A MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE PHARMACOKINETICS, EFFICACY, AND SAFETY OF BRIVARACETAM IN NEONATES WITH REPEATED ELECTROENCEPHALOGRAPHIC SEIZURES

Published: 11-04-2017
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This study has the purpose to assess the pharmacokinetic (the science determining the fate of substances administered to the human body), safety and efficacy of brivaracetam (the study drug) in neonates who have seizures that are not adequately...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Encephalopathies
Study type	Interventional

Summary

ID

NL-OMON50223

Source
ToetsingOnline

Brief title
PETITE

Condition

- Encephalopathies

Synonym
repeated electroencephalographic seizures; seizures

Research involving
Human

Sponsors and support

Primary sponsor: UCB Pharma
Source(s) of monetary or material Support: de opdrachtgever;UCB Biopharma SPRL

Intervention

Keyword: BRIVARACETAM, ELECTROENCEPHALOGRAPHIC SEIZURES, NEONATES

Outcome measures

Primary outcome

1. Plasma concentration of brivaracetam (BRV) 30-60 min after the BRV infusion

on day 1

2. Plasma concentration of brivaracetam (BRV) 2-4 hours after the BRV infusion

on day 1

3. Plasma concentration of brivaracetam (BRV) 8-12 hours after the BRV infusion

on day 1

4. Plasma concentrations of BRV on other occasions

5. Plasma concentration of the BRV metabolite ucb-42145 (acid) 30-60 min after

the BRV infusion on day 1

6. Plasma concentration of the BRV metabolite ucb-42145 (acid) 2-4 hours after

the BRV infusion on day 1

7. Plasma concentration of the BRV metabolite ucb-42145 (acid) 8-12 hours after

the BRV infusion on day 1

8. Plasma concentration of the BRV metabolite ucb-100406-1 (hydroxy) 30-60 min

after the BRV infusion on day 1

9. Plasma concentration of the BRV metabolite ucb-100406-1 (hydroxy) 2-4 hours

after the BRV infusion on day 1

10. Plasma concentration of the BRV metabolite ucb-100406-1 (hydroxy) 8-12 hours after the BRV infusion on day 1

11. Plasma concentration of the BRV metabolite ucb-107092-1 (hydroxyacid) 30-60 min after the BRV infusion on day 1

12. Plasma concentration of the BRV metabolite ucb-107092-1 (hydroxyacid) 2-4 hours after the BRV infusion on day 1

13. Plasma concentration of the BRV metabolite ucb-107092-1 (hydroxyacid) 8-12 hours after the BRV infusion on day 1

14. Area under the BRV plasma concentration time curve

15. Distribution volume of BRV

16. Plasma clearance of BRV

17. Plasma concentration of the concomitant antiepileptic drug phenobarbital AEDs if administered

Secondary outcome

1. Percentage of responders to brivaracetam (BRV) treatment from Baseline to 3 hours after the initial BRV dose

2. Percentage of subjects with at least 80% reduction in nonsevere seizure burden from Baseline to 3 hours after the initial BRV treatment

3. Percentage of subjects with at least 50% reduction in severe seizure burden from Baseline to 3 hours after the initial BRV treatment

4. Absolute change in average seizure burden measured by continuous video-electroencephalography (VEEG) from Baseline to the end of the 96-hour Evaluation Period

5. Percent reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period

6. Percentage of BRV responders at the end of the 96-hour Evaluation Period

7. Percentage of subjects who are seizure-free (100% reduction in seizure burden from Baseline) at 24 hours following the start of initial BRV treatment, categorized by subjects with nonsevere or severe seizure burden at Baseline

8. Time to reduction in seizure burden for BRV responders

9. Percentage of Subjects with Seizure Freedom at the end of Down-Titration Period

10. Percentage of Subjects with at least 50% reduction in electroencephalographic neonatal seizures (ENS) frequency per hour from Baseline to the end of the 96-hour Evaluation Period

11. Percentage of subjects who are seizure-free by time interval over the 96-hour evaluation period

12. Absolute change of clinical seizures correlated with continuous VEEG from Baseline to the end of the 96-hour Evaluation Period

13. Absolute change of clinical seizures correlated with continuous VEEG by time interval over the 96-hour evaluation period

14. Percentage of Subjects with clinical seizures correlated with continuous VEEG from Baseline to the end of the 96-hour Evaluation Period

15. Percentage of Subjects with clinical seizures correlated with continuous VEEG by time interval over the 96-hour evaluation period

16. Absolute change from Baseline in clinical seizure burden by time interval over the 96-hour evaluation period

17. Percentage change from Baseline in clinical seizure burden by time interval over the 96-hour evaluation period

18. Categorized percentage change from Baseline to the end of the 96- hour Evaluation Period in seizure burden

19. Percentage of responders to BRV treatment by time interval over the 96-hour evaluation period

20. Percentage of subjects who switch over from BRV to another antiepileptic drug (AED) during the 96-hour Evaluation Period

21. Percentage of responders to other treatment from Baseline to the end of the 96-hour Evaluation Period

22. Percentage of responders to other treatment by time interval over the 96-hour evaluation period

Study description

Background summary

The PETITE study is about the drug brivaracetam (study drug). Brivaracetam is approved in Europe for oral and intravenous use as add-on therapy to other medication to treat focal seizuresin patients 4 years of age and older. In the US brivaracetam is approvd as stand-alone and add-on therapy to treat focal epilepsy, for oral use in patients 4 years of age and older and for oral and intravenous use in patients 16 years of age and older.

Brivaracetam is not approved for the treatment of newborn children with electroencephalo-graphic seizures. The purpose of the current study is to investigate this indication in this population.

An electroencephalographic seizure is an uncontrolled neuronal discharge in any part of the brain and may be caused by encephalopathy (different syndromes of bad functioning of the brain). An electroencephalogram (EEG), also called brain movie, is a test that detects electrical activity in the brain using small, flat metal discs (electrodes) attached to the scalp. This activity shows up as

wavy lines on an EEG recording. In this study the EEG is coupled in parallel with a video recorder to align seizures and brain electrical activity.

Study objective

This study has the purpose to assess the pharmacokinetic (the science determining the fate of substances administered to the human body), safety and efficacy of brivaracetam (the study drug) in neonates who have seizures that are not adequately controlled with other treatments, and to identify the best dose of the study drug.

This study aims to determine the fate of the study drug administered to the child and to identify the optimal dose of the study drug.
The primary objective of this study is to evaluate the PK of BRV in neonates who have seizures that are not adequately controlled with previous AED treatment, and to identify the optimal BRV dose (Exploratory Cohort) for the treatment of subjects enrolled into the Confirmatory Cohorts of this study. Secondary objectives include the evaluation of the short-term safety and tolerability of BRV in neonates and the evaluation of the efficacy of BRV in severe and nonsevere seizure burden (defined as total minutes of ENS per hour) in neonates with seizures that are not adequately controlled with previous AED treatment.

Study design

Screening
The study starts with a Screening Period to see whether the child may participate in this study. This study is designed with a 2-step approach: to confirm or adjust the expected dosing in the first step (Exploratory Group), and to evaluate the efficacy of the study drug in the second step (Confirmatory Group).

The study drug brivaracetam will be given intravenously (directly into the vein).

Exploratory group:
In this Exploratory group (first step), the child will be treated with AEDs per standard of care. Should the standard medication not help controlling seizures, the child will enter the 48-hour Evaluation Period and receive up to 4 doses of the study drug. The study drug will be given intravenously (directly into the vein). The study drug will be dosed at the lower range of the dose used in children and adult patients. Therefore, treatment effects cannot be guaranteed. To ensure the child*s seizures are effectively treated during the Evaluation Period, the administration of AEDs per standard of care will continue.

Confirmatory group:

The child will participate in the Confirmatory Group. This means the child will be treated in the Screening Period with one or more of the following anti-epileptic drugs (AEDs) per standard of care for the treatment of neonatal seizures: phenobarbital (PB), midazolam (MDZ), phenytoin (PHT), levetiracetam (LEV; at a dose of *60mg/kg/day), or lidocaine (LDC). .

In this Confirmatory group (second, the child will be treated with AEDs per standard of care. Should the standard medication not help controlling seizures, the child will enter the 96-hour Evaluation Period and receive the study drug in intervals of 12 hours at a dose based on the results of the Exploratory Group.

During the Evaluation Period a continuous video-EEG will be recorded. In case the child does not need or not benefit from study drug treatment, the study doctor will propose not to continue the treatment after completion of the Evaluation Period. An extra safety assessment will be performed 30 days after final study drug administration then. Depending on the age of the newborn child at the time of enrollment, and whether or not the child would benefit from continued study treatment, the individual study duration may be longer.

In case the child does not need or not benefit from study drug treatment, the study doctor will propose not to continue the treatment after completion of the Evaluation Period. An extra safety assessment will be performed 30 days after final study drug administration then. Depending on the age of the newborn child at the time of enrollment, and whether or not the child would benefit from continued study treatment, the individual study duration may be longer.

Extension Period
Newborns who benefit from study drug treatment may enter the Extension Period. Newborns participating in the Extension Period need to stay at the study site if the study drug is administered intravenously. Newborns able to swallow oral study drug are allowed to be treated at home.

If the child enters the Extension Period, the route of administration of the study drug could be replaced by administration of oral solution, if this is appropriate for the child.
If your study doctor considers at any time that the study drug is not working for the child, another drug will be used right away, as considered appropriate by the study doctor.
30 days after final study drug administration an extra safety assessment will also be performed in this phase. In this case the total study duration could last up to 75 days.

Follow-up Study
At the end of the current study, all newborns who benefit from study drug treatment will be offered entry into a Follow-up study, if they meet the

eligibility criteria for that study.

Intervention

brivaracetam 10mg/ml - 5ml vial (sterile solution for intravenous infusion)
brivaracetam 10mg/ml - 300ml oral solution for use

Study burden and risks

Participation in the study could last up to a maximum of 75 days in total. During that time, the patient will stay at the hospital NICU in first instance. During the extension period, newborns able to swallow oral study drug are allowed to be treated at home. Newborns participating in the extension period need to stay at the study site if the study drug is administered intravenously or via the enteral route.
For an overview of the risks and benefits associated with participation in this study, see also the informed consent form.

Contacts

Public
UCB Pharma

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BE
Scientific
UCB Pharma

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BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. An Independent Ethics Committee (IEC)-approved written ICF is signed and dated by the parent(s) or legal representative(s).
2a. Confirmation on VEEG of *2 minutes of cumulative ENS or *3 identifiable ENS prior to entering the Evaluation Period (ENS is defined as a seizure lasting for at least 10 seconds on VEEG), despite receiving previous AED treatment for the treatment of electroencephalographic seizures.
The occurrence of ENS during an up to 1-hour period must be confirmed either by the local or central VEEG reader prior to drug administration. Preferably, the central VEEG reader should confirm the required ENS.
3. Subject is male or female and must be at least 34 weeks of CGA. In addition, term neonates up to 27 days of PNA and preterm neonates up to 40 weeks of PMA and 27 days of PNA can be enrolled.
4. Subject weighs at least 2.3kg at the time of enrollment.
5. Subjects with or without concomitant hypothermia treatment.

Exclusion criteria

1a. Subject receiving AED treatment other than PB, MDZ, PHT, LEV (*60mg/kg/day), or LDC for the treatment of seizures prior to or at the time of enrollment (Confirmatory Cohorts only).
2. Subject with seizures responding to previous AED treatment immediately prior to BRV treatment, pyridoxine treatment, or correction of metabolic disturbances (hypoglycemia, hypomagnesemia, or hypocalcemia).
3. Subject requires extra corporeal membrane oxygenation.
4. Subject has seizures related to prenatal maternal drug use or drug withdrawal.
5. Subject has known severe disturbance of hemostasis, as assessed by the Investigator.
6. Subject has a poor prognosis for survival, as judged by the Investigator.
7a. Subject has 2x upper limit of normal (ULN) of any of the following: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), with the following exception:
For subjects with perinatal asphyxia, elevation of AST, ALT or ALP <5x ULN is acceptable, if initial and peak elevation of liver function tests (LFTs) occurs within 5 days after birth, and the time course of LFT elevation is compatible with hepatic injury due to perinatal asphyxia.
The determination of ULN will be based on the subject's gestational age

(GA) and the site*s normal range values for the respective GA.
8a. Subject has direct (conjugated) bilirubin levels >2mg/dL.
9. Subject requiring or expected to require phototherapy or exchange transfusion due to elevated bilirubin.
10. Subject with rapidly increasing bilirubin that may preclude the subject from inclusion in the study at the discretion of the Investigator.

Study design

Design

Study phase:	2
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:	11-04-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	14-09-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-02-2020

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-07-2020
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	EUCTR2015-002756-27-NL
CCMO	NL60876.078.17