TITLE PAGE

POST-AUTHORISATION SAFETY STUDY

Title	A Global, Postmarketing Observational Safety Study to Evaluate the Safety and Tolerability of Fycompa® (Perampanel) as Add-on Therapy in Epilepsy Patients Aged ≥ 12 Years
Study Protocol Number:	E2007-G000-402
Version Identifier of the Final Study Report	Final
Date of Last Version of the Final Study Report	25 Aug 2017
EU PAS Register Number	EUPAS10320
Active Substance	ATC Code: N03A X22 Active Substance: 2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate (4:3)
Medicinal Product	Fycompa (perampanel)
Product Reference	EU/1/12/776/001 - 023
Procedure Number	EMA/H/C/2434/MEA/004
Marketing Authorisation Holder	Eisai Europe Limited
Joint PASS	No
Research Question and Objectives	The objective of the study is to address the need for additional safety information on adverse events (AEs) of interest in the categories of important identified risks, important potential risks, and important missing information in the Committee for Medicinal Products for Human Use (CHMP)-approved EU Risk Management Plan (RMP) for perampanel given as add-on therapy in patients with epilepsy. This will be achieved by assessment of events of dizziness, blurred vision, somnolence, aggression, balance disorders, ataxia, falls, unintended pregnancy, weight gain, suicidality, drug abuse, misuse, dependence, withdrawal, off-label use, skin photosensitivity, unintended pregnancy while taking levonorgestrel-containing contraceptives, and outcomes associated with any suspected drug-drug interaction.
Countries of Study	Austria, Belgium, Czech Republic, Denmark, France, Israel, Sweden, and United Kingdom
Author	PPD Neurology Business Group, Eisai Inc.
GCP Statement:	This study was performed in full compliance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation is archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited.

MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder	Eisai Europe Limited European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK
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1. ABSTRACT

1.1 Title

A Global, Postmarketing Observational Safety Study to Evaluate the Safety and Tolerability of Fycompa® (Perampanel) as Add-on Therapy in Epilepsy Patients Aged ≥12 Years

1.2 Keywords

Safety study, observational, non-interventional, real-life, epilepsy, perampanel, post-authorisation safety study (PASS).

1.3 Rationale and Background

The Committee for Medicinal Products for Human Use (CHMP) had requested Eisai to conduct a PASS as a source of additional safety data for identified safety risks and missing safety information. Therefore, E2007-G000-402 (Study 402) was designed as an observational, cohort study to evaluate the safety profile of perampanel when prescribed as add-on therapy in subjects with epilepsy, to assess these adverse events (AEs) under conditions of common (real-life) use in the epilepsy population.

1.4 Research Questions and Objectives

The objective of the study was to address the need for additional safety information on AEs of interest in the categories of important identified risks, important potential risks, and important missing information in the CHMP-approved Risk Management Plan (RMP) for perampanel given as add-on therapy in subjects with epilepsy.

This was achieved by assessment of events of dizziness, blurred vision, somnolence, aggression, balance disorders, ataxia, falls, unintended pregnancy, weight gain, suicidality, drug abuse, misuse, dependence, withdrawal, off-label use, skin photosensitivity, unintended pregnancy while taking levonorgestrel-containing contraceptives, and outcomes associated with any suspected drug-drug interaction.

Further, the safety of perampanel was evaluated in the following subject subpopulations:

- Subjects with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction, or any evidence of risk factors for QT prolongation
- Subjects with a history of psychotic disorder or suicide behavior in the previous 2 years
- Subjects exposed to vigabatrin
- Subjects with a history of substance abuse
- Elderly subjects (≥65 years) with epilepsy
- Subjects with a history of drug or alcohol dependency

- Subjects who were pregnant or lactating
- Subjects with renal, respiratory, or underlying liver disease

Eisai targeted patients for each of these subpopulations by enrolling study sites with access to subjects who had the baseline characteristics requested by CHMP.

1.5 Study Design

At the time of the study, Fycompa was indicated for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.

This was a global, observational, cohort study in subjects with epilepsy. Multiple treating physicians prescribed perampanel to approximately 500 subjects, who then were observed for approximately 52 weeks.

Subjects could have been enrolled if there was a therapeutic change in the adjunctive treatment of epilepsy (ie, a new anti-epileptic drug [AED] was indicated) and the treating physician elected to prescribe perampanel. There was a Prescription Treatment Phase only in the study. During this phase, there was an initial Screening Visit. The treating physicians determined clinic visits according to common clinical practice; visits no less frequently than every 6 months were recommended.

There was an End of Study (EOS) Visit at Week 52. For subjects who discontinued the study or study drug prior to Week 52, there was an Early Termination Visit and Follow-up Visit 2 weeks later.

AEs and concomitant medications associated with serious adverse events (SAEs) and other AEDs were collected throughout the study. Disease severity and change in clinical status from initiation of treatment were clinically assessed at Screening and EOS, respectively.

The study began on 05 Jun 2014 and the cut-off date for this interim report was 09 Jan 2017. It was anticipated that each subjects would participate for a maximum of 52 weeks. The end of the study was defined as the date of the last study visit for the last subject in the study. Subjects may have continued therapy beyond 52 weeks, according to the clinical judgment of the investigator; however, for this interim analysis, only data collected within the 52-week study period were included.

1.6 Setting

The study took place in epilepsy subjects who were prescribed adjunctive treatment in countries where perampanel had received marketing approval.

1.7 Subjects and Study Size, Including Dropouts

The study population was to consist of approximately 500 epilepsy subjects treated in an adjunctive therapy setting. An agreed interim analysis was to occur once 200 subjects had

completed 52 weeks of treatment. However, due to the slow recruitment and the relatively high numbers of subjects not completing 52 weeks of treatment, the Pharmacovigilance Risk Assessment Committee (PRAC) agreed that this interim analysis would be conducted when the first 200 subjects completed the study. In this report, 116 subjects completed 52 weeks of treatment, of which 24 completed the study and 92 were considered ongoing. A total of 130 subjects discontinued.

1.8 Variables and Data Sources

1.8.1 Primary Variable

The primary variable of this study was the incidence of treatment-emergent AEs (TEAEs) of interest, defined as dizziness; blurred vision; somnolence; aggression; balance disorders; ataxia; falls; unintended pregnancy; weight gain; suicidality; drug abuse; misuse; dependence; withdrawal; off-label use; skin photosensitivity; unintended pregnancy while taking levonorgestrel-containing contraceptives; and outcomes associated with any suspected drug-drug interaction.

1.8.2 Secondary Variables

The secondary variables for this study were:

- Summary scores for the Hospital Anxiety and Depression Scale (HADS)
- Incidence of TEAEs in the subjects subpopulations of interest, as appropriate
- Clinical Global Impression of Change (CGI-C)

The incidence of unintended pregnancy and off-label use was specified as a secondary variable in the protocol; however, since this was also included as a primary endpoint, the statistical analysis plan (SAP) was amended to remove this from the list of secondary variables. This report presents analyses for the variables as defined in the SAP.

1.8.3 Data Sources

Data from epilepsy subjects were collected prospectively utilizing case report forms (CRFs), and safety information was collected from subjects at clinic visits that occurred over a period of 52 weeks as clinically indicated by the treating physician. In addition, information on SAEs, pregnancy, and unintended pregnancy was collected.

It was intended to compare the safety data collected in the study with the historical safety data obtained in previous perampanel studies.

1.9 Results

Subjects in this study consented to procedures and assessments during a 52-week time period. Some subjects had their EOS Visit later than 52 weeks after the Screening Visit; therefore, procedures and assessments that were conducted outside the time of consent, including EOS assessments CGI-C, HADS, and TEAEs reporting, were excluded from

analysis in this interim report. Consequently, the results presented here have a slight imbalance towards subjects who discontinued treatment before 52 weeks. An addendum to the informed consent form was created to mitigate this imbalance in order to include data collected from EOS Visits after 52 weeks. These analyses will be presented in the final clinical study report (CSR).

1.9.1 Subject Disposition and Analysis Sets

A total of 383 subjects entered the study; 2 subjects were dosed with study drug but failed screening due to participation in another study involving administration of an investigational drug or device. A total of 381 subjects continued in the study and comprised the Enrolled Population; all subjects (381 [100%] subjects) received at least 1 dose of study drug. One subject in the Enrolled Population did not have a postbaseline safety assessment and was excluded in the Safety Analysis Set (380 [99.7%] subjects).

Of the 381 subjects in the Enrolled Population, a total of 116 subjects completed 52 weeks of treatment (24 [6.3%] subjects completed the study and 92 [24.1%] subjects were considered ongoing), 135 (35.4%) subjects in the study had not yet completed the 52 weeks of treatment and therefore are ongoing treatment, and 130 (34.1%) subjects discontinued from the study. The primary reasons for discontinuation were AE (83 [21.8%] subjects), inadequate therapeutic effect (25 [6.6%] subjects), and subject choice (10 [2.6%] subjects).

1.9.2 Demographic and Baseline Characteristics

The mean age (SD) of subjects was 37.9 (14.86) years. The study population was balanced with regard to gender (male, 50.8%) and the majority were white (91.5%). The mean time (SD) since diagnosis was 22.96 (14.578) years, with the majority of subjects having a complex partial seizure type (58.2%), followed by secondary generalised tonic-clonic (48.9%).

At the time of data cut, the numbers of subjects enrolled in each of the subgroup categories were insufficient for analysis. In the Safety Analysis Set, 22 (5.8%) subjects had cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction, or any evidence of risk factors for QT prolongation. Additional common subgroups (>1% of all subjects) included elderly subjects (≥65 years) with epilepsy (19 [5.0%]), subjects exposed to vigabatrin (11 [2.9%]), subjects with renal disease (5 [1.3%]), and subjects with underlying liver disease (4 [1.1%]).

Overall, 77 (20.3%) subjects in the Safety Analysis Set were taking 1 AED, 142 (37.4%) subjects were taking 2 AEDs, and 108 (28.4%) subjects were taking 3 AEDs at baseline. There were 18 (4.7%) subjects who were prescribed perampanel as monotherapy at baseline. The most common AEDs (≥20% of subjects overall) were levetiracetam (38.2%), lamotrigine (25.5%), carbamazepine (24.5%), and lacosamide (23.7%). These proportions of AED use were similar at EOS.

1.9.3 Safety

The mean duration of exposure was 32.41 weeks and ranged from 0.3 to 52.0 weeks. The mean (SD) daily dose was 4.49 (1.781) mg/day and mean (SD) maximum dose was 5.8 (2.41) mg.

Of the 380 subjects included in the Safety Analysis Set, 227 (59.7%) reported at least 1 TEAE, the majority of which were mild to moderate in severity. There were 205 (53.9%) subjects who had at least 1 TEAE considered to be possibly or probably related to study drug by the investigator. A total of 28 (7.4%) subjects had a serious TEAE: 1 (0.3%) subject died and 27 (7.1%) subjects had other SAEs. A total of 101 (26.6%) subjects had a TEAE that led to treatment discontinuation. This discontinuation incidence included subjects who had a TEAE that started before the interim report data cut but led to discontinuation after the interim report data cut.

The system organ class (SOC) with the highest incidence of TEAEs were nervous system disorders (34.2%), psychiatric disorders (24.5%), and general disorders and administration site conditions (13.4%). The majority of events in these SOCs were of mild to moderate severity. The TEAEs with the highest incidence were dizziness (15.5%), fatigue (9.7%), irritability (7.6%), seizure (7.1%), and aggression (5.0%). All of the events of dizziness, fatigue, and irritability were considered as treatment-related by the investigator, as well as most of the events of aggression (4.7%) and some of the events of seizure (3.9%).

There was 1 death observed during the study. The primary cause of death was brain oedema and was assessed by the investigator as not related to treatment.

Of the 380 subjects in the Safety Analysis Set, 28 (7.4%) subjects experienced at least 1 AE that met the criteria for serious. The highest incidence of SAEs by SOC was nervous system disorders (3.9%) followed by psychiatric disorders (2.4%). The most common SAEs (occurring in more than 1 subject) were seizure (1.8%), ataxia (0.5%), status epilepticus (0.5%), and psychotic disorder (0.5%). All ataxia, status epilepticus, and psychotic disorder events as well as 4 events of seizure were considered related to treatment by the investigator. One subject who was excluded from the Safety Analysis Set because of screen failure reported an SAE of status epilepticus while taking perampanel. The event was considered as not related to treatment by the investigator.

TEAEs resulting in discontinuation of perampanel or interruption of study drug and/or dose adjustment occurred in 101 (26.6%) subjects and 77 (20.3%) subjects in the Safety Analysis Set, respectively. This discontinuation incidence included subjects who had a TEAE that started before the interim report data cut but led to discontinuation after the interim report data cut. The highest incidence of TEAEs resulting in treatment discontinuation or interruption of study drug and/or dose adjustment by SOC was nervous system disorders (15.0% and 11.1%, respectively), psychiatric disorders (12.4% and 8.9%, respectively), and general disorders and administration site conditions (4.5% and 4.7%, respectively). The most common (>2% incidence) TEAEs leading to treatment discontinuation were dizziness (6.8%), aggression (3.7%), seizure (3.7%), fatigue (3.2%), and irritability (2.4%).

The most common (≥1% incidence) TEAEs resulting in interruption of study drug and/or dose adjustment were dizziness (6.1%), irritability (4.2%), fatigue (3.2%), vertigo (1.8%), seizure (1.6%), gait disturbance (1.1%), balance disorder (1.1%), and aggression (1.1%).

There were 25 (6.6%) subjects who do not have partial seizures with or without secondary generalisation that used perampanel off-label in this study; however, some of the subjects using perampanel off-label may have been treated for primary generalized tonic-clonic seizures, which gained approval during the course of the study. A total of 18 (4.7%) subjects used perampanel off-label as monotherapy. Subjects with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction, or any evidence of risk factors for QT prolongation using perampanel off-label will be presented in the final CSR. One subject reported a TEAE of accidental overdose that was not associated with another TEAE, and 1 subject reported a TEAE of intentional overdose that was associated with a TEAE of suicide attempt. These events were assessed as probably related and possibly related to study drug by the investigator, respectively.

One pregnancy was reported for a woman in the Safety Analysis Set exposed to perampanel in the study. The subject underwent an induced abortion and there was no interruption or change in the dose of perampanel.

A total of 111 (29.2%) subjects had a TEAE of special interest, the most common (≥1% incidence) being dizziness (15.5%), aggression (5.5%), balance disorders (4.2%), weight gain (2.6%), somnolence (2.4%), suicidality (1.8%), outcomes associated with suspected drug-drug interaction (1.6%), and blurred vision (1.1%). The frequency of TEAEs of interest reported in this interim analysis was generally lower than the incidence observed in clinical trials, with the exception of slight increases in the incidence of suicidality and aggression (<1% difference). As previously mentioned, all events of dizziness and most events of aggression were considered related to treatment by the investigator. Most events related to balance disorders (includes terms of balance disorder, ataxia, and fall) and weight gain were considered to be related to treatment by the investigator; only 1 (0.3%) event of fall and 1 (0.3%) event of weight increased were considered to be not related. All events of somnolence and suicidality were considered to be related to treatment. While most TEAEs of special interest were of mild to moderate severity, 3 (0.8%) events of dizziness, 1 (0.3%) event of aggression, 1 (0.3%) event of somnolence, 1 (0.3%) event of balance disorder, 1 (0.3%) event of suicidal ideation, and 1 (0.3%) event of suicide attempt were severe.

1.9.4 Efficacy

The CGI-C assessment was performed at the EOS Visit or upon early termination (End of Treatment). Due to the aforementioned informed consent issue, many subjects whose EOS Visit occurred after 52 weeks did not have their CGI-C assessment data included in this interim analysis. As a result, the CGI-C results were biased toward the large number of subjects whose CGI-C assessment was performed upon early termination. An addendum to the informed consent form was created to mitigate this imbalance and include data collected from EOS Visits after 52 weeks. These analyses will be presented in the final CSR.

Of the 135 subjects in the Safety Analysis Set who had a CGI-C assessment, the majority of subjects (42.2%) had no change in disease severity compared to baseline, followed by minimally worse (23.0%), much worse (14.8%), and much improved (10.4%) disease severity compared to baseline.

1.9.5 Other Analyses

At the End of Treatment, 16 (6.0%) subjects and 6 (2.3%) subjects experienced a 5% and 10% increase in weight, respectively. At any visit, 28 (10.6%) subjects and 31 (11.7%) subjects experienced 5% and 10% increase in weight, respectively. Due to the informed consent issue, these incidences may be underestimated due to the subjects whose EOS Visit occurred after 52 weeks and did not have their final weight included in this interim analysis.

Due to a change in the version of the HADS assessment during the study, as well as the post-Week 52 assessment data that was not included due to the informed consent issue, the HADS results are not presented in this interim analysis. The presentation of HADS will be provided in the final CSR.

1.10 Discussion

This observational study was requested by the CHMP to address the need for additional safety information on AEs of interest in the categories of important identified risks, important potential risks, and important missing information in the EU RMP for perampanel given as add on therapy in subjects with epilepsy. No unusual or unexpected safety signals were observed. The frequency of TEAEs of interest reported in this interim analysis were generally lower than the incidence, based on that observed in clinical trials, with the exception of slight increases in the incidence of suicidality and aggression (<1% difference). The majority of TEAEs of interest were of mild to moderate severity. The analysis of the HADS score and CGI-C assessment were affected by the exclusion of key EOS Visit data due to issues with informed consent; these data will be reported in the final CSR. Analysis of the incidence of TEAEs in the subject subpopulation of interest was not performed due to insufficient sample size at the time of data cut; these data will also be reported in the final CSR.

1.11 Marketing Authorisation Holder

Eisai Europe Limited
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AL10 9SN UK

1.12 Names and Affiliations of Principal Investigators

The name(s) and affiliations of the principal investigator(s) will be provided in the final CSR.

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AED	anti-epileptic drug
CGI-C	Clinical Global Impression of Change
CHMP	Committee for Medicinal Products for Human Use
CRF	case report form
CSR	clinical study report
EOS	End of Study
HADS	Hospital Anxiety and Depression Scale
ICH	International Council for Harmonisation
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
PASS	post-authorisation safety study
PRAC	Pharmacovigilance Risk Assessment Committee
PT	preferred term
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SOC	system organ class
RMP	Risk Management Plan
TEAE	treatment-emergent adverse event

3. INVESTIGATORS

A list of all collaborating institutions and investigators will be made available upon request. This list will be cataloged in Annex 1 of the final clinical study report (CSR).

4. OTHER RESPONSIBLE PARTIES

Role	Name
Study Director	Antonio Laurenza, MD Executive Director, Clinical Development, Neurology Business Group Eisai Inc.
Head of Pharmacovigilance & Medical Information and EU QPPV	Yvonne Lamb, MB BS, MFPM Head of International Pharmacovigilance and EUQPPV Eisai Europe Limited

5. MILESTONES

Milestone	Planned Date	Actual Date	Comments
Start of data collection	Jun 2014	05 Jun 2014	
End of data collection (Final CSR)	Jan 2018		The data cut for the Interim report was 09 Jan 2017.
Registration in the EU PAS register	June 2014	17 Jul 2015	The failure to register prior to the start of data collection was identified by MAH as a deviation in 2015.
Interim report	Q1 2017		
Final report of study results	Q3 2018		The agreed final CSR date was revised several times in the annual study progress reports because of slower than expected recruitment rate.

6. RATIONALE AND BACKGROUND

Study E2007-G000-402 (Study 402) was implemented as a European Union postmarketing commitment study following the 24 May 2012 Committee for Medicinal Products for Human Use (CHMP) positive opinion for the perampanel Marketing Authorization Application (MAA) as adjunctive treatment in subjects aged 12 years or greater affected with partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy. During the review of the MAA, the CHMP commented that, as a first-in-class medicine, perampanel had a limited safety database for long-term use. CHMP therefore requested Eisai to conduct a post-authorisation safety study (PASS) as a source of additional safety data for identified safety risks and missing safety information.

CHMP specifically requested Eisai to perform a study that assessed the following safety parameters: dizziness, blurred vision, somnolence, aggression, balance disorders, ataxia, falls, unintended pregnancy, weight gain, suicidality, drug abuse, misuse, dependence, withdrawal, off-label use, skin photosensitivity, unintended pregnancy while taking levonorgestrel-containing contraceptives, outcomes associated with any suspected drug-drug interaction, use in patients with a history of cardiovascular disease, use in patients with a history of psychotic disorder or suicidal behavior in the previous 2 years, use in patients with exposure to vigabatrin, use in patients with a history of substance abuse, use in the elderly (≥65 years) with epilepsy, use in patients with a history of drug or alcohol dependency, and use in patients with renal, respiratory, or underlying liver disease. Eisai agreed to undertake such a study as part of postmarketing pharmacovigilance activities. Eisai also agreed to submit a full protocol to CHMP by 31 Aug 2012, an interim report upon 200 subjects completing 52 weeks of treatment, and a completed CSR by Dec 2017.

Study 402 was designed as a postmarketing, observational, cohort study to evaluate the safety profile of perampanel prescribed as add-on therapy in subjects with epilepsy, with assessment of the aforementioned safety events and patient populations.

Epilepsy subjects 12 years of age or greater participated in Study 402. It was estimated that approximately 500 subjects on perampanel add-on therapy would be enrolled. Subjects were included in the study only if perampanel was initiated no more than 7 days before the subject's Screening Visit. Planned exclusion criteria were: participation in another study involving administration of an investigational drug or device while participating in this observational study, prior participation in a perampanel clinical study, or hypersensitivity to perampanel.

The planned duration of study treatment for each subject was approximately 52 weeks (in the case of subjects who discontinued prior to 52 weeks, an additional 2 weeks for follow-up). Anti-epileptic drug (AED) doses for study treatments, including perampanel, were administered according to the respective Summary of Product Characteristics (SmPC) and clinical judgment.

7. RESEARCH QUESTIONS AND OBJECTIVES

At the time of study design, Fycompa was indicated for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.

The objective of the study was to address the need for additional safety information on adverse events (AEs) of interest in the categories of important identified risks, important potential risks, and important missing information in the CHMP-approved Risk Management Plan (RMP) for perampanel given as add-on therapy in patients with epilepsy by assessment of events of dizziness, blurred vision, somnolence, aggression, balance disorders, ataxia, falls, unintended pregnancy, weight gain, suicidality, drug abuse, misuse, dependence, withdrawal, off-label use, skin photosensitivity, unintended pregnancy while taking levonorgestrel-containing contraceptives, and outcomes associated with any suspected drug-drug interaction.

Further, the safety of perampanel was evaluated in the following subpopulations:

- Subjects with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction, or any evidence of risk factors for QT prolongation
- Subjects with a history of psychotic disorder or suicide behavior in the previous 2 years
- Patients exposed to vigabatrin
- Subjects with a history of substance abuse
- Elderly subjects (≥65 years) with epilepsy
- Subjects with a history of drug or alcohol dependency
- Subjects who were pregnant or lactating
- Subjects with renal, respiratory, or underlying liver disease

Eisai targeted subjects for each of these subpopulations by enrolling study sites with access to subjects who had the baseline characteristics requested by CHMP.

The safety data generated from the study were primarily compared with the known safety profile of perampanel from clinical studies. The comparison of the real-life population of subjects enrolled in Study 402 with the population from perampanel clinical trials allowed comparing of the treatment-emergent AE (TEAE) incidence rate from real-life clinical practice with the incidence observed in the perampanel clinical trials database. Furthermore, a comparison with the TEAEs observed in the specified subpopulations of subjects was also made in order to get a better understanding of whether any of these particular potential risk factors (eg, old age and cardiovascular disease) define groups with greater or lesser risk.

8. AMENDMENTS AND UPDATES

The original protocol, dated 22 Aug 2012, was amended once in response to CHMP request (EMA/H/0002434 Final Assessment Report, Nov 2012).

E2007-G000-402 Protocol v.2.0, 04 Dec 2012

- Removed "Long-term" from study title.
- Revised name and affiliation of main author.
- Subjects with renal, respiratory, or underlying liver disease were included as subpopulations of special interest as requested in the RMP assessment report.
- Cases of suspected drug interactions were considered as primary variables. In particular, unintended pregnancy while taking levonorgestrel-containing contraceptives and unintended pregnancy exposures were to be specifically reported using serious AE (SAE) procedures and considered to be SAEs for regulatory reporting purposes only if they met protocol-specific criteria.
- Defined the term "elderly" (≥65 years).
- Identified milestone dates for progress reports and interim reports; revised CSR date.
- Added language about frequency of clinic visits.
- Decreased the number of planned sites to reduce variability by concentrating on US and EU countries.
- Added ataxia, falls, unintended pregnancy while taking levonorgestrel-containing contraceptives, and outcomes associated with any suspected drug-drug interaction to list of AEs of interest.
- Added subjects with history of substance abuse and those with renal, respiratory or underlying liver disease to list of subjects subpopulations to be analyzed.
- Added clarification text for analysis of historical data.
- Added suspected cases of drug-drug interactions to list of AEs of interest.
- Qualified pregnancy, intended or unintended for reporting purposes.
- Added exposure through unintended pregnancy resulting from suspected interaction with levonorgestrel-containing contraceptives, and regulatory reporting requirements.
- Specified check of last menstrual period for females
- Expanded on rationale for study size by adding expected incidence rates for AEs of interest.
- Replaced blank ENCePP Checklist with a populated one.

9. RESEARCH METHODS

9.1 Study Design

This was a global, observational, cohort study in subjects with epilepsy. Multiple treating physicians prescribed perampanel to approximately 500 subjects, who then were observed for approximately 52 weeks. This duration of study was agreed with CHMP, and it was judged an appropriate length of time to evaluate the safety and tolerability of perampanel in clinical practice.

Subjects could have been enrolled if there was a therapeutic change in the adjunctive treatment of epilepsy (ie, a new AED was indicated) and the treating physician elected to prescribe perampanel. There was a Prescription Treatment Phase only in the study. During this phase, there was an initial Screening Visit. The treating physicians determined regular clinic visits according to common clinical practice; no less frequently than every 6 months was recommended.

There was an End of Study (EOS) Visit at Week 52. For Subjects who discontinued the study or study drug prior to Week 52, there was an Early Termination Visit and Follow-up Visit 2 weeks later.

The planned treatment for this study consisted of perampanel tablets administered orally according to prescribing information and the treating physician's clinical judgment.

TEAEs and concomitant medications associated with SAEs and other AEDs were collected throughout the study. Disease severity and change in clinical status from initiation of treatment was clinically assessed at Screening and EOS, respectively.

The study began on 05 Jun 2014 and the cut-off date for this interim report was 09 Jan 2017. It was anticipated that each subject was to participate for a maximum of 52 weeks. The end of the study was defined as the date of the last study visit for the last subject in the study. Subject may have continued therapy beyond 52 weeks, according to the clinical judgment of the investigator; however, for this interim analysis, information was collected only for the 52-week study period.

The schedule of procedures and assessments for the study is presented in Table 1.

Table 1 Schedule of Procedures/Assessments in Study E2007-G000-402

Phase	Prescription Treatment			
Visit	**Screening**	**Unscheduled**	**End of Study/ Early Termination**	**Follow-up[a]**
Week	**0**	**As clinically indicated[b]**	**52/ET**	**ET + 2 weeks**
Procedures/Assessments				
Assign subject number	X			
Weight	X	X	X	X
Demography	X			
Medical history including LMP	X	X	X	X
Epilepsy history	X			
Informed consent/assent	X			
Inclusion/exclusion criteria	X			
Concomitant medication(s) and AED prior/concomitant use[c]	X	X	X	X
CGI-C			X	
Perampanel dosing information and intended use		X	X	
Adverse events/events of interest	X	X	X	X
HADS	X		X	

AEDs = anti-epileptic drugs; CGI-C = Clinical Global Impression of Change; ET = Early Termination; HADS = Hospital Anxiety and Depression Scale; LMP = last menstrual period; SAEs = serious adverse events.
a: Required only for subjects who discontinue prior to Week 52.
b: Regular clinic visits will be determined by the treating physicians according to common clinical practice, though no less frequently than every 6 months will be recommended.
c: Only AEDs and concomitant medications associated with SAEs will be collected.
Source: E2007-G000-402 Study Protocol

9.2 Setting

The study took place in epilepsy subjects who were prescribed adjunctive treatment in countries where perampanel had received marketing approval.

9.3 Subjects

Subjects who did not meet all of the inclusion criteria or who met any of the exclusion criteria were not eligible to receive treatment.

9.3.1 Inclusion Criteria

1. Male or female subjects aged ≥12 years (or as regionally appropriate) at the time of informed consent
2. Subjects prescribed perampanel for the adjunctive treatment of epilepsy within 7 days of the Screening Visit
3. Subjects who provided informed consent

9.3.2 Exclusion Criteria

1. Participation in another study involving administration of an investigational drug or device whilst participating in this observational study
2. Prior participation in a perampanel clinical study
3. Hypersensitivity to perampanel

9.4 Variables

9.4.1 Primary Variable

The primary variable included incidence of TEAEs of interest defined as: dizziness, blurred vision, somnolence, aggression, balance disorders, ataxia, falls, unintended pregnancy, weight gain, suicidality, drug abuse, misuse, dependence, withdrawal, off-label use, skin photosensitivity, unintended pregnancy while taking levonorgestrel-containing contraceptives, and outcomes associated with any suspected drug-drug interaction.

9.4.2 Secondary Variables

The secondary variables included:

- Incidence of unintended pregnancy and off-label use.
- Summary scores for the Hospital Anxiety and Depression Scale (HADS)
- Incidence of TEAEs in the subject subpopulations of interest, as appropriate
- Clinical Global Impression of Change (CGI-C)

9.5 Data Sources and Measurement

Data from epilepsy subjects were collected prospectively utilizing case report forms (CRFs), and safety information was collected from subjects at clinic visits that occurred over a period of 52 weeks as clinically indicated by the treating physician. In addition, information on SAEs, pregnancy, and unintended pregnancy was collected.

It was intended to compare the safety data collected in the study with the historical safety data obtained in previous perampanel studies.

9.6 Bias

Not applicable as this study was designed as a postmarketing, observational, cohort study.

9.7 Study Size

Approximately 100 to 200 sites were planned to be involved and about 500 subjects planned to participate and receive perampanel as an add-on therapy. An agreed interim analysis was to occur once 200 subjects had completed 52 weeks of treatment. However, due to the slow recruitment and the relatively high numbers of subjects not completing 52 weeks of treatment, the Pharmacovigilance Risk Assessment Committee (PRAC) agreed that this interim analysis would be conducted when the first 200 subjects completed the study. In this data cut, 24 subjects completed the study, 92 subjects completed the study and continued treatment, and 130 subjects discontinued.

The primary variable included the incidence of the following TEAEs of interest: dizziness, blurred vision, somnolence, aggression, balance disorders, ataxia, falls, unintended pregnancy, weight gain, suicidality, drug abuse, misuse, dependence, withdrawal, off-label use, skin photosensitivity, unintended pregnancy while taking levonorgestrel-containing contraceptives, and outcomes associated with any suspected drug-drug interaction. With 500 subjects in this study, the probability of observing at least 1 of these events of interest was > 0.99. Based on the ISS, the expected incidence of the individual events is shown in Table 2. Since the probability of observing at least 1 event was 0.78 when the incidence rate was as low as 0.3%, the sample size was expected to be large enough to detect safety signals, and there should have been even a small increase in the incidence of the rarest events in this wider setting.

Table 2 Expected Incidence of Individual Adverse Events of Interest

Event of Interest	Incidence in Clinical Trials
Dizziness	42.0%
Blurred vision[a]	6.5%
Somnolence	19.6%
Aggression[b]	5.1%
Balance disorders[c]	15.3%
Unintended pregnancy	0.6%
Weight gain	5.8%
Suicidality[d]	1.0%
Drug abuse	0.1%
Drug misuse	0.1%
Drug dependence	0.1%
Drug withdrawal	0.1%
Skin photosensitivity	0.2%

a: includes terms of blurred vision and diplopia.
b: includes terms of aggression, anger, and paranoia.
c: includes terms of balance disorder, ataxia, and fall.
d: includes terms of suicidal ideation, intentional drug overdose, and suicide attempt.
Source: E2007-G000-402 Study Protocol

9.8 Data Transformation

Data required by the protocol was collected on the appropriate CRFs and entered into a validated data management system that was compliant with all regulatory requirements. As defined by the International Council for Harmonisation (ICH) guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Marketing Authorisation Holder on each subject.

Data collection on the CRF followed the instructions described in the CRF Completion Guidelines. The treating physician had ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The treating physician or designee signed the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs were the sole property of Eisai and should not have been made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

Where applicable, all software applications used in the collection of data was properly validated following standard computer system validation that was compliant with all regulatory requirements.

9.9 Statistical Methods

A complete description of all statistical analyses is found in the statistical analysis plan (SAP).

9.9.1 Main Summary Measures

All descriptive statistics for continuous variables were reported using mean, SD, median, minimum and maximum. Categorical variables were summarized as number (percentage) of subjects.

9.9.2 Main Statistical Methods

9.9.2.1 Analysis Sets

The Enrolled Population was the group of subjects who signed a consent form, met all inclusion and exclusion criteria, and were assigned a subject identifier.

The Safety Analysis Set was the group of enrolled subjects who received at least 1 dose of study drug, met all the inclusion and exclusion criteria, and had at least 1 postdose safety assessment.

The Safety Analysis Set was used in all analyses.

9.9.2.2 Safety Analyses

The safety endpoints were considered primary for this study.

Study Day 1 for all safety analyses was defined as the date of the first dose of study drug. Safety variables included TEAEs, weight, and HADS. TEAEs were defined as AEs that emerged during treatment and up to 30 days after the last dose, having been absent at pretreatment (Baseline); reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment; or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. Only those AEs that were treatment emergent were included in summary tables. The AE verbatim descriptions (investigator terms) were classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1. TEAEs were summarized and reported as the number (%) of subjects with TEAEs by system organ class (SOC) and preferred term (PT), and by maximum severity (mild, moderate, or severe).

TEAEs were also summarized by relationship to study drug (possibly related, probably related, and not related). Treatment related TEAEs included those events considered by the investigator to be possibly or probably related to study treatment, and were summarized by SOC and PT, and by maximum severity.

The following TEAEs of special interest were summarized: dizziness; blurred vision (included terms of blurred vision and diplopia); somnolence; aggression (included terms of

aggression, anger, and paranoia); balance disorders (included terms of balance disorder, ataxia, and fall); drug abuse; drug misuse; drug dependence; drug withdrawal; weight gain; suicidality (included terms of suicidal ideation, intentional drug overdose, suicide attempt); off-label use (subjects who were dose greater than 12 mg, subjects without partial onset seizures with or without secondarily generalized seizures, or subjects taking perampanel as monotherapy); skin photosensitivity; unintended pregnancy while taking levonorgestrel containing contraceptives; and subjects with an AE considered by the investigator to be possibly associated with a drug-drug interaction.

Descriptive statistics for weight and changes from baseline at final visit were presented. The number and proportion of subjects with at least a 5% and a 10% increase in weight from Baseline were presented at final visit and at any time during study.

9.9.2.3 Efficacy Analyses

The efficacy variables were considered secondary in this study.

CGI-C results were summarized for the Safety Analysis Set.

9.9.2.4 Other Safety Analyses

The HADS was made up of 7 questions each for anxiety and depression. The total score for each domain was derived. The change from Baseline was calculated between baseline and Final Visit/End of Treatment.

9.9.2.5 Interim Analyses

An agreed interim analysis was to occur once 200 subjects had completed 52 weeks of treatment. However, due to the slow recruitment and the relatively high numbers of subjects not completing 52 weeks of treatment, it was agreed by PRAC that this interim analysis would be conducted when the first 200 subjects completed the study.

9.9.3 Missing Values

If the day and month were missing, events were to be considered treatment-emergent if the year was equal to or after the year of the first dose date; if days were missing, events were to be considered treatment-emergent if the year was after the year of the first dose, or if the year was equal to the year of the first dose date and the month was equal to or after the month of the first dose date.

For the purpose of summarizing maximum severity, if the severity of an AE was missing for a subject, then, if this subject had another AE with the same PT that had “severe” severity, the maximum severity of the AE was to be noted as “severe’; otherwise the maximum severity was to be noted as missing. Similarly, for the purpose of summarizing closest relationship, if the relationship of an AE to study drug was missing, the AE was to be noted to be probably related if there was another probably related AE with the same PT, otherwise this relationship was to be noted as missing.

No special handling of missing data was planned for the analysis of any of the other safety variables.

Data exceptions or outliers were determined by inspection of the tables, listings, and graphs in consultation with the clinical study team. The effect of outliers on analyses may have been assessed by reanalyzing the data without the outliers.

All the listings display the original missing values.

9.9.4 Sensitivity Analyses

Not applicable.

9.9.5 Amendments to the Statistical Analysis Plan

There was 1 global amendment to the original protocol. Changes made during this amendment are detailed in the study protocol. In the protocol, the secondary safety variables were defined as the incidence of unintended pregnancy and off-label use, summary scores for the HADS, and the incidence of TEAEs in the subject population. Since unintended pregnancy and off-label use are primary endpoints, these were deleted from the list of secondary endpoints in the SAP. Additionally, the definitions of the Enrolled Population and the Safety Analysis Set were amended to remove the screen failures from both populations.

9.10 **Quality Control**

Data from CRFs were entered into a clinical database as specified in the Marketing Authorisation Holder's data management plan. Quality control and data validation procedures were applied to ensure the validity and accuracy of the clinical database. Data queries requiring clarification were documented and returned to the investigational site for resolution. Only authorized personnel made corrections to the clinical database, and all corrections were documented in an audit trail. The final database was archived by Eisai according to regulatory requirements.

In order to provide the Marketing Authorisation Holder with accurate, complete, and legible data, the following criteria were to be maintained:

- All CRFs were completed by the examining personnel, and reviewed and signed by the treating physician.
- It was each treating physician's responsibility to ensure that all CRF entries corresponded to the entries on the subject's medical records

All statistical programs were maintained on systems maintained by the Marketing Authorisation Holder.

10. RESULTS

Subjects in this study consented to procedures and assessments during a 52-week time period. Some subjects had their EOS Visit later than 52 weeks after the Screening Visit; therefore, procedures and assessments that were conducted outside the time of consent, including EOS assessments CGI-C, HADS, and TEAEs reporting (Table 1), were excluded from analysis in this interim report. Consequently, the results presented here have a slight imbalance towards subjects who discontinued treatment before 52 weeks. An addendum to the informed consent form was created to mitigate this imbalance in order to include data collected from EOS Visits after 52 weeks. These analyses will be presented in the final CSR.

10.1 Participants

A summary of enrolled subjects and screen failures is presented in Table 14.1.1.1. Subject disposition at End of Screening is listed by subject in Listing 16.2.1.1 and reason for discontinuation from study is listed by subject in Listing 16.2.1.2. A total of 383 subjects entered the study; 2 subjects were dosed with study drug but failed screening due to participation in another study involving administration of an investigational drug or device (Listing 16.2.1.1 and Listing 16.2.6). A total of 381 subjects continued in the study and comprised the Enrolled Population; all subjects (381 [100%] subjects) received at least 1 dose of study drug. One subject in the Enrolled Population did not have a postbaseline safety assessment and was excluded in the Safety Analysis Set (380 [99.7%] subjects).

Of the 381 subjects in the Enrolled Population, a total of 116 subjects completed 52 weeks of treatment: 24 (6.3%) subjects completed the study and 92 (24.1%) subjects were considered ongoing. An additional 135 (35.4%) subjects in the study had not yet completed the 52 weeks of treatment, and therefore are ongoing treatment. However, some of the subjects that were reported as ongoing treatment have actually completed the study, but the EOS Visit was conducted after the 52-week study duration specified in the informed consent form. As mentioned above, data collected at these visits were not included in the database for analysis; only information collected for the 52 week study period is presented in this interim report.

At the time of the interim report data cut, 130 (34.1%) subjects discontinued from the study (Table 3). The primary reasons for discontinuation were AE (83 [21.8%] subjects), inadequate therapeutic effect (25 [6.6%] subjects), and subject choice (10 [2.6%] subjects).

Subject disposition and other reasons for discontinuation from study are provided in Table 14.1.2.2. Distribution of subjects by country and site is presented in Table 14.1.1.2.

Table 3 Subject Disposition and Primary Reason for Discontinuation from Study – All Enrolled Subjects

Category	Perampanel (N=381) n (%)
Enrolled Population, n	381
Not treated, n	0
Treated, n (%)	381 (100.0)
Completed the study, n (%)	24 (6.3)
Discontinued from the study, n (%)	130 (34.1)
Ongoing treatment, n (%)	135 (35.4)
Ongoing at Week 52, n (%)	92 (24.1)
Primary reason for discontinuation[a], n (%)	
Adverse event[b]	83 (21.8)
Lost to follow-up	7 (1.8)
Subject choice	10 (2.6)
Inadequate therapeutic effect	25 (6.6)
Progression of disease	0
Withdrawal of consent	3 (0.8)
Pregnancy	0
Study terminated by sponsor	0
Other	2 (0.5)

CRF = case report form, N = total number of subjects in treatment group, n = number of subjects in individual group
a: As reported on the Subject Disposition CRF.
b: Corresponding adverse event(s) leading to withdrawal from the study or study drug or both were reported on the Adverse Event CRF.
Source: Table 14.1.2.1

10.2 Descriptive Data

10.2.1 Demographic Characteristics

The demographic characteristics are summarized for the Safety Analysis Set in Table 4 and listed by subject in Listing 16.2.2.1. Epilepsy-specific medical history is summarized in Table 14.1.4.2 and listed by subject in Listing 16.2.2.2. Medical history and current medical conditions are listed by subject in Listing 16.2.3.

The mean age (SD) of subjects was 37.9 (14.86) years. The study population was balanced with regard to gender (male, 50.8%) and the majority were white (91.5%). The mean time (SD) since diagnosis was 22.96 (14.578) years, with the majority of subjects having a complex partial seizure type (58.2%), followed by secondary generalised tonic-clonic (48.9%).

Table 4 Demography and Baseline Characteristics – Safety Analysis Set

Category	Perampanel (N=380)
Age (year)[a]	
n	380
Mean (SD)	37.9 (14.86)
Median	37.0
Min, Max	12, 79
Age group, n (%)	
≥12 to <18 years	36 (9.5)
≥18 to <65 years	325 (85.5)
≥65 years	19 (5.0)
Sex, n (%)	
Male	193 (50.8)
Female	187 (49.2)
Race, n (%)	
White	321 (91.5)
Black or African American	2 (0.6)
Chinese	1 (0.3)
Other Asian	5 (1.4)
Other	22 (6.3)
Missing	29
Weight (kg)	
n	352
Missing	28
Mean (SD)	73.09 (18.827)
Median	72.10
Min, Max	18.4, 148.7

Max = maximum, Min = minimum, N = total number of subjects in treatment group, n = number of subjects in individual group, SD = standard deviation
a: Age was calculated at Date of Informed Consent/Assent.
Source: Table 14.1.4.1

10.2.2 Patient Subgroups

Subject subgroups are summarized in Table 5. At the time of data cut, the numbers of subjects enrolled in each of the subgroup categories were insufficient for analysis. In the Safety Analysis Set, 22 (5.8%) subjects had cardiovascular disease, hypertension, congestive

heart failure, history of myocardial infarction, or any evidence of risk factors for QT prolongation. Additional common subgroups (>1% of all subjects) included elderly subjects (≥65 years) with epilepsy (19 [5.0%]), subjects exposed to vigabatrin (11 [2.9%]), subjects with renal disease (5 [1.3%]), and subjects with underlying liver disease (4 [1.1%]).

Table 5 Subject Subgroups – Safety Analysis Set

Category	Perampanel (N=380) n (%)
Subjects with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction, or any evidence of risk factors for QT prolongation	22 (5.8)
Subjects with a history of psychotic disorder or suicide behavior in the previous 2 years	2 (0.5)
Subjects exposed to vigabatrin	11 (2.9)
Subjects with a history of substance abuse	0
Elderly subjects (≥65 years) with epilepsy	19 (5.0)
Subjects with a history of drug or alcohol dependency	3 (0.8)
Subjects who are pregnant or lactating	1 (0.3)
Subjects with renal disease	5 (1.3)
Subjects with respiratory disease	0
Subjects with underlying liver disease	4 (1.1)

Percentages are based on the total number of subjects with non-missing values.
N = total number of subjects in treatment group, n = number of subjects in individual group.
Source: Table 14.1.4.3

10.2.3 Concomitant Medications

The number of AEDs taken at study baseline is summarized in Table 14.1.5.3, and at EOS in Table 14.1.5.5. AEDs taken at baseline and at EOS are presented in Table 14.1.5.4 and Table 14.1.5.6, respectively.

There was no exclusion criterion for number of concomitant AEDs, but most subjects were being treated with 1 to 3 AEDs at baseline. Overall, 77 (20.3%) subjects in the Safety Analysis Set were taking 1 AED, 142 (37.4%) subjects were taking 2 AEDs, and 108 (28.4%) subjects were taking 3 AEDs at baseline. There were 18 (4.7%) subjects who were prescribed perampanel as monotherapy. The most common AEDs (≥20% of subjects overall) were levetiracetam (38.2%), lamotrigine (25.5%), carbamazepine (24.5%), and lacosamide (23.7%). At EOS, the proportions of subjects taking 1 to 3 AEDs were similar to baseline, as well as the type of AED: 73 (19.2%) subjects were taking 1 AED, 147 (38.7%) subjects were taking 2 AEDs, and 111 (29.2%) subjects were taking 3 AEDs at baseline, with the most common AEDs (≥20% of subjects overall) being levetiracetam (39.7%), carbamazepine (27.9%), lamotrigine (25.8%), lacosamide (23.4%), and clobazam (20.5%). Seven (1.8%) subjects were not taking any other AEDs at EOS.

A summary of all prior and concomitant medications taken by subjects in the Safety Analysis Set is presented in Table 14.1.5.1 and Table 14.1.5.2, respectively. Prior and concomitant medications are listed by subject in Listing 16.2.4.

10.3 Outcome Data

Of the 381 subjects in the Enrollment Population, 380 (99.7%) subjects were included in the Safety Analysis Set (Table 14.1.3.1). Subjects included in the Safety Analysis Set are listed by subject in Listing 16.2.1.3.

10.4 Main Results

10.4.1 Safety Results

10.4.1.1 Extent of Exposure

Cumulative extent of exposure and summary statistics for the modal dose, mean, median, maximum, and last daily dose of perampanel are presented in Table 14.3.1.1 and Table 14.3.1.1.9, respectively. Dosing and extent of exposure are listed by subject in Listing 16.2.6.

All subjects included in the Safety Analysis set had at least 1 dose of perampanel and at least 1 postbaseline safety assessment. The mean duration of exposure was 32.41 weeks and ranged from 0.3 to 52.0 weeks. A total of 373 (98.2%) subjects were exposed for more than 1 week, 225 (59.2%) subjects for more than 26 weeks, and 100 (26.3%) subjects exposed for 52 weeks. The mean daily dose (SD) was 4.49 (1.781) mg/day and mean maximum dose (SD) was 5.8 (2.41) mg. A total of 172 (45.3%) subjects had a mean daily dose less than 4 mg/day, 192 (50.5%) subjects had a mean daily dose between 4 and less than 8 mg/day, and 16 (4.2%) subjects had a mean daily dose between 8 and less than 12 mg/day. No subjects had a mean daily dose greater than 12 mg/day.

10.4.1.2 Adverse Events

10.4.1.2.1 Overview of Adverse Events

Table 6 presents an overview of TEAEs for the Safety Analysis Set. All AEs are listed by subject in Listing 16.2.7.

Of the 380 subjects included in the Safety Analysis Set, 227 (59.7%) reported at least 1 TEAE, the majority of which were mild to moderate in severity. There were 205 (53.9%) subjects who had at least 1 TEAE considered to be possibly or probably related to study drug by the investigator. A total of 28 (7.4%) subjects had a serious TEAE: 1 (0.3%) subject died and 27 (7.1%) subjects had other SAEs. A total of 101 (26.6%) subjects had a TEAE that led to treatment discontinuation. This incidence included subjects who had a TEAE that started before the interim report data cut but led to discontinuation after the interim report data cut.

Table 6 Overview of Treatment-Emergent Adverse Events – Safety Analysis Set

Category	Perampanel (N=380) n (%)
TEAEs	227 (59.7)
Treatment-related TEAEs[a]	205 (53.9)
Severe TEAEs	29 (7.6)
Serious TEAEs	28 (7.4)
Deaths	1 (0.3)
Other SAEs	27 (7.1)
Life threatening	3 (0.8)
Requires inpatient hospitalization or prolongation of existing hospitalization	23 (6.1)
Persistent or significant disability or incapacity	0
Congenital anomaly/birth defect	0
Important medical events	6 (1.6)
TEAEs leading to study drug dose adjustment	164 (43.2)
TEAEs leading to study drug withdrawal	101 (26.6)
TEAEs leading to study drug dose increase	12 (3.2)
TEAEs leading to study drug dose reduction	62 (16.3)
TEAEs leading to study drug dose interruption	4 (1.1)

MedDRA Version 19.1
MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects in treatment group, n = number of subjects in individual group, SAE = serious adverse event, TEAE = treatment-emergent adverse event.
a: Includes TEAEs considered by the Investigator to be possibly or probably related to study drug or TEAEs with missing causality.
Source: Table 14.3.2.1

10.4.1.2.2 COMMON ADVERSE EVENTS

TEAEs reported during the study are summarized by MedDRA SOC and PT in Table 14.3.2.2. The SOCs with the highest incidence of TEAEs were nervous system disorders (34.2%), psychiatric disorders (24.5%), and general disorders and administration site conditions (13.4%). The majority of events in these SOCs were of mild to moderate severity (Table 14.3.2.9). Common TEAEs (≥2% of subjects) reported during the study are summarized by PT by decreasing order of frequency in Table 7. The TEAEs with the highest incidence were dizziness (15.5%), fatigue (9.7%), irritability (7.6%), seizure (7.1%), and aggression (5.0%). All of the events of dizziness, fatigue, and irritability were considered as treatment-related by the investigator, as well as most of the events of aggression (4.7%) and some of the events of seizure (3.9%) (Table 14.3.2.7). Events of dizziness and aggression are considered TEAEs of special interest are discussed further in Section 10.4.1.3.7.

Table 7 Treatment-Emergent Adverse Events Occurring in ≥2% of Subjects by Decreasing Frequency by Preferred Term – Safety Analysis Set

MedDRA PT	Perampanel (N=380) n (%)
Subjects with any TEAE	227 (56.7)
Dizziness	59 (15.5)
Fatigue	37 (9.7)
Irritability	29 (7.6)
Seizure	27 (7.1)
Aggression	19 (5.0)
Vertigo	14 (3.7)
Headache	11 (2.9)
Weight increased	10 (2.6)
Balance disorder	9 (2.4)
Depression	9 (2.4)
Somnolence	9 (2.4)

MedDRA Version 19.1
Subject with 2 or more AEs in the same SOC (or with the same PT) is counted only once for that SOC (or PT).
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects in treatment group, n = number of subjects in individual group, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event.
Source: Table 14.3.2.3

10.4.1.2.3 Analysis of Adverse Events

At least 1 TEAE occurred in 227 (59.7%) subjects in the Safety Analysis Set during exposure to perampanel in the study. Table 7 presents common TEAEs, ie, those with an incidence of greater than or equal to 2%. The incidence of all TEAEs is summarized by MedDRA PT (in decreasing order of frequency in the total perampanel group) in Table 14.3.2.3 and by MedDRA SOC and PT in Table 14.3.2.2. Additional summaries are provided of TEAEs by relationship to study treatment in Table 14.3.2.8, by MedDRA SOC and PT for all treatment-related TEAEs in Table 14.3.2.7; by MedDRA SOC, PT, and maximum severity in Table 14.3.2.9; by MedDRA SOC and PT. A summary of non-serious TEAEs is presented in Table 14.3.2.4.

10.4.1.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

10.4.1.3.1 Deaths

There was 1 death observed during the study (Table 8). The subject was a 37 year old male with a history of status epilepticus. Concomitant AEDs included levetiracetam and

lacosamide. The subject initiated therapy with perampanel on 07 Apr 2016 (2 mg once daily [QD]) of perampanel, increased the dose to 4 mg QD on 19 Apr 2016, and then decreased the dose to 2 mg QD on 22 Apr 2016. On 24 Sep 2016, the subject was believed to have had a probable seizure during the night, leading to cardiac arrest. Cardiopulmonary resuscitation was started and heart function reappeared after 15 minutes. The subject was hospitalized. On 25 Sep 2016, the subject experienced malignant brain oedema. The subject died on 01 Oct 2016 due to malignant brain oedema, which was classified as not related to the study medication by the treating physician.

Table 8 Listing of Adverse Events Leading to Death

Subject ID Age (y), Sex, Race	Date of Death/ Study Day of Death[a]	Last Dose Prior to Death (mg)	Cause of Death (Investigator Term/Preferred Term)	AE Start Date/ Study Day	Relationship to Study drug	Duration of Treatment[b] (d)	Day of Death in Relation to Last Dose[c]
26041004 37, M, W	01 Oct 2016/ 178	2	Malignant brain edema/Brain oedema	25 Sep 2016/ 172	Not related	171	7

AE = adverse event, ID = identification, M = male, W = white
a: Study Day of Death = date of death - date of first dose of study drug + 1
b: Duration of treatment = date of last dose of study drug – date of first dose of study drug + 1
c: Number of days between end of study drug and death.
Source: Table 14.3.2.10

10.4.1.3.2 Serious Adverse Events

A summary of treatment-emergent SAEs by MedDRA SOC and PT is provided in Table 14.3.2.11. A listing by subject of all SAEs is provided in Table 14.3.2.12.

Of the 380 subjects in the Safety Analysis Set, 28 (7.4%) subjects experienced at least 1 AE that met the criteria for serious. The highest incidence of SAEs by SOC was nervous system disorders (3.9%) followed by psychiatric disorders (2.4%). The most common SAEs (occurring in more than 1 subject) were seizure (1.8%), ataxia (0.5%), status epilepticus (0.5%), and psychotic disorder (0.5%). All ataxia, status epilepticus, and psychotic disorder events as well as 4 events of seizure were considered related to treatment by the investigator (Table 14.3.2.12).

One subject who was excluded from the Safety Analysis Set because of screen failure reported an SAE of status epilepticus while taking perampanel. The event was considered as not related to treatment by the investigator (Listing 16.2.7).

10.4.1.3.3 TEAEs Leading to Discontinuation

TEAEs resulting in discontinuation of perampanel occurred in 101 (26.6%) subjects in the Safety Analysis Set (Table 14.3.2.13). This incidence included subjects who had a TEAE that started before the interim report data cut but led to discontinuation after the interim report data cut. A listing of subjects with TEAEs that led to study or perampanel withdrawal is provided in Table 14.3.2.14.

The highest incidence of TEAEs resulting in treatment discontinuation by SOC was nervous system disorders (15.0%), psychiatric disorders (12.4%), and general disorders and administration site conditions (4.5%). The most common (>2% incidence) TEAEs leading to treatment discontinuation were dizziness (6.8%), aggression (3.7%), seizure (3.7%), fatigue (3.2%), and irritability (2.4%) (Table 14.3.2.13).

10.4.1.3.4 TEAEs Requiring Interruption and/or Dose Reduction of Perampanel

In total, 77 (20.3%) subjects in the Safety Analysis Set had a TEAE that resulted in interruption of study drug and/or dose adjustment (ie, reduction or increase) during exposure to perampanel across the study (Table 14.3.2.15). The highest incidence of TEAEs requiring interruption and/or dose reduction of perampanel by SOC was nervous system disorders (11.1%), psychiatric disorders (8.9%), and general disorders and administration site conditions (4.7%). The most common of these events (≥1% incidence) were dizziness (6.1%), irritability (4.2%), fatigue (3.2%), vertigo (1.8%), seizure (1.6%), gait disturbance (1.1%), balance disorder (1.1%), and aggression (1.1%). A listing of subjects with TEAEs that required interruption and/or dose adjustment is provided in Listing 16.2.7.

10.4.1.3.5 Study Drug Overdose, Misuse, Abuse, and Medication Error

Subjects using perampanel off-label are presented in Table 14.3.2.5.2. There were 25 (6.6%) subjects who do not have partial seizures with or without secondary generalisation

that used perampanel in this study. Some of the subjects using perampanel off-label may have been treated for primary generalized tonic-clonic seizures, which gained approval during the course of the study. A total of 18 (4.7%) subjects used perampanel off-label as monotherapy. Subjects with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction, or any evidence of risk factors for QT prolongation using perampanel off-label will be presented in the final CSR.

One subject reported a TEAE of accidental overdose that was not associated with another TEAE, and 1 subject reported a TEAE of intentional overdose that was associated with a TEAE of suicide attempt. These events were assessed as probably related and possibly related to study drug by the investigator, respectively (Table 14.3.2.2 and Listing 16.2.7).

10.4.1.3.6 PREGNANCY

One pregnancy was reported for a woman in the Safety Analysis Set exposed to perampanel in the study (Table 14.3.2.2 and Listing 16.2.7).

The subject was a 34 year old female with epilepsy since Dec 2014. Surgical history included gamma knife radiosurgery (20 Jan 2016) and insertion of intra-uterine contraceptive device (20 Feb 2015 - 20 Oct 2016). Ongoing medical history included depression and anxiety since 2015. Concomitant medications included levetiracetam, lacosamide, escitalopram, clonazepam, and lorazepam. The subject initiated therapy with perampanel on 14 Apr 2016 (2 mg QD). The dose of perampanel was increased to 4 mg QD on 12 May 2016 and to 6 mg QD on 17 Jun 2017, and then decreased to 4 mg QD and 2 mg QD on 02 Sep 2016 and 15 Sep 2016, respectively. The last dose of perampanel was taken on 21 Sep 2016.

On 15 Apr 2016, the subject had a positive pregnancy test as a result of an ectopic pregnancy. The subject was administered methotrexate for induced abortion on 15 May 2016 and tested negative for human chorionic gonadotropin on 01 Jun 2016. The TEAE of ectopic pregnancy was considered to be not related to study drug by the investigator and there was no interruption or change in the dose of perampanel.

Concurrent with the pregnancy, on 01 May 2016, the subject reported concentration and attention difficulties due to anxiety and depression. On 15 Aug 2016, the subject experienced worsening of depression and reported suicidal ideation on 01 Sep 2016. The events of depression and suicidal ideation resolved and the event of concentration and attention difficulties improved; all 3 events were considered to be related to study drug by the investigator.

10.4.1.3.7 OTHER TEAES OF INTEREST

The following TEAEs of special interest, as requested in the RMP assessment report, were examined for the Safety Analysis Set during perampanel exposure: dizziness; blurred vision (included terms of blurred vision and diplopia); somnolence; aggression (included terms of aggression, anger, and paranoia [from standard MedDRA query for hostility/aggression]); balance disorders (included terms of balance disorder, ataxia, and fall); drug abuse; drug

misuse; drug dependence; drug withdrawal; weight gain; suicidality (included terms of suicidal ideation, intentional drug overdose, suicide attempt); off-label use (subjects who were dose greater than 12 mg, subjects without partial onset seizures with or without secondarily generalized seizures, or subjects taking perampanel as monotherapy); skin photosensitivity; unintended pregnancy while taking levonorgestrel containing contraceptives; and subjects with an AE considered by the investigator to be possibly associated with a drug-drug interaction.

A total of 111 (29.2%) subjects had a TEAE of special interest, the most common (≥1% incidence) being dizziness (15.5%), aggression (5.5%), balance disorders (4.2%), weight gain (2.6%), somnolence (2.4%), suicidality (1.8%), outcomes associated with suspected drug-drug interaction (1.6%), and blurred vision (1.1%) (Table 9). The frequency of TEAEs of interest reported in this interim analysis was generally lower than the incidence observed in clinical trials (Table 2), with the exception of slight increases in the incidence of suicidality and aggression (<1% difference).

As previously mentioned in Section 10.4.1.2.2, all events of dizziness and most events of aggression were considered related to treatment by the investigator. Most events related to balance disorders (includes terms of balance disorder, ataxia, and fall) and weight gain were considered to be related to treatment by the investigator; only 1 (0.3%) event of fall and 1 (0.3%) event of weight increased were considered to be not related. All events of somnolence and suicidality were considered to be related to treatment as assessed by the investigator (Table 14.3.2.8).

While most TEAEs of special interest were of mild to moderate severity, 3 (0.8%) events of dizziness, 1 (0.3%) event of aggression, 1 (0.3%) event of somnolence, 1 (0.3%) event of balance disorder, 1 (0.3%) event of suicidal ideation, and 1 (0.3%) event of suicide attempt were severe (Table 14.3.2.9).

Table 9 Treatment-Emergent Adverse Events of Special Interest – Safety Analysis Set

MedDRA PT	Perampanel (N=380) n (%)
Subjects with any event of special interest	111 (29.2)
Dizziness	59 (15.5)
Blurred vision[a]	4 (1.1)
Somnolence	9 (2.4)
Aggression[b]	21 (5.5)
Balance disorders[c]	16 (4.2)
Drug abuse	0
Drug misuse	0
Drug dependence	0
Drug withdrawal	0
Skin photosensitivity	0
Unintended pregnancy while taking levonorgestrel-containing contraceptives	1 (0.3)
Outcomes associated with suspected drug-drug interaction	6 (1.6)
Weight gain[d]	10 (2.6)
Suicidality[e]	7 (1.8)

MedDRA Version 19.1
Subject with 2 or more events is counted only once for that event.
MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects in treatment group, n = number of subjects in individual group, PT = preferred term,
a: includes terms of blurred vision, and diplopia.
b: includes terms of aggression, anger, and paranoia.
c: includes terms of balance disorder, balance, ataxia, and fall.
d: includes terms of weight gain, weight, and gain.
e: includes terms of suicidal ideation, suicide, suicide attempt, intentional drug overdose, and drug overdose.
Source: Table 14.3.2.5.1

Due to the low number of subjects the prespecified subpopulations of interest for this interim report (Section 10.2.2), the safety analysis of perampanel for these subjects, including those with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction, or any evidence of risk factors for QT prolongation, was not evaluated. Per the SAP, TEAEs of special interest were to be summarized for subgroups containing at least 25 subjects. Examination of subgroups with sufficient sample size will be presented in the final CSR.

10.4.2 Efficacy Results

A summary of CGI-C is presented for the Safety Analysis Set in Table 14.2 and listed by subject in Listing 16.2.5. The CGI-C assessment was performed at the EOS Visit or upon early termination (End of Treatment). Due to the aforementioned informed consent issue, many subjects whose EOS Visit occurred after 52 weeks did not have their CGI-C assessment data included in this interim analysis. As a result, the CGI-C results were biased toward the large number of subjects whose CGI-C assessment was performed upon early termination. An addendum to the informed consent form was created to mitigate this imbalance and include data collected from EOS Visits after 52 weeks. These analyses will be presented in the final CSR.

Of the 135 subjects in the Safety Analysis Set who had a CGI-C assessment, the majority of subjects (42.2%) had no change in disease severity compared to baseline, followed by minimally worse (23.0%), much worse (14.8%), and much improved (10.4%) disease severity compared to baseline.

10.5 Other Analyses

10.5.1 Vital Signs, Physical Findings, and Other Observations Related to Safety

10.5.1.1 Vital Signs

Summary statistics for mean and mean change from Baseline by Visit for weight in the Safety Analysis Set are provided in Table 14.3.3.1. Summary statistics for the subjects with weight increase is provided in Table 14.3.3.2. A listing of all individual vital signs results by subject is provided in Listing 16.2.8.1.

At the End of Treatment, 16 (6.0%) subjects and 6 (2.3%) subjects experienced a 5% and 10% increase in weight, respectively. At any visit, 28 (10.6%) subjects and 31 (11.7%) subjects experienced 5% and 10% increase in weight, respectively. Due to the informed consent issue, these incidences may be underestimated due to the subjects whose EOS Visit occurred after 52 weeks and did not have their final weight included in this interim analysis.

10.5.1.2 HADS Results

Due to a change in the version of the HADS assessment during the study, as well as the post-Week 52 assessment data that was not included due to the informed consent issue, the HADS results is not presented in this interim analysis. The presentation of HADS will be provided in the final CSR.

10.6 Adverse Events/Adverse Reactions

Safety data was considered a primary endpoint for this study and is presented in Section 10.4.

11. DISCUSSION

11.1 Key Results

A total of 381 subjects were included in the Enrolled Population. Of these, 116 subjects completed 52 weeks of treatment (24 [6.3%] subjects completed the study and 92 [24.1%] subjects were considered ongoing), 135 (35.4%) subjects had not yet completed the 52 weeks of treatment and therefore are ongoing treatment, and 130 (34.1%) subjects discontinued. Some subjects who completed 52 weeks of the study did not have their EOS Visit data included in this interim analysis due to informed consent issues, resulting in a potential bias toward subjects who discontinued treatment early.

The mean age (SD) of subjects was 37.9 (14.86) years. The study population was balanced with regard to gender (male, 50.8%) and the majority were white (91.5%). The mean time (SD) since diagnosis was 22.96 (14.578) years, with the majority of subjects having a complex partial seizure type (58.2%), followed by secondary generalised tonic-clonic (48.9%). Most subjects were taking 1 to 3 concomitant AEDs.

Of the 380 subjects included in the Safety Analysis Set, 227 (59.7%) reported at least 1 TEAE, the majority of which were mild to moderate in severity. A total of 111 (29.2%) subjects had a TEAE of special interest, the most common (≥1% incidence) being dizziness (15.5%), aggression (5.5%), balance disorders (4.2%) weight gain (2.6%), somnolence (2.4%), suicidality (1.8%), outcomes associated with suspected drug-drug interaction (1.6%), and blurred vision (1.1%). The frequency of TEAEs of interest reported in this interim analysis was generally lower than the incidence observed in clinical trials, with the exception of slight increases (<1% difference) in the incidence of suicidality and aggression (incidence of aggression based on standard MedDRA query for hostility/aggression). All events of dizziness, somnolence, and suicidality were considered to be related to treatment. Most events related to balance disorders and weight gain were considered to be related to treatment by the investigator; only 1 (0.3%) event of fall and 1 (0.3%) event of weight increased were considered to be not related. While most TEAEs of special interest were of mild to moderate severity, 3 (0.8%) events of dizziness, 1 (0.3%) event of aggression, 1 (0.3%) event of somnolence, 1 (0.3%) event of balance disorder, 1 (0.3%) event of suicidal ideation, and 1 (0.3%) event of suicide attempt were severe.

The analysis of the HADS score and CGI-C assessment were affected by the exclusion of key EOS Visit data due to issues with informed consent; these data will be reported in the final CSR. Analysis of the incidence of TEAEs in the subject subpopulation of interest was not performed due to insufficient sample size at the time of data cut; these data will also be reported in the final CSR.

11.2 Limitations

The study approach and methods used to evaluate AEs of interest in the categories of important identified risks, important potential risks, and important missing information in the

RMP followed GCP standards and no sources of bias have been identified that would call into question the validity of the data.

Due to the aforementioned informed consent issue, many subjects whose EOS Visit occurred after 52 weeks did not have their safety and efficacy assessment data included in this interim analysis. Consequently, results may be biased toward the large number of subjects whose assessments were performed upon early termination. Additionally, it should be noted that the probability of observing events of interest was calculated based on having 500 subjects in the planned final analysis.

11.3 Interpretation

No unusual or unexpected safety signals were observed. The frequency of TEAEs of interest reported in this interim analysis were generally lower and without clinically significant difference from the incidence observed in clinical trials.

11.4 Generalisability

The generalisability of the study results will not be presented in this interim report.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

This observational study was requested by the CHMP to address the need for additional safety information on AEs of interest in the categories of important identified risks, important potential risks, and important missing information in the EU RMP for perampanel given as add on therapy in subjects with epilepsy. No unusual or unexpected safety signals were observed. The frequency of TEAEs of interest reported in this interim analysis were generally lower than the expected incidence observed in clinical trials, with the exception of slight increases in the incidence of suicidality and aggression (<1% difference). The majority of TEAEs of interest were of mild to moderate severity. The analysis of the HADS score and CGI-C assessment were affected by the exclusion of key EOS Visit data due to issues with informed consent; these data will be reported in the final CSR. Analysis of the incidence of TEAEs in the subject subpopulation of interest was not performed due to insufficient sample size at the time of data cut; these data will also be reported in the final CSR.

14. REFERENCES

Not applicable.

15. ANNEXES

Annex 1. List of Stand-alone Documents

Number	Document reference number	Date	Title
1	E20007-G000-402 Interim CSR	26 May 2017	Statistical Tables
2	E20007-G000-402 Interim CSR	26 May 2017	Individual Subject Listings
3	E20007-G000-402 Interim CSR	26 May 2017	Listing of AE of Special Interest Terms