A Double-blind, Randomized, Placebo-controlled, Multicenter, Parallel-group Study with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Adjunctive Perampanel in Primary Generalized Tonic-Clonic Seizures

Published: 02-08-2011
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Primary Objective* To demonstrate the efficacy of adjunctive perampanel therapy, compared to placebo on primary generalized tonic-clonic (PGTC)seizuresSecondary Objectives* To evaluate the safety and tolerability of perampanel in subjects with...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Seizures (incl subtypes)
Study type	Interventional

Summary

ID

NL-OMON38310

Source
ToetsingOnline

Brief title
Eisai E2007-G000-332

Condition

- Seizures (incl subtypes)

Synonym
epilepsy, primary generalized tonic-clonic seizures

Research involving

Human

Sponsors and support

Primary sponsor: Eisai
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Epilepsy, Perampanel

Outcome measures

Primary outcome

Efficacy: Efficacy will be assessed by seizure counts (via seizure diary) and CGIC.

Secondary outcome

Pharmacokinetic: Plasma concentrations of perampanel will be determined in blood samples collected at designated timepoints.

Safety: Safety will be assessed by monitoring of adverse events (AEs), withdrawal from treatment, suicidality (C-SSRS), prior and concomitant medication usage, clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, and changes in physical and neurological examinations. In addition, a withdrawal questionnaire will be administered to assess potential withdrawal signs and symptoms that might be associated with the discontinuation of perampanel.

Other Criteria for Evaluation: Perampanel exposure vs response (seizure frequency) and vs AEs

Study description

Background summary

Currently only three new AEDs, levetiracetam, lamotrigine, and topiramate, are indicated for the treatment of primary generalized tonic-clonic seizures. This study is designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of perampanel on PGTC seizure frequency in adolescents and adults maintained on one to two stable antiepileptic drugs.
The study follows the standard design utilized for the studies of previously approved AEDs in this indication (levetiracetam, lamotrigine, and topiramate).

Study objective

Primary Objective
* To demonstrate the efficacy of adjunctive perampanel therapy, compared to placebo on primary generalized tonic-clonic (PGTC)
seizures

Secondary Objectives
* To evaluate the safety and tolerability of perampanel in subjects with inadequately controlled PGTC seizures

Exploratory Objectives
* To evaluate the pharmacokinetics (PK) of perampanel in subjects with inadequately controlled PGTC seizures
* To explore the efficacy of adjunctive perampanel therapy compared to placebo, on the physician-rated Clinical Global Impression of Change
scale (CGIC)
* To explore the relationship between plasma perampanel concentrations, efficacy, and safety using population pharmacokinetic/ pharmacodynamic (PK/PD) modeling

Study design

This will be a double-blind, randomized, placebo-controlled, multicenter, parallel-group, adjunctive-therapy study. Males and females 12 years and older who have a diagnosis of PGTC seizures receiving one to two AEDs, and experiencing * 3 PGTC seizures during the Baseline Period, will be included in this trial. Subjects will be administered up to 8 mg/day of perampanel or perampanel-matched placebo in the Core Study. The study will consist of three phases: Prerandomization, Randomization, and Extension. The Core Study will consist of the Prerandomization and Randomization Phases. The Prerandomization Phase will consist of two periods: Screening (up to 4 weeks) and Baseline (4- or 8- weeks), during which subjects will be assessed for overall eligibility to

participate in the study, including seizure activity. The Randomization Phase will consist of three periods: Titration (4 weeks), Maintenance (13 weeks), and Follow-up for subjects not rolling over into the Extension Phase (4 weeks). The

Extension Phase (Part A and Part B) will be comprised of the Conversion (6 weeks), Maintenance (84 weeks), and Follow-up (4 weeks) Periods and will last approximately 94 weeks, or until perampanel is made commercially available for the treatment of primary generalized tonic-clonic (PGTC) seizures. (see section 8.1 Protocol V4.0 dd 12-Apr-12)

Intervention

Investigational drug: Perampanel, oral tablets, up to 8 mg/day (Core Study); up to 12 mg/day (Extension Phase)
Comparator drug/reference therapy: Perampanel-matched placebo oral tablets

Study burden and risks

The most important side effects of Permapanel are sleepiness and dizziness. Other common side effects are: spinning sensation (vertigo), blurred vision, feeling sick (nausea), feeling very tired (fatigue), irritability, weight gain, decreased appetite, back pain, difficulty with walking (ataxia), unsteady gait (gait disturbance), balance problems (balance disorder), falling down (fall), slow speech (dysarthria), anxiety, double vision (diplopia), increased appetite, aggression and anger.

Procedures Core Study:
- Diary regarding seizures
- 3x Physical and neurological examinations
- 9x Vital signs
- 1x ECG
- 8x Pregnancy Test (1x blood, 9x urine, only women of childbearing potential)
- 1 x Urine drug testing
- 8x Questionnaires
- 8x Blood tests
- 3 x additional questionnaires about quality of life
(- 5 x questionnaire Healthcare resource utilization: to be interviewed by site staff)

Procedures Extension Phase:
- Diary regarding seizures
- 5x Vital signs
- 7x Pregnancy Test (urine, only women of childbearing potential)
- 1 x Urine drug testing
- 7x Questionnaires
- 4x Blood tests

Contacts

Public
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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Ages 12 years and older; in India less than 65 years of age
* Clinical diagnosis of PGTC seizures in the setting of idiopathic generalized epilepsy (with or without other subtypes of primary generalized seizures) and experiencing * 3 PGTC seizures during the 8-week period prior to randomization
* Have had a routine electroencephalogram (EEG) up to 5 years prior to or during the Baseline Period with electroencephalographic features consistent with primary generalized epilepsy; other concomitant anomaly should be explained by adequate past medical history
* On a fixed dose of one to a maximum three concomitant AEDs for a minimum of 30 days prior to Baseline; only one inducer AED (i.e., carbamazepine,

oxcarbazepine, or phenytoin) out of the maximum of three AEDs will be allowed
* A vagal nerve stimulator (VNS) will be allowed, but it must have been implanted * 5 months prior to Baseline (stimulator parameters can not be changed for 30 days prior to Baseline and for the duration of the study)
* Have had a computed tomography (CT) or magnetic resonance imaging (MRI) within the last 10 years (for adults) and 5 years (for adolescents) that ruled out a progressive cause of epilepsy
* A ketogenic diet will be allowed as long as the subject has been on this diet for 5 weeks prior to randomization

Exclusion criteria

* Participated in a study involving administration of an investigational compound or device within the 30 days prior to Baseline, or within approximately 5 half-lives of the previous investigational compound, whichever is longer
* Pregnant and/or nursing
* Participated in previous perampanel studies
* A history of status epilepticus that required hospitalization within 12 months prior to Baseline
* Seizure clusters where individual seizures cannot be counted
* A history of psychogenic seizures
* Any suicidal ideation with intent with or without a plan at or within 6 months prior to Visit 2 (i.e., answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale (C-SSRS)
* Evidence of clinically significant disease (e.g., cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or study conduct
* Concomitant diagnosis of Partial Onset Seizures (POS)
* Progressive neurological disease
* Clinical diagnosis of Lennox-Gastaut syndrome
* History of drug or alcohol dependency or abuse within 2 years prior to Screening
* Have 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
* If felbamate is used as a concomitant AED, subjects must be on felbamate for at least 2 years, with a stable dose for 60 days prior to Baseline. They must not have a history of white blood cell (WBC) count below * 2500/*L (2.50 1E+09/L), platelets < 100,000/*L, liver function tests (LFTs) > 3 times the upper limit of normal (ULN), or other indication of hepatic or bone marrow dysfunction while receiving

felbamate.
* Concomitant use of vigabatrin: Subjects who took vigabatrin in the past must be discontinued for approximately 5 months prior to Baseline, and must have documentation showing no evidence of a vigabatrinassociated clinically significant abnormality in an automated visual perimetry test
* Concomitant use of medications known to be inducers of CYP3A (with the exception of carbamazepine, oxcarbazepine, and phenytoin) within 30 days prior to Baseline. Concomitant use of barbiturates (except for seizure control indication) within 30 days prior to Baseline
* Use of intermittent rescue benzodiazepines (i.e., one to two doses over a 24-hour period considered one-time rescue) two or more times within the 30 days prior to Baseline

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-09-2011
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	Perampanel

Ethics review

Approved WMO Date:	02-08-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-12-2011
Application type:	First submission
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	07-03-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	16-04-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	06-06-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	12-06-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-000265-12-NL
ClinicalTrials.gov	NCT01393743
CCMO	NL37471.068.11