# A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BRIVARACETAM IN SUBJECTS (>=16 TO 80 YEARS OLD) WITH PARTIAL ONSET SEIZURES

Published: 15-03-2011
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To evaluate the efficacy of BRV at doses of 100 and 200mg/day compared to PBO as adjunctive treatment in adult focal epilepsy subjects with partial onset seizures not fully controlled despite current treatment with 1 or 2 concomitant AEDsTo assess...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Neurological disorders NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON38244

**Source**
ToetsingOnline

**Brief title**
Study of Brivaracetam with partial onset seizures

### Condition

- Neurological disorders NEC

**Synonym**
epilepsy - seizure

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** UCB Biosciences GmbH
**Source(s) of monetary or material Support:** UCB BioSciences GmbH

## Intervention

**Keyword:** Brivaracetam, efficacy, safety, seizures

## Outcome measures

### Primary outcome

The primary efficacy variable is the POS (Type I) frequency per 28 days during

the 12-week Treatment Period.

The primary efficacy outcome for the USA will be the percent reduction in POS

(Type I) frequency over PBO based on ANCOVA.

The primary efficacy outcome for European authorities will be the 50% responder

rate based on percent reduction in POS (Type 1) frequency from Baseline to the

12-week Treatment Period.

### Secondary outcome

• Percent reduction in POS (Type I) frequency from Baseline to the 12-week

Treatment Period

• Categorized percent reduction in POS (Type 1) frequency from Baseline to the

12-week Treatment Period

• Seizure freedom rate (all seizure types) during the 12-week Treatment Period

• All seizure frequency (Type I + II + III) during the 12-week Treatment Period

• Time to nth (n=1, 5, 10) Type I seizure during the 12-week Treatment Period

# Study description

**Background summary**

Epilepsy is one of the most common and challenging neurological disorders. It has been estimated that over 50 million people are affected worldwide (Engel and Pedley, 1998; Sander and Shorvon, 1996; Hauser et al, 1993; Loiseau et al, 1990). The prevalence of epilepsy is around 1%. The annual incidence in developed countries is approximately 50 to 70 cases per 100,000. In developing countries, the figure is higher due to more limited obstetric services and the greater likelihood of cerebral infection and trauma. The incidence varies greatly with age, with high rates occurring in childhood, falling to low levels in early adult life, but with a second peak in those aged over 65 years. In many people, particularly children, the condition may remit, although a significant proportion will have epilepsy lifelong. The disease duration is often determined by the underlying cause. Sudden unexpected death, a complication of great concern, occurs in 1 to 5 per 1000 patient years, particularly if the seizure disorder remains uncontrolled. The treatment for epilepsy remains difficult, and there is an ongoing medical need for new AEDs. For a considerable proportion of patients, seizure freedom can still not be reached with currently available AEDs (Nasreddine et al, 2010; Kwan and Brodie, 2001).

Diagnosis of epilepsy is based on the recurrence of seizures. Seizures may be caused by an underlying brain disorder or lesion or due to genetic conditions. Characterization of the epileptic syndrome has profound implications for treatment and prognosis. The major dichotomy for the diagnosis of epilepsy being the differentiation between focal epilepsies (ie, related to a focal brain dysfunction) which are the most frequent and account for approximately 60 to 70% of all cases, and generalized epilepsy syndromes which represent approximately 25 to 30% of all epilepsy syndromes. In about 10% of cases, other specific syndromes are classified or the classification remains uncertain.

The classification of epileptic syndromes and seizure types is - and always was

- a matter of ongoing debate. First published in 1960 and last updated officially in 1981 for seizures and 1989 for epilepsies (Commission on Classification and Terminology of the International League Against Epilepsy (ILAE, 1981 and 1989), these ILAE classifications were based on concepts that, for the most part, predate modern technologies and concepts (Engel, 2006; International League Against Epilepsy [http://www.ilae-epilepsy.org]). The availability of these modern techniques, like long-term video electroencephalograms (EEG) and high-resolution magnetic resonance imaging (MRI), providing much more precise knowledge in regard to seizure type classifications and epileptic syndromes, led some epilepsy groups and scientists towards introducing competing classification systems (like the Cleveland Clinic Epilepsy Classification) and even debating how useful the currently used ILAE classification system is at all (Lüders et al, 2006).

This ongoing debate regarding the classification systems for epilepsies and seizures is also reflected within the latest Report of the Commission on Classification and Terminology (Classification Task Force) which proposes a thoroughly revised terminology and concept for the diagnosis of epilepsy syndromes and also to some extent seizure types (Berg et al, 2010). Despite this ongoing debate, for the purpose of this study the seizure type classification will follow the 1981 ILAE classification of epileptic seizures which speaks of partial seizures, classified as simple partial seizures (no alteration of consciousness), complex partial seizures (with alteration of consciousness), and secondarily generalized seizures and on the other hand defines generalized seizure types, referred to as absence seizures (typical and atypical), myoclonic seizures, clonic seizures, tonic seizures, tonic-clonic seizures, and atonic seizures. Apart from myoclonic seizures, consciousness is almost invariably impaired from the onset of the seizure (Commission on Classification and Terminology of the ILAE, 1981). Likewise, the classification of epilepsy syndromes will be used according to the 1989 ILAEpublication (Commission on Classification and Terminology of the ILAE,1989).

**Study objective**

To evaluate the efficacy of BRV at doses of 100 and 200mg/day compared to PBO as adjunctive treatment in adult focal epilepsy subjects with partial onset seizures not fully controlled despite current treatment with 1 or 2 concomitant AEDs

To assess the safety and tolerability of BRV.

**Study design**

This is a randomized, double-blind, PBO-controlled, multicenter, therapeutic confirmatory study evaluating 2 active doses of BRV. The subject population will be adults (>=16 years to 80 years) with refractory POS whether or not

secondarily generalized. Subjects under 18 years may be included only where legally permitted and ethically accepted. Subjects will complete an 8-week prospective Baseline Period, followed by a 12-week Treatment Period. Subjects receiving concomitant LEV are excluded from this study. Subjects may be eligible for conversion to a LTFU study (N01379) upon completion of the Treatment Period. There is a 4-week Down-Titration Period followed by a 2-week Study Drug Free Period for subjects not entering the LTFU study.

A 1:1:1 central randomization (random permuted blocks) stratified for country, LEV use (LEV naïve versus prior LEV use only), and number of AEDs previously used but discontinued prior to study entry (<=2 versus >2 AEDs) will be used to ensure the balance across treatment groups (PBO, BRV 100mg/day, BRV 200mg/day) within each combination of stratification levels. Randomization will not be stratified by study center due to the expected small number of randomized subjects per study center.

No restrictions are placed on the proportion of randomized subjects within each stratification level, either overall or on a regional basis.

At UCB Clinical Trial Supply, kit numbers will be allocated according to the package list generated by a validated program by UCB. This list will be provided to the Interactive Voice Response System (IVRS).

Concomitant LEV is exclusionary. Furthermore, LEV use within 90 days prior to study entry
(Visit 1) is not allowed.

**Intervention**

Oral film-coated tablets of BRV 10mg, BRV 25mg, BRV 50mg, and matching PBO tablets to oral film-coated 10mg, 25mg, and 50mg BRV tablets will be used in this study. The tablets of BRV (10mg, 25mg, 50mg) or matching PBO will be packaged in blister cards that are cross-designed in such a way as to keep the blind.

After an 8-week Baseline Period and once the subject has fulfilled the eligibility criteria, he/she will be randomized to enter the double-blind Treatment Period (V3 to V7), which will last 12 weeks.

During the Treatment Period, subjects will be treated with BRV 100mg/day, BRV 200mg/day, or matching PBO, in a double-blinded manner. Study medication should be given as 2 equally divided doses administered twice daily. The first intake of newly dispensed study medication should occur in the evening of the day of the visit. Subjects should take tablets according to instructions provided by Investigator.

At the end of the Treatment Period (V7), the subject will either enter the LTFU

study N01379 or down-titrate. Subjects who continue treatment will enter the LTFU study at a dose of BRV 150mg/day.

The Down-Titration Period (4 weeks) will consist of the following:
• For subjects randomized to 100mg/day, the Down-Titration Period will consist of the following: 1 week at 50mg/day, 1 week at 20mg/day, followed by 2 weeks of PBO.
• For subjects randomized to 200mg/day, the Down-Titration Period will consist of the following: 1 week at 150mg/day, 1 week at 100mg/day, 1 week at 50mg/day, followed by 1 week at 20mg/day.

The down-titration procedure needs to be applied in case of early discontinuation.

**Study burden and risks**

After taking the medication, you might experience one or more side effects or discomforts. The most common side effects from taking brivaracetam include: somnolence (sleepiness), dizziness, insomnia (difficulty and/or lack of sleep), constipation, and blurred vision. Also you may experience vertigo (dizziness characterized by a sensation of whirling motion), headache, nausea (stomach upset), vomiting, abdominal pain (stomach pain), diarrhea, dry mouth, toothache, asthenia (lack or loss of strength and energy), fatigue (feeling tired), feeling drunk, gait disturbance (balance or walk disorder), infections (e.g. nasopharyngitis , upper respiratory and/or urinary), anorexia ( decreased appetite), back pain, muscle pain, pain in extremities, balance disorder, abnormal coordination, diplopia (double vision), postural dizziness (related to changes in position), nystagmus (uncontrollable and rapid movement of the eyeball in any direction) paraesthesia (numbness), tremor (shakiness), depression (feelings of sadness/low mood), euphoric (excessively happy/elevated) mood, nervousness, irritability, dysmenorrhoea (abnormally difficult or painful menstruation ) , cough, nasal congestion, pharyngolaryngeal pain, throat irritation, pruritus (itching ), hypotension (low blood pressure), orthostatic hypotension ( low blood pressure related with changes in position) , neutropenia / neutrophil count decreased( decrease of white blood cell number). Some of the side effects may be more frequent when first starting the medicine. Some of the side effects may bother you when operating a machine. Harm to an unborn child.
An increased risk of suicide and suicidal thoughts has been seen in people who take these types of medications.

If you decide to participate, you will be asked to come back to see your study doctor for at least 7 visits and a maximum of about 9 visits. The total duration of the study is approximately 26 weeks.
At each visit, your study doctor will make sure that you meet all study requirements and decide if you may continue in the study. After a first visit (Screening visit) at which all the necessary information about your health is

collected and scheduling of the different examinations arranged, you will be asked to return once a month for Visits 2 and 3. You will start the study medicine on the evening of Visit 3.
Your study doctor will supply you with the study medicine in the form of tablets to take by mouth. You will have to take 2 tablets in the morning and 2 tablets in the evening. At each visit, your study doctor will give you enough tablets to last to the next visit and he/she will give you clear instructions about how to take them. The study medication must be taken ONLY by the person for whom it was prescribed.
You will be contacted by phone 1 week after starting study medicine. You will be asked to return 1 week later for Visit 4 and then 2 weeks later for Visit 5. You will be asked to return once a month for Visits 6 and 7.
After Visit 7, your study doctor may suggest that you enter a long-term follow-up study (all patients in this long-term follow-up study will receive brivaracetam) and continue with regular visits, but you may decide together with your study doctor to stop the study medicine. For your own safety and comfort, stopping the medicine will be done gradually over 4 weeks if you choose not to enter the long-term follow-up study. You should never stop the medicine abruptly (quickly). During the 4 week period, you will take 3 tablets in the morning and 3 tablets in the evening. You will be asked to return at the end of the 4 week period of gradually coming off the study medicine. Finally, you will be asked to return 2 weeks after taking the last tablets for a final check on your health.
During this study, you will have physical and neurological examinations conducted at Visit 1 and 3 and at the end of the study. Your blood pressure and pulse rate will be measured at each visit. Your height will be measured as Visit 1. You will be weighed at all visits.
An electrocardiogram (ECG), which is a recording of the heart activity, will be done at Visit 1, Visit 4, Visit 5, and at Visit 7 or when you decide to stop the study medicine, and possibly at the end of the study.
Urine samples will be obtained a maximum of eight times during the study for standard safety tests. Additional urine samples may be required if any repeat tests need to be performed.
Blood samples (maximum 21ml per blood sampling) will be taken a maximum of 8 times during the study for standard safety tests, to measure the amount of brivaracetam and to measure the amount of other antiepileptic drugs in your body. Additional blood samples may be required if any repeat tests need to be performed for standard safety tests. The total amount of blood that will be taken for the entire study is about 170ml.
If you have not had one within the last 5 years, a routine electroencephalogram (EEG, which is a tracing of brain activity) will be done between Visit 1 and 3, to check the electrical activity of your brain. A brain scan (either Computed Tomography (CT) or Magnetic Resonance Image (MRI) which are both tests that produce pictures of the brain) will also be done between Visits 1 and 3, if you have not had one within the last 2 years.
You will be asked to keep a daily diary to record all the seizures that you have and other information about your health during the study. Your study

doctor will ask you how you are feeling and whether you are having any problems, at each of your visits. At 2 visits, you will be asked to complete 2 health-related questionnaires and at 1 of those visits you are also asked to complete an evaluation scale.

# Contacts

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**Scientific**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:
1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent form is signed and dated by the subject or by the parent(s) or legal representative. The consent form or a specific assent form, where required, will be signed and dated by minors.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol

(eg, able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.
3. Subjects (male or female) from 18 to 80 years, both inclusive.
4. Subjects with a body weight >=40kg.
5. Female subjects without childbearing potential (premenarcheal, postmenopausal for at least 2 years, bilateral oophorectomy or tubal ligation, complete hysterectomy) are eligible. Female subjects with childbearing potential are eligible if they use a medically accepted contraceptive method. Oral or depot contraceptive treatment with at least 30µg ethinylestradiol per intake [or 50µg ethinylestradiol per intake if associated with any strong enzyme inducer (eg carbamazepine, phenobarbital, primidone, phenytoin, oxcarbazepine, St. John*s Wort, rifampicin)], monogamous relationship with vasectomized partner, or double-barrier contraception are acceptable methods. The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the Investigator of any potential change in status. Abstinence will be considered as an acceptable method of contraception if the Investigator can document that the subject agrees to be compliant.
6. Well-characterized focal epilepsy/epileptic syndrome according to the 1989 International League Against Epilepsy (ILAE) classification.
7. Presence of an EEG reading compatible with the clinical diagnosis of focal epilepsy within the last 5 years.
8. Presence of a brain MRI/computed tomography (CT) scan performed within the last 2 years.
9. Subjects having at least 8 Type I seizures [POS; focal seizures (according to the 1981 ILAE classification)] during the 8-week Baseline Period with at least 2 Type I seizures during each 4-week interval of the Baseline Period.
10. Subjects having at least 2 partial onset seizures whether or not secondarily generalized per month during the 3 months preceding V1.
11. Subjects being uncontrolled while treated by 1 or 2 permitted concomitant AED(s). Vagal Nerve Stimulation (VNS) is allowed and will be counted as a concomitant AED.
12. Permitted concomitant AED(s) and VNS being stable and at optimal dosage for the subject from at least 1 month (3 months for phenobarbital, phenytoin, and primidone) before V1 and expected to be kept stable during the Baseline and Treatment Period. Benzodiazepine taken more than once a week (for any indication) will be considered as a concomitant AED.

## Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:
1. Subject previously randomized within this study or any other prior study with BRV as a dosing arm.
2. Seizure type IA (1981 ILAE classification) nonmotor as only seizure type.
3. Subject has participated in another study of an investigational medication (or a medical device) within the last 30 days or is currently participating in another study of an investigational medication (or a medical device).

4. Subject is currently treated with LEV.
5. Subject has taken LEV within 90 days prior to V1.
6. Subject has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the subject*s ability to participate in this study.
7. Subject has a known hypersensitivity to any components of the investigational medicinal product or comparative drugs as stated in this protocol.
8. Subject not able to read and understand the informed consent form, or seizure diary card instructions.
9. Subject has obvious cognitive impairment or mental retardation as per Investigator assessment.
10. Subjects whose seizures could not be reliably counted on a regular basis due to their fast and repetitive occurrence (clusters or flurries).
11. Subject has history or presence of status epilepticus during the year preceding V1 or during Baseline.
12. Subject has history or presence of known psychogenic nonepileptic seizures.
13. Subject on felbamate with less than 18 months exposure before V1.
14. Subject currently on vigabatrin. Subject with history of vigabatrin use but either no visual fields examination report available including standard static (Humphrey or Octopus) or kinetic perimetry (Goldman) or results of these examinations are abnormal.
15. Subject taking any drug with possible central nervous system (CNS) effects except if stable from at least 1 month before V1 and expected to be kept stable during the Treatment Period.
16. Subject taking any drug that may significantly influence the metabolism of BRV cytochrome P450 (potent inducers) except if the dose has been kept stable at least 1 month before V1, and is expected to be kept stable during the Treatment Period.
17. Subject has history of cerebrovascular accident, including transient ischemic attack, in the last 6 months.
18. Subject is suffering from severe cardiovascular disease or peripheral vascular disease
19. Subject has presence of any sign (clinical or imaging techniques) suggesting rapidly progressing (ie, not expected to stay stable during study participation) brain disorder or brain tumor. Stable arteriovenous malformations, meningiomas, or other benign tumors may be acceptable.
20. Subject has any clinical conditions (eg, bone marrow depression, chronic hepatic disease, and/or severe renal impairment) which impair reliable participation in the study or necessitate the use of medication not allowed by protocol.
21. Subject has presence of a terminal illness.
22. Subject has presence of a serious infection.
23. Subject has history of severe adverse hematologic reaction to any drug.
24. Subject is suffering from severe disturbance of hemostasis.
25. Subject has impaired hepatic function: ALT/SGPT (alanine aminotransferase/serum glutamic pyruvate transaminase), AST/SGOT (aspartate aminotransferase/serum glutamic oxaloacetic transaminase), alkaline phosphatase of more than 2 times the upper limit of the reference range.
26. Gamma-glutamyltransferase (GGT) values of more than 3 times the upper limit of the reference range. A result of GGT exceeding 3 times the upper limit can only be

accepted if attributable to hepatic enzyme induction caused by concomitant antiepileptic treatment and other hepatic enzymes are below 2 times the upper limit of the reference range.
27. Subject has clinically significant deviations from reference range values for laboratory parameters: creatinine clearance calculated <30mL/min, platelets <100,000/µL, or neutrophil cells <1,800/µL.
28. Subject has clinically significant ECG abnormalities according to the Investigator.
29. Subject has a lifetime history of suicide attempt (including an active attempt, interrupeted 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 5 of the Columbia-Suicide Severity Rating Scale at screening
30. Subject has ongoing psychiatric disease other than mild controlled disorder.
31. Subject has known allergic reaction or intolerance to pyrrolidine derivatives and/or investigational product excipients.
32. Subject has known multiple drug allergies or severe drug allergy.
33. Subject is pregnant or lactating woman.
34. Subject has known alcohol or drug addiction or abuse within the last 2 years.
35. Investigators, co-Investigators, their spouses or children, or any study collaborators. If the Investigator has any other doubts concerning the eligibility, he/she should consult UCB Study Physician or representative for clarification.

# Study design

## Design

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|---|---|
| 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): | 09-03-2012 |
| Enrollment: | 16 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | N/A |
| Generic name: | Brivaracetam |

# Ethics review

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|---|---|
| Approved WMO Date: | 15-03-2011 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 25-07-2011 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 08-09-2011 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 30-12-2011 |
| Application type: | Amendment |
| Review commission: | MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht) |
| Approved WMO Date: | 02-01-2012 |
| Application type: | Amendment |
| Review commission: | MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht) |
| Approved WMO Date: | 16-01-2012 |
| Application type: | Amendment |
| Review commission: | MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht) |

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|---|---|
| Approved WMO Date: | 16-02-2012 |
| Application type: | Amendment |
| Review commission: | MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht) |
| Approved WMO Date: | 19-04-2012 |
| Application type: | Amendment |
| Review commission: | MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht) |
| Approved WMO Date: | 01-06-2012 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC 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 | EUCTR2010-019361-28-NL |
| ClinicalTrials.gov | NCT01261325 |
| CCMO | NL34940.068.11 |