoconazole (400 mg once daily for 10 days) increased perampanel AUC by 20% and prolonged perampanel half-life by 15% (67.8 h vs 58.4 h). Larger effects cannot be excluded when perampanel is combined with a CYP3A inhibitor with longer half-life than ketoconazole or when the inhibitor is given for longer treatment duration. Strong inhibitors of other cytochrome P450 isoforms could potentially also increase perampanel concentrations</p> <p>This is communicated in the PIL.</p>

AEDs = anti-epileptic drugs; SmPC = Summary of Product Characteristics; PIL = Patient Information Leaflet.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
1. The applicant should perform in vitro study(ies) to investigate the potential contribution of (i) non-CYP enzymes and (ii) CYP isoforms to the metabolism of perampanel. The study results should be provided.	31 May 2013
2. The applicant should perform simulation studies to estimate the fraction of perampanel metabolised by CYP3A and to explore the possible effect of additional metabolic pathways identified in in-vitro studies on the human pharmacokinetics of perampanel and the impact of potential drug-drug interactions with inhibitors and inducers of the identified pathways.	30 Jun 2013
3. Depending on the outcome of in-vitro and in-silico studies, the applicant should perform in vivo drug-drug interaction study(ies) to verify non-CYP metabolism contributing $\geq 25\%$ to the clearance of perampanel. The applicant should submit the study protocol(s) for review prior to study start or provide a justification as to	30 Sep 2013

Description	Due date
why additional in vivo studies are unnecessary.	
4. A Post-Marketing Observational Safety Study to Evaluate the Long-Term Safety and Tolerability of Fycompa (Perampanel) as Add-on Therapy in Epilepsy Patients should be conducted. A detailed protocol should be submitted for review prior to study beginning. The Clinical Study Report to be submitted.	31 Aug 2012 30 Jun 2017

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Perampanel showed potent anticonvulsant activities in several animal models of seizures.

The choice of the dose range (4 mg to 12 mg) was justified by safety results from the 3 phase II studies (203, 208 and 231), whose objective was to determine the maximum tolerated dose.

- **Adjunctive Treatment in Epilepsy**

The three Phase III studies were conducted to demonstrate efficacy and safety of perampanel as adjunctive treatment in epilepsy. These studies were similar in design and differed only in the fixed dose evaluated.

Doses up to 12mg/day were tested in a population of subjects aged 12 years and older.

The 50% responder rate was considered the Primary efficacy endpoint for EU registration as recommended by the CHMP guidance (CPMP/EWP/566/98, Rev.2 Corr, 2010).

Even though the efficacy appears modest in the overall population as compared to recent approved AEDs the results of the essentially similar 3 phase III studies were consistent for the primary efficacy endpoint and showed statistically significant efficacy when compared with placebo for doses of 4 mg to 12 mg for studies 305 and 306.

One of the secondary end points for all three Phase III studies was 50% or greater reduction in seizure frequency per 28 days during the maintenance period relative to the pre-randomization phase.

Consistent statistically significant efficacy results were found for this secondary endpoint between studies 305 and 306.

These results are supported by those on the main secondary efficacy endpoint (percent change in seizure frequency during the double-blind period) and in the subgroup analysis in patients with complex partial plus secondarily generalized seizures at the doses of 4 mg, 8 mg, and 12 mg in the 3 pivotal phase III studies (304, 305, and 306).

- **Monotherapy in Epilepsy**

Efficacy in monotherapy is not proven because of the different patient population i.e. refractory epilepsy versus non-refractory epilepsy and because the effective dose as well as safety under monotherapy may be different compared to an agent given in combination with other concomitant anti-epileptics with different antiepileptic agents.

Uncertainty in the knowledge about the beneficial effects

Study 304 failed to reach significance. In this study, the placebo effect was high (26.4% instead of between 2 to 25% as stated in Note for Guidance/CHMP/EWP/556/98/Rev.2/Corr July 2010). Efficacy was statistically demonstrated on the primary efficacy endpoint at 8 mg and 12 mg doses in study 304 when patients from Central and South America region were excluded. In this region, placebo effect was high (33.3%) compared to placebo effect in North America (US and Canada, 21.9%).

The applicant has provided a thorough justification for the results seen and additionally provided evidence that the drug is likely to be effective in the EU population. The sensitivity analyses and the different analysis populations suggest the results are robust. The secondary endpoints provide a similar picture, and there are no uncertainties that fundamentally question the evidence for benefit.

Although efficacy has been satisfactorily demonstrated for doses up to 8 mg the separation between the 8 and 12 mg dose strength was less clear regarding the dose response. The applicant provided a discussion with supportive data which showed that the 12 mg dose is associated with an increased number of adverse events. However, benefit of 12 mg dose is observed in patients previously treated with 8 mg dose, who tolerate the 8 mg dose, and whose response to treatment is not completely satisfactory with 8 mg. Data pooled from the Phase III studies and OLE study 307 were assessed in order to estimate whether the 12 mg dose can provide higher benefit when compared with the 8mg dose. The results of this analysis showed an improved efficacy in the same subjects when the dose increases from 8 mg to 12 mg. The 50% responder rate rose from 37.8% on 8mg to 43.5% with 12mg in the same subject from the double-blind maintenance period to the blinded conversion period. Seizure frequency decreased from -32.42% to -43.27% from the double-blind maintenance period. The benefit-risk ratio of the 12 mg dose is positive in a sub-group of patients.

Efficacy in the subgroup of 143 adolescents appears consistent with those of adults when data of the 3 phase III studies were pooled. One randomised, double-blind, placebo-controlled study of adjunctive therapy with perampanel on cognition, growth, safety, tolerability, and PK in adolescents (12 to <18 years of age) is still ongoing (Study 235) and is awaited.

A limited number of elderly subjects were included across the clinical program. Twenty eight patients were 65 years or older (28/1480, 1.9%). However, analysis of safety information in 905 perampanel-treated elderly subjects (in double-blind studies conducted in non epilepsy indications) revealed no age-related differences in adverse events. In combination with the lack of age-related difference in perampanel exposure, the results indicate that dose-adjustment in the elderly is not required.

Risks

Unfavourable effects

Based on the available data, there are a number of adverse events that seems to be drug-related, which are: 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, and increased appetite.

Safety data collected from Phase III studies have demonstrated that TEAEs occurred more frequently in the perampanel 12 mg group (89.0%), than the 8mg group (81.2%) and placebo (66.5%) and are mainly related to the central nervous system (dizziness, somnolence, irritability, headache, fall, and ataxia).

The rate of SAEs was also slightly higher for the 12 mg (8.2%) and 8mg (5.6%) when compared with placebo (5.0 %).

Discontinuation rate due to TEAEs was notably higher in the 12mg group (19.2%) when compared with the 8mg (7.7%) and placebo (4.5%)

A dose-related increase was noted in 7 of the most frequent TEAEs that occurred with perampanel (dizziness, ataxia, aggression, anxiety, vertigo, irritability, and fall) which resulted in discontinuation.

- **Neurological disorders**

The most common TEAEs reported during pivotal phase III studies and in the second pool (including all treated patients with partial onset seizures) were dizziness (reported incidences in phase III studies: 9 % in placebo group versus 28 % in perampanel group; this rate increases to 42.7% for patients in 12 mg group) and somnolence (reported incidences in phase III studies: 7.2% in placebo group versus 14.5 % in perampanel group). Somnolence seems more frequent during the first weeks of treatment.

- **Psychiatric disorders**

15.3 % of the patients exposed to perampanel in phase III studies experienced psychiatric disorders, with the following most frequently reported TEAEs: insomnia, anxiety, and aggression, for which complementary data were requested. No SAEs or drop-outs related to aggressiveness were found. Most of the events were mild and recovered spontaneously. Aggression is included in section 4.8 of the SPC. In addition a warning on the risk of aggression is added in the SmPC.

- **Drug abuse, drug dependence and withdrawal**

Perampanel has an abuse and dependence potential which seems similar to alprazolam. Nevertheless, patients with epilepsy are not expected to be at particularly high risk for recreational abuse of the drug and this is expected to limit the availability of perampanel to inappropriate populations of diverters and abusers. Drug abuse is clearly identified in the risk management plan as an "important potential risk". Routine pharmacovigilance seems to be sufficient to monitor this effect. In addition a warning has been included in the SmPC section 4.4 as a routine risk minimisation measure. Nevertheless, perampanel should be prescribed with caution particularly in subjects with history of abuse.

- **Falls**

14.2% of the patients exposed to perampanel during the phase III studies experienced injury, poisoning and procedural complications (incidence higher in the 12 mg group). The most reported TEAEs was fall. A warning on the risk of fall has been added in section 4.4 of the SPC.

Uncertainty in the knowledge about the unfavourable effects

There is remaining uncertainty around the elimination of perampanel as a result of the poor quality of the in vivo metabolism studies and gaps and inconsistencies in the clinical pharmacology data that cause concern regarding the potential for drug-drug interactions that have not been considered as part of the development programme for perampanel. Of particular note for perampanel is that it is metabolised in part to reactive metabolites, there is a history of idiosyncratic immune-mediated adverse drug reactions for antiepileptic drugs which may be mediated through the formation of reactive metabolites, there is evidence from the literature that mortality from serious skin reactions with anti-epileptic drugs is significantly greater for drugs with long half-lives (> 24 h) and perampanel has a long half-life.

The Applicant has provided reassurance that shunting (which occurs when a route of metabolism that normally accounts for the majority of drug elimination is blocked, forcing a greater portion of the elimination down what is normally a minor route and resulting in unusually large quantities of a minor metabolite) to reactive metabolic pathways is not expected. Further reassurance, in the form of additional clinical pharmacology studies to better understand the enzymes responsible for the elimination of perampanel and for the formation of the reactive metabolites, is required.

Benefit-risk balance

Importance of favourable and unfavourable effects

More than 50 million adults and children suffer from epilepsy world-wide. Over the past 15 years, several AEDs have been developed with the objective of improving efficacy, tolerability, and ease of use when compared with classic currently-used AEDs such as carbamazepine, phenytoin, valproic acid, phenobarbital, and benzodiazepines. Approximately 60 % of newly diagnosed patients are seizure-free with monotherapy and an additional 10-20% with polytherapy. It follows that about 30% of patients are not satisfactorily controlled. In addition many patients suffer from significant adverse effects.

Thus, the development of new antiepileptic drugs could expand treatment options.

Perampanel is a new active substance with a new mechanism of action that despite the modest size of effect as compared to recent approved AEDs has demonstrate consistent efficacy as adjunctive therapy in the treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older at doses of 4 mg, 8 mg and 12 mg. The 12 mg dose is associated with more treatment adverse events than the 8 mg dose, with a dose-dependent relationship on undesirable effects, and more serious adverse events than 8 mg (8.2% vs 5.6%). However, benefit of 12 mg dose is observed in patients previously treated with 8 mg dose, who tolerate the 8 mg dose, and whom response to treatment is not completely satisfactory with 8 mg.

Moreover, the incidence rates of discontinuations due to AEs associated with the 12 mg/day dose are consistent with the rates reported for the highest approved doses used in double-blind clinical studies evaluating other recently approved AEDs.

Benefit-risk balance

Consistent level of efficacy has been proven throughout the phase III clinical programme.

Analyses of the safety database have not revealed any serious toxicity. Perampanel does not seem to cause any clinically significant changes in laboratory values, blood pressure, heart rate, ECGs, or photosensitivity.

The 12 mg dose is associated with more treatment adverse events than the lower doses, with a dose-dependent relationship on undesirable effects, and more serious adverse events than 8 mg (8.2% vs 5.6%). However, the benefit-risk ratio of the 12 mg dose is positive in a sub-group of patients who tolerate the dose of 8 mg, and when the clinical response is considered insufficient based on individual benefit- risk assessment.

There is remaining uncertainty around the elimination of perampanel as a result of the gaps and inconsistencies in the clinical pharmacology data that requires further investigation on the potential for drug-drug interactions that have not been considered as part of the development program for perampanel.

Based on the results of the phase III clinical programme and the supportive data from the open label trials, the benefits of perampanel as adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older outweighed the identified adverse events and the remaining uncertainty around the elimination of perampanel.

Discussion on the benefit-risk balance

The initial indication sought in this MA application was for treatment (understood as monotherapy) of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.

The three Phase III studies were conducted to demonstrate efficacy and safety of perampanel as adjunctive treatment in epilepsy.

Improvement in seizure frequency proved to be maintained during long-term open-label treatment up to 4 years.

Efficacy in monotherapy is not proven because of the different patient population i.e. refractory epilepsy versus non-refractory epilepsy and because the effective dose as well as safety under monotherapy may be different compared to an agent given in combination with other concomitant anti-epileptics containing different antiepileptic agents.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the risk-benefit balance of Fycompa in the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of perampanel and taking into consideration the applicant's claim that this substance is not a constituent of a previously authorised product in the Union, the CHMP considers that perampanel is qualified as a new active substance

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/79/2010 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.