A PROSPECTIVE, MULTINATIONAL, OPEN-LABEL, SINGLE-ARM, EXPLORATIVE STUDY TO EVALUATE THE TOLERABILITY AND EFFICACY OF LACOSAMIDE WHEN ADDED TO LEVETIRACETAM WITH WITHDRAWAL OF THE CONCOMITANT SODIUM CHANNEL BLOCKING ANTIEPILEPTIC DRUG IN SUBJECTS WITH UNCONTROLLED PARTIAL-ONSET SEIZURES

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The primary objective of this study is to assess the overall effectiveness of LCM (optimizedwithin the range of 200mg/day to 600mg/day) when added to a stable dose of LEV (in thelabel range of 1000mg/day to 3000mg/day) with withdrawal of the...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Seizures (incl subtypes)
Study type	Interventional

Summary

ID

NL-OMON37460

Source
ToetsingOnline

Brief title
Optimising Combination Therapy On Partial Onset Seizures (OCToPOS)

Condition

- Seizures (incl subtypes)

Synonym
epilepsy, partial onset seizures

Research involving
Human

Sponsors and support

Primary sponsor: UCB Biosciences Inc
Source(s) of monetary or material Support: UCB Biosciences

Intervention

Keyword: epilepsy, Lacosamide, partial-onset seizures

Outcome measures

Primary outcome

There are 2 analysis sets defined for this study; the safety set (SS) is all

subjects who received at least 1 dose of LCM; and the full analysis set (FAS)

is all subjects in the SS who have at least 1 seizure diary data assessment

during LCM treatment.

The primary efficacy variable to support the objective of evaluating overall

effectiveness is the retention rate at the end the 21-week Treatment Period

Secondary outcome

Percent change in partial-onset seizure frequency per 28 days from Baseline to

the 12-week Maintenance Period

Percent change in partial-onset seizure frequency per 28 days from Baseline to

the 21-week Treatment Period

50% response where a responder is a subject experiencing >=50% reduction in

partial-onset seizure frequency per 28 days from Baseline to the 12-week

Maintenance Period

50% response where a responder is a subject experiencing >=50% reduction in

partial-onset seizure frequency per 28 days from Baseline to the 21-week

Treatment Period

75% response where a responder is a subject experiencing >=75% reduction in

partial-onset seizure frequency per 28 days from Baseline to the 12-week

Maintenance Period

75% response where a responder is a subject experiencing >=75% reduction in

partial-onset seizure frequency per 28 days from Baseline to the 21-week

Treatment Period

Seizure-free status (yes/no) during the 12-week Maintenance Period in subjects

who completed the entire Maintenance Period

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

Clinical Global Impression of Change (CGIC) at the end of the Maintenance Period

Patient Global Impression of Change (PGIC) at the end of the Maintenance Period

Study description

Background summary

In the past decade, several new options for the medical treatment of epilepsy have been
introduced, including novel AEDs and vagus nerve stimulation (VNS). The newer AEDs
differ from older agents in several important ways, including mechanism of action (MOA),

spectrum of activity, and pharmacokinetic (PK) characteristics (Herman and Pedley, 1998).
Despite this increase in treatment options, more than 30% of patients have inadequate seizure control on currently-available AEDs or experience significant adverse drug effects (Beghi and Sander, 2008), and less than 50% of newly diagnosed patients become seizure free after initial monotherapy treatment with an AED (Kwan and Brodie, 2000; Mohanraj and Brodie, 2006).
Antiepileptic drug polytherapy typically is recommended for those patients not achieving adequate seizure control following 2 AED monotherapy treatments (Kwan and Brodie, 2006); however, evidence-based guidelines for optimal AED combinations are not available. When selecting an adjunctive AED, a number of factors may be used to identify the optimal combination treatment, including rational criteria for a lack of PK interactions, minimized toxicity, or a consideration of MOA. A common assumption is that adding an AED with a different MOA would provide a better potential for additive or even synergistic efficacy and/or a more favorable tolerability profile than combining 2 AEDs that share the same MOA (Deckers et al, 2000; St. Louis, 2009), yet clinical experience with nonoverlapping mechanisms has not shown a consistent improvement in efficacy or tolerability in patients (Deckers et al, 2000; Brodie and Mumford, 1999; Stafstrom, 2010).
Lacosamide belongs to a novel class of functionalized amino acids and is approved for the adjunctive treatment of partial-onset seizures in adults. Lacosamide*s mode of action is proposed to be mediated by a selective enhancement of slow inactivation of voltage-gated sodium channels which may explain the anticonvulsant effects of LCM (Errington et al, 2008).
Previous analyses of pooled double blind, placebo-controlled, Phase 2/3 studies (Ben Menachem et al, 2007; Halasz et al, 2009; Chung and Sperling, 2010; Chung and Ben Menachem, 2010) have demonstrated that LCM provides additional efficacy when added to a broad range of AEDs. In addition, recent posthoc analyses (Sake et al, 2010) suggest improved tolerability and efficacy when LCM is combined with non-sodium channel blocking antiepileptic drugs (NSCB-AEDs). This excludes *traditional* SCB-AEDs, which are defined as carbamazepine, oxcarbazepine, lamotrigine, and phenytoin.

Based on the results of the posthoc analyses for LCM, future prospective studies evaluating single AED combinations (eg, LCM plus 1 other drug) are needed to better evaluate the potential for additive or synergistic effects of LCM in combination with AEDs not considered *traditional* sodium channel blockers (ie, NSCB-AEDs). Lacosamide and LEV have the potential to be an optimal treatment combination since the MOA are not overlapping (ie, enhancement of sodium channel slow inactivation and binding to synaptic vesicle protein 2A, respectively), and both drugs have favorable efficacy and tolerability profiles. Thus, the goal of the current study is to prospectively evaluate the therapeutic potential of LCM added to a stable dose of LEV in subjects with partial-onset seizures not adequately controlled by a dual LEV and SCB-AED regimen.
In the double-blind, placebo-controlled Phase 2/3 studies conducted for the development of LCM, LCM was administered in fixed titration schedules and added to stable concomitant AEDs. In contrast, the dose of LCM and concomitant AEDs is adjusted in routine clinical practice based on the patient*s individual clinical response. Since recent independent published case reports have suggested that a stepwise progressive reduction of concomitant SCB-AEDs when titrating LCM may improve tolerability and clinical outcome (Griffiths et al, 2010; Novy et al, 2011), the titration scheme in the current study was designed to optimize AED treatment conversion from a SCB-AED to LCM, and is a truer replication of clinical practice. This study will allow the dose of LCM to be titrated to an optimally effective dose as the dose of the SCB-AED is progressively withdrawn.
Further information on LCM PK, efficacy, and safety profiles, as well as nonclinical results, can be obtained from the current version of the LCM Investigator*s Brochure.

Study objective

The primary objective of this study is to assess the overall effectiveness of LCM (optimized
within the range of 200mg/day to 600mg/day) when added to a stable dose of LEV (in the
label range of 1000mg/day to 3000mg/day) with withdrawal of the concomitant SCB-AED in
subjects with partial-onset seizures not adequately controlled on their dual LEV and
SCB-AED regimen.
Other objectives of this study are to evaluate seizure reduction during the study versus
Baseline and to evaluate the safety of LCM when LCM (optimized within the range of
200mg/day to 600mg/day) is added to LEV (in the label range of 1000mg/day to 3000mg/day) with withdrawal of the concomitant SCB-AED in subjects with partial-onset

seizures not adequately controlled on their dual SCB-AED and LEV regimen.

Study design

SP0980 is a Phase 3b, prospective, multinational, open-label, single-arm, explorative study in
subjects with uncontrolled partial-onset seizures. The objective of this study is to assess the
overall effectiveness of LCM (optimized within the range of 200mg/day to 600mg/day) when
added to a stable dose of LEV (in the label range of 1000mg/day to 3000mg/day) with
withdrawal of the concomitant SCB-AED in subjects with partial-onset seizures not
adequately controlled on their dual LEV and SCB-AED regimen (defined as subjects who
have experienced on average at least 2 seizures per 28 days during the 8-week period prior to
the Screening Visit [8-week Retrospective Seizure Baseline]).
The study consists of a 4-week Screening Period, a 21-week Treatment Period (comprised of
a 9-week Dose Adjustment Period, and a 12-week Maintenance Period), and an up to a
4-week Taper/Safety Follow-Up Period.

Intervention

The objective of this study is to assess the overall effectiveness of LCM (optimized within the range of 200mg/day to 600mg/day) when added to a stable dose of LEV (in the label range of 1000mg/day to 3000mg/day) with withdrawal of the concomitant SCB-AED in subjects with partial-onset seizures not adequately controlled on their dual LEV and SCB-AED regimen (defined as subjects who have experienced on average at least 2 seizures per 28 days during the 8-week period prior to the Screening Visit [8-week Retrospective Seizure Baseline]).
The study consists of a 4-week Screening Period, a 21-week Treatment Period (comprised of a 9 week Dose Adjustment Period, and a 12 week Maintenance Period), and an up to a 4 week Taper/Safety Follow-Up Period.

Study burden and risks

during the study the patient will have several times an ECG, will have to answer questions, will undergo physical and neurological tests and blood sampling and will complete a diary. However, some of these procedures are also routinely done as part of these patients' usual epilepsy treatment.
The patients are also informed about the tests and procedures that will be done

at each visit.

Contacts

Public
UCB Biosciences Inc

8010 Arco Corporate Drive
NC 27617 Raleigh
US
Scientific
UCB Biosciences Inc

8010 Arco Corporate Drive
NC 27617 Raleigh
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject or legal representative.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and medication intake according to the judgment of the investigator.
3. Subject is male or female, at least 18 years of age.
4. Subject has a diagnosis of epilepsy with partial-onset seizures according to the International Classification of Epileptic Seizures (1981).
5. Subject is taking LEV in combination with 1 SCB-AED (defined as carbamazepine,

lamotrigine, oxcarbazepine, phenytoin, or eslicarbazepine) as adjunctive treatment for epilepsy.
6. The minimum required seizure frequency during the 8-week Retrospective Seizure Baseline is on average >=2 partial-onset seizures (IA, IB, or IC) per 28 days (based on investigator assessment of subject report) with at least 1 seizure per 4-week period within the 8-week Retrospective Seizure Baseline. Additionally, subjects must experience at least 1 seizure during the 4-week Prospective Seizure Baseline. In the case of simple partial seizures, only those with motor signs (IA1) will be counted towards meeting this inclusion criterion.
7. Subject has been maintained on a stable dose of LEV and a SCB-AED for at least 4-weeks prior to the Screening Visit (Visit 1) and during the 4-week Prospective Seizure Baseline, with or without additional concurrent stable VNS. The VNS must have been in place for at least 6 months prior to the Screening Visit (Visit 1) with constant settings for at least 4-weeks prior to the Screening Visit (Visit 1) and throughout the duration of the study.

Exclusion criteria

1. Subject has previously participated in this study or subject has previously been exposed to LCM.
2. Subject has participated in another study of an investigational medicinal product (IMP) or an experimental medical device within the last 2 months or is currently participating in another study of an IMP or a medical device.
3. Female subject who is pregnant or nursing, and/or a woman of childbearing potential who is not surgically sterile, 2 years postmenopausal or does not practice 2 combined methods of contraception, unless sexually abstinent, for the duration of the study. Male subject who does not agree to practice 2 combined methods of contraception (eg, condom, spermicide), unless sexually abstinent, for the duration of the study.
4. Subject has a history of chronic alcohol or drug abuse within the last 2 years.
5. Subject has a seizure disorder characterized primarily by isolated auras (ie, simple partial seizures without observable motor signs).
6. Subject has a history of primary generalized seizures.
7. Subject has a history of status epilepticus within the 12-month period prior to Visit 1.
8. Subject has seizures that are uncountable due to clustering (ie, an episode lasting less than
30 minutes in which several seizures occur with such frequency that the initiation and completion of each individual seizure cannot be distinguished) during the 8-week Retrospective Seizure Baseline and during the 4-week Prospective Seizure Baseline.
9. Subject has a current or previous diagnosis of pseudoseizures, conversion disorders, or other nonepileptic ictal events which could be confused with seizures.
10. Subject has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize the subject*s health or would compromise the subject*s ability to participate in this study.
11. Subject has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by

a positive response (*Yes*) to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.
12. Subject has a known hypersensitivity to any components of LCM tablets.
13. Subject has taken an AED other than the current SCB-AED and LEV during the 4-weeks prior to the Screening Visit (Visit 1), excepting 1-time use of benzodiazepines as rescue medication (less than or equal to 3 doses within 24 hours).
14. Subject has a medical condition that could reasonably be expected to interfere with drug absorption, distribution, metabolism, or excretion.
15. Subject has an acute or sub-acute progressive central nervous system disease.
16. Subject has a known history of severe anaphylactic reaction or serious blood dyscrasias.
17. Subject has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels >=2x the upper limit of normal (ULN) or has alkaline phosphatase levels >=3xULN at Visit 1.
18. Subject has impaired renal function (ie, creatinine clearance [CLcr] is lower than 30mL/min) at Visit 1. Creatinine clearance will be estimated as follows:
Adult males: CLcr = (140-age) x weight in kg/(72 x serum creatinine in mg/dL)
Adult females: CLcr = [(140-age) x weight in kg/(72 x serum creatinine in mg/dL)] x 0.85
19. Subject has sick sinus syndrome without a pacemaker, or atrioventricular (AV) block, or subject has any other clinically significant ECG abnormalities.
20. Subject has a known sodium channelopathy, such as Brugada syndrome.
21. Subject has experienced a myocardial infarction in the last 3 months.
22. Subject has New York Heart Association Class III or Class IV heart failure.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	25
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Keppra®
Generic name:	levetiracetam
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	VIMPAT®
Generic name:	lacosamide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-03-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-06-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-11-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-02-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2011-002461-37-NL
ClinicalTrials.gov	NCT01484977
CCMO	NL38748.091.12