OPEN-LABEL, SINGLE-ARM, MULTICENTER, LONG-TERM STUDY TO EVALUATE SAFETY AND EFFICACY OF BRIVARACETAM USED AS ADJUNCTIVE TREATMENT IN PEDIATRIC SUBJECTS WITH EPILEPSY;P/297/2019 (POS indication)

Published: 01-05-2017
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Primary objective* To document the long-term safety and tolerability of BRVSecondary objective* To assess the efficacy of BRV during long-term exposureOther objectives* To explore direct cost parameters* To assess the effect of BRV on behavior using...

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

Summary

ID

NL-OMON50183

Source
ToetsingOnline

Brief title
N01266

Condition

- Seizures (incl subtypes)

Synonym
epilepsy; seizures

Research involving
Human

Sponsors and support

Primary sponsor: UCB Pharma
Source(s) of monetary or material Support: UCB Biopharma SA

Intervention

Keyword: Brivaracetam, Epilepsy, Repeated electroencephalographic seizures

Outcome measures

Primary outcome

Incidence of treatment-emergent adverse events (TEAEs) during the study.

Incidence of treatment-emergent serious adverse events (SAEs) during the study

Secondary outcome

For subjects *2 years of age (based on daily record card (DRC) data):

1. Absolute change in 28-days adjusted partial-onset seizures (POS) frequency

from Baseline to the end of the Evaluation Period in subjects with POS only

2. Percent change in 28-days adjusted partial-onset seizures (POS) frequency

from Baseline to the end of the Evaluation Period in subjects with POS only

3. 50% responder rate for total seizures (all types)

For subjects <2 years of age (based on EEG data [recorded at least 24 hours])

or subjects with typical absence seizures (based on EEG data):

4. Absolute change in average daily frequency of partial-onset-seizures (POS)

in subjects with POS only

5. Percent change in average daily frequency of partial-onset-seizures (POS) in

subjects with POS only

6. 50% responder rate for total seizures (all types)

Study description

Background summary

N01266 is designed for pediatric subjects *1 month to <17 years of age who have completed core studies (LTFU subjects) and for at least 100 subjects *4 years to <17 years of age with POS who have not participated in a core study (directly enrolled subjects). The total enrollment planned for N01266 is approximately 600 subjects.

N01266 will provide long-term safety and tolerability data on BRV in pediatric subjects with epilepsy, while providing access to BRV for subjects who may benefit from long-term treatment. The enrollment of directly enrolled subjects is intended to provide both long-term safety and tolerably data and efficacy data for subjects 4 years to <17 years of age with POS to supplement data collected for subjects with POS in N01263.

Study objective

Primary objective
* To document the long-term safety and tolerability of BRV

Secondary objective
* To assess the efficacy of BRV during long-term exposure

Other objectives
* To explore direct cost parameters
* To assess the effect of BRV on behavior using the Achenbach CBCL in subjects *18 months of age
* To explore the effect of BRV on cognition using the BRIEF-P/BRIEF in subjects *2 years of age
* To assess the effect of BRV on cognition using the Bayley-III scales in subjects <18 months of age (applicable only to LTFU subjects enrolled in English-speaking countries)
* To explore the effect of BRV on health-related quality of life (HRQoL) using the PedsQL in subjects *1 month of age

Study design

This is a Phase 3, open-label, single-arm, multicenter, long-term study to evaluate the safety and efficacy of brivaracetam (BRV) in children with epilepsy. This study is designed for pediatric subjects *1 month to <17 years

of age who have completed other pediatric BRV studies (herein referred to as *long-term follow-up* [LTFU] subjects) and for at least 100 subjects *4 years to <17 years of age with POS who had not previously enrolled in a pediatric BRV study (herein referred to as *directly enrolled subjects*), with a planned total enrollment of approximately 600 subjects.

Brivaracetam (tablet and oral solution) should be administered twice daily (bid) in 2 equally divided doses. All LTFU subjects must be able to tolerate the minimum dose specified in the core study to be eligible for entry into the Evaluation Period of N01266. All directly enrolled subjects must be able to tolerate at least 1mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266, as indicated in Section 7.2.

Subjects will receive BRV treatment in this study for at least 3 years, until approval of BRV has been obtained for pediatric subjects in their age range, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines, or until the investigational product development in the related age range of the pediatric population is stopped by the Sponsor, whichever comes first.

Intervention

Brivaracetam 10mg/ml - 300ml solution for oral use.
Brivaracetam - 10mg/25mg/50mg tablets for oral use.

Study burden and risks

Subjects will receive BRV treatment in this study for at least 3 years, until approval of BRV has been obtained for pediatric subjects in their age range, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines, or until the investigational product development in the related age range of the pediatric population is stopped by the Sponsor, whichever comes first.

The LTFU subjects will enter directly into the Evaluation Period at the Entry Visit (EV) and will continue BRV treatment at the individualized dose they were receiving at the completion of their core study. Directly enrolled subjects will enter N01266 at the Screening Visit (ScrV) and then participate in up to 3 weeks of an Up-Titration Period. If a directly enrolled subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than 1mg/kg/day) for 7±2 days during the Up-Titration Period, the subject will attend the EV and enter the Evaluation Period on that dose.

For LTFU subjects, the EV is the first study visit. For directly enrolled subjects, the EV occurs after subjects have completed the ScrV and at least 1

Titration Visit (TV), and have maintained acceptable tolerability and seizure control on the same daily dose of BRV (no lower than the minimum specified dose) for 7±2 days of the Up-Titration Period. For subjects who continue in this study until it ends, the Evaluation Period will extend from the EV until the final evaluation visit (Final Visit, FV). For subjects who prematurely discontinue the study, the Evaluation Period will last from the EV until the Early Discontinuation Visit (EDV), followed by a maximum 4-week Down-Titration Period, a 2-week Safety (Drug-Free) Period, and a final Safety Visit (SV). Subjects already enrolled in N01266 may participate in EP0065 (an intravenous [iv] BRV study for pediatric subjects), if eligible, and then resume participation in N01266.

During the Evaluation Period, Minimal Evaluation Visits (MEVs) and Full Evaluation Visits (FEVs) will be performed alternatively every month during the first 3 months and every 3 months thereafter, with a Yearly Evaluation Visit (YEV) every 12 months.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met as specified. , # Inclusion criteria for all subjects, - An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the parent(s) or legal representative(s). The Consent form or a specific Assent form, where required, will be signed and dated by minors., - 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 (including BRV oral solution or tablets) according to the judgment of the Investigator., - For female subjects, the subject is, 1) Not of childbearing potential OR Of childbearing potential, and
- Is not sexually active
- Has a negative pregnancy test, OR , 2) Of childbearing potential, and Is sexually active, Has a negative pregnancy test, - Understands the consequences and potential risks of inadequately protected sexual activity, understands and properly uses contraceptive methods, and is willing to inform the Investigator of any contraception changes. Medically acceptable contraceptive methods for the study include, but are not limited to:, Oral or depot contraceptive treatment with at least ethinylestradiol 30*g per intake or ethinylestradiol 50*g per intake if also taking one of the following: carbamazepine, phenobarbital, primidone, phenytoin, oxcarbazepine, St. John's Wort, or rifampicin, Barrier contraception: intrauterine device, diaphragm with spermicide, male or female condom with spermicide, Abstinence from sexual intercourse, # Inclusion criteria for LTFU subjects only, - Male or female subjects having participated in a core study with BRV with a confirmed diagnosis of epilepsy and for whom a reasonable benefit from long-term administration of BRV is expected., # Inclusion criteria for directly enrolled subjects only, - Subject is a male or female *4 years to <17 years of age., - Subject has a clinical diagnosis of POS according to the ILAE classification., - Subject has an EEG compatible with the clinical diagnosis of POS. , - Subject has been observed to have uncontrolled POS after an adequate course of treatment (in the opinion of the Investigator) with at least 1 AED (concurrently or sequentially)., - Subject had at least 1 seizure (POS) during the 3 weeks before the ScrV., - Subject is taking at least 1 AED. All AEDs need to be at a stable dose for at least 7 days before the ScrV. Vagal nerve stimulator stable for at least 2 weeks before the ScrV is allowed and will be counted as a concomitant AED. Benzodiazepines 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 are met as specified. , # Exclusion criteria for all subjects, -Subject is a pregnant or nursing female., -Subject has severe medical, neurological, or psychiatric disorders or laboratory values, which may have an impact on the safety of the subject., -Subject has planned participation in any clinical study of another investigational drug or device., -Subject has any medical condition, which in the Investigator*s opinion, warrants exclusion., -Subject has >1.5x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >1.0xULN total bilirubin (*1.5xULN total bilirubin if known Gilbert*s syndrome)., -Subject has chronic liver disease., # Exclusion criteria for LTFU subjects only, - Subject had hypersensitivity to BRV or excipients or comparative drugs as stated in this protocol during the course of the core study., - Subject had poor compliance with the visit schedule or medication intake in the core study., - Subject *6 years of age has a lifetime history of suicide attempt (including actual attempt,interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response (*Yes*) to Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at the EV. , If a subject has active suicidal ideation without a specific plan as indicated by a positive response (*Yes*) to Question 4 of Columbia-Suicide Severity Rating Scale (C-SSRS) at the EV, the subject should be referred immediately to a Mental Healthcare Professional and may be excluded from the study based upon the Investigator*s judgment of benefit/risk of continuing the subject in the study/on study medication., # Exclusion criteria for directly enrolled subjects only, - Subject has previously received BRV., - Subject had concomitant use of LEV at the ScrV. In addition, the use of LEV is prohibited for at least 4 weeks prior to the ScrV., - Subject has epilepsy secondary to a progressive cerebral disease or tumor, or any other progressively neurodegenerative disease. Stable arteriovenous malformations, meningiomas or other benign tumors may be acceptable according to Investigator*s opinion., - Subject has a history of primary generalized epilepsy., - Subject has a history of status epilepticus in the month immediately prior to the ScrV or during the Up Titration Period., - Subject has a history or presence of pseudoseizures., - Subject is suffering only from febrile seizures., - Subject is on felbamate with less than 18 months continuous exposure. Subject who has taken felbamate for a combined duration of treatment and wash out of <18 months before the ScrV., - Subjects treated with vigabatrin who have visual field defects., - Subject has an allergy to pyrrolidone derivatives or investigational product excipients or a history of multiple drug allergies., - Subject has any clinically significant acute or chronic illness as determined during the physical examination or from other information available to the Investigator (eg, bone marrow depression, chronic hepatic disease, severe renal impairment, psychiatric disorder)., - Subject has an underlying disease or is receiving a treatment that may interfere with the

absorption, distribution, metabolism, and elimination of the study drug. , - Subject has any medical condition that might interfere with his/her study participation (eg, serious infection or scheduled elective surgery)., - Subject has a terminal illness., - Subject has any clinically significant deviations from reference range values for laboratory parameters as determined by the Investigator., - Subject has a clinically relevant ECG abnormality according to the Investigator., - Subject had major surgery within 6 months prior to the ScrV., - Subject received any investigational drug or device within the 30 days prior to the ScrV. The use of AEDs marketed for adults but not approved for pediatric use is not considered to be *investigational* for the purposes of this study., - Investigators* and co Investigators* children may not be included as subjects in the study., - Subject has a lifetime history of suicide attempt (including an actual 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 C SSRS Baseline/Screening at the ScrV.

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:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Briviact
Generic name:	Brivaracetam
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-05-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-10-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2011-000374-60-NL
ClinicalTrials.gov	NCT01364597
CCMO	NL61397.078.17

Study results

Summary results
Trial never started

First publication
31-05-2022