# STATISTICAL ANALYSIS PLAN

**Study: N01349**

**Product: Brivaracetam**

**A MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE PHARMACOKINETICS, EFFICACY AND SAFETY OF BRIVARACETAM IN NEONATES WITH REPEATED ELECTROENCEPHALOGRAPHIC SEIZURES – PHASE 2/3**

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| Final SAP | 26 April 2018 |
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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AC | active control |
| AE | adverse event |
| AED | antiepileptic drug |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AUC | area under the curve |
| Bayley-III® | Bayley scales of Infant and Toddler ®, Third Edition |
| bid | (bis in die) twice daily |
| BRV | brivaracetam |
| BZD | benzodiazepine |
| CF | conversion factor |
| CGA | corrected gestational age |
| CI | confidence interval |
| CNS | central nervous system |
| COVID-19 | Coronavirus Disease 2019 |
| CRF | case report form |
| CSR | clinical study report |
| D | day |
| DBP | diastolic blood pressure |
| DEM | Data Evaluation Meeting |
| DMC | Data Monitoring Committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EEG | electroencephalogram |
| eg | exempli gratia=for example |
| EMA | European Medicines Agency |
| EMU | epilepsy monitoring unit |
| ENS | electroencephalographic neonatal seizures |
| EPV | Extension Period Visit |
| ER | emergency room |
| EudraCT | European Union Drug Regulating Authorities Clinical Trial |
| FAS | Full Analysis Set |
| GA | gestational age |
| H | hour/-s |
| HDL | high-density lipoproteins |
| HIE | hypoxic-ischemic encephalopathy |
| HR | heart rate |
| ICF | Informed Consent form |
| IPD | important protocol deviations |
| iv | intravenous |
| IVRS | interactive voice response system |
| LDC | lidocaine |
| LEV | levetiracetam |
| LOQ | limit of quantification |

| | |
|---|---|
| MDZ | midazolam |
| MedDRA© | Medical Dictionary for Regulatory Activities© |
| N-PASS | Neonatal pain, agitation and sedation scale |
| PB | phenobarbital |
| PCST | possibly clinically significant treatment-emergent |
| PDILI | Potential drug-introduced liver injury |
| PHT | phenytoin |
| PK | pharmacokinetic |
| PK-PPS | Pharmacokinetic Per-Protocol Set |
| PNA | postnatal age |
| PP | per protocol |
| PPS | Per-Protocol Set |
| PRO | patient reported outcome |
| PT | preferred term |
| RR | respiratory rate |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SOC | system organ class |
| SS | Safety Set |
| $t_{1/2}$ | elimination half-life |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| VEEG | (multichannel) video-electroencephalography |
| WHO-DRL | World Health Organization Drug Reference List |

# 1 INTRODUCTION

This statistical analysis plan (SAP) defines the scope of the statistical analyses and provides a detailed description of statistical methodology for the statistical analyses to support the final clinical study report (CSR). The SAP is based on the following study document: N01349 Protocol Amendment (6.0): 28 October 2019.

# 2 PROTOCOL SUMMARY

## 2.1 Study objectives

### 2.1.1 Primary objective

The primary objective is to evaluate the pharmacokinetics (PK) of brivaracetam (BRV) in neonates who have seizures that are not adequately controlled with previous antiepileptic drug (AED) treatment, and to identify the optimal BRV dose (Exploratory cohort) for the treatment of subjects enrolled into the Confirmatory Cohorts of this study.

### 2.1.2 Secondary objectives

The secondary objectives are:

- To evaluate the efficacy of BRV in severe and non-severe seizure burden (defined by total minutes of electroencephalographic neonatal seizures (ENS) per hour) in neonates with seizures that are not adequately controlled with previous AED treatment
- To evaluate the short-term safety and tolerability of BRV in neonates

## 2.2 Study variables

### 2.2.1 Pharmacokinetic variables (Exploratory and Confirmatory Cohorts)

#### 2.2.1.1 Primary PK variables

The primary PK variable is as follows:

- Plasma concentrations of BRV following first dose on Day 1

#### 2.2.1.2 Other PK variables

- Plasma concentration of BRV on other occasions
- Plasma concentrations of BRV metabolites ucb-42145 (acid), ucb-100406-1 (hydroxy), and ucb-107092-1 (hydroxyacid)
- Area Under the Curve (AUC), $t_{1/2}$, volume of distribution, and clearance of BRV
- Plasma concentrations of concomitant AEDs if administered 3h (±1h) after start of the initial BRV administration

### 2.2.2 Efficacy variables (Confirmatory Cohorts only)

The variables for the evaluation of BRV efficacy are described in Section 2.2.2.1 (Secondary efficacy variables) and Section 2.2.2.2 (Other efficacy variables).

#### 2.2.2.1 Secondary efficacy variables

The main secondary efficacy variable is the proportion of responders to BRV treatment from Baseline to 3 hours after the initial BRV dose. Responders to BRV treatment is defined in Section 8.1.

In addition, the secondary efficacy variables will include:

- Proportion of subjects with at least 80% reduction in non-severe seizure burden from Baseline to 3 hours after the initial BRV treatment
- Proportion of subjects with at least 50% reduction in severe seizure burden from Baseline to 3 hours after the initial BRV treatment
- Absolute reduction in average seizure burden measured by continuous video-electroencephalography (VEEG) from Baseline to the end of the 96-hour Evaluation Period
- Percent reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period
- Proportion of BRV responders at the end of the 96-hour Evaluation Period
- Proportion 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 non-severe or severe seizure burden at Baseline
- Time to reduction in seizure burden for BRV responders (defined as the first time point when BRV responder criteria are met)
- Seizure freedom at the end of the Down-Titration Period
- Rate of at least 50% reduction in ENS frequency per hour from Baseline to the end of the 96-hour Evaluation Period
- Proportion of subjects who are seizure-free by time interval at 3 hours, at 3-hour intervals thereafter through 24 hours, and every 12 hours to 24 hours thereafter up until the end of the 96-hour Evaluation Period following the start of the initial BRV treatment
- Absolute difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion
- Percent difference in clinical seizures at the end of the 24-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion

#### 2.2.2.2 Other efficacy variables

Other efficacy variables will include:

- Absolute reduction from Baseline in seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment
- Percentage reduction from Baseline in seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36

hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment

- Categorized percentage reduction from Baseline to the end of the 96-hour Evaluation Period in seizure burden (<-25% [worsening], -25% to <25% [no change], 25% to <50%, 50% to <80%, and ≥80%)
- Proportion of BRV responders by time interval at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment
- Proportion of subjects who switch over from BRV to another AED during the 96-hour Evaluation Period

  Proportion of responders to other treatment during the 96-hour Evaluation Period (including at the end of the 96-hour Evaluation Period, and by time intervals: 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment)

### 2.2.3 Safety variables (Exploratory and Confirmatory Cohorts)

#### 2.2.3.1 Secondary safety variable

The secondary safety variable is as follows:

- Adverse Events (AEs) as reported by the Investigator

#### 2.2.3.2 Other safety variables

- Change from Baseline in vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation [pulse oximetry] including apneas, and body temperature) to 3, 6, 9, 12, 15, 18, 21, 24, 48, 72 and 96 hours
- Change from Baseline in safety laboratory tests to the end of the Evaluation Period
- Change from Baseline in heart rate at 3 hours, 24 hours, 48 hours, and 96 hours after the start of initial BRV treatment
- Change from Baseline in physical and neurological examination 24 hours, 48 hours, 72 hours, and 96 hours after the start of initial BRV treatment (Sarnat scale; for subjects with hypoxic-ischemic encephalopathy (HIE) only)
- Change from Baseline in electroencephalogram (EEG) parameters (assessment of sedation) to the end of the Evaluation Period (Confirmatory Cohorts only)
- Change from Baseline in severity of HIE to the end of the Evaluation Period (Thompson score; for subjects with HIE only)
- Change from Baseline in N-PASS score (neonatal pain and agitation measures) to the end of the Evaluation Period

- Change from Baseline in biometric parameters at the Safety Follow-Up Visit: length, body weight, and head circumference (head circumference Baseline measurement should be taken within 7 days prior to drug administration, or at birth for subjects ≤7 days old)
- Withdrawal and rebound phenomena
- Mechanical ventilation:
  - Number and percentage of subjects requiring mechanical ventilation during the Evaluation Period
  - Duration of mechanical ventilation during the Evaluation Period
- Neurodevelopmental tests done after 1 year for subjects who enter the long-term follow-up study in countries where a validated translation of the Bayley Scales of Infant and Toddler development ®, Third Edition (Bayley-III ®) score is available.

## 2.3 Study design and conduct

N01349 is a Phase 2/3, multicenter, open-label, single-arm study to evaluate the PK, efficacy, and safety of BRV in neonates with repeated EEG seizures.

N01349 consists of a 2-step design and includes a descriptive comparison with a historical control group (matched in age and condition) from literature treated with AEDs per System Organ Class (SOC) and diagnostic methods.

For the Exploratory Cohort (first step), enrolled subjects will receive one or more AEDs for the treatment of ENS per SOC (first-line, second-line, or subsequent treatment; choice of treatment, dose and dosing frequency are at the discretion of the Investigator) prior to receiving BRV. Subsequently, an initial iv dose of BRV (0.5mg/kg) will be administered. At the discretion of the Investigator, 3 additional iv BRV doses, up to a total of 4 iv BRV doses (0.5 mg/kg bid), can be administered during the 48-hour Evaluation Period. This treatment, which is the first use of BRV in neonates, is 4-fold less than the highest dose of 4mg/kg/day (2mg/kg bid) that has been used previously in infants ≥1 month old.

For the Confirmatory Cohorts (second step), 3 consecutive cohorts are planned, and the efficacy of BRV will be evaluated. The iv dose of BRV selected for the Confirmatory Cohorts will be determined by the evaluation of BRV plasma concentrations from the Exploratory Cohort, as well as by previous PK modeling of N01263 data, to be within the range of plasma concentrations observed in children ≥1month old who received 4mg/kg/day. A dosage of BRV 4mg/kg/day for neonates is predicted to be approximately equivalent to the highest BRV dosage (200mg/day) that has been studied in the adult Phase 3 program (eg, N01358 and N01258). The PK and safety of BRV will be evaluated in all cohorts.

The recommendation to confirm or adjust the originally calculated BRV dose of the Confirmatory Cohorts of study N01349 will be given by the Data Monitoring Committee (DMC) after review of PK and safety data of the Exploratory Cohort.

At the end of the Evaluation Period, subjects from both the Exploratory and Confirmatory Cohorts may enter the BRV Extension Period.

All subjects who participate in the BRV Extension Period must be offered entry into a long-term study, if they meet the eligibility criteria. Before entering the long-term study, subjects must be on oral BRV.

If appropriate (in the event of screen failures), re-screening will be allowed for the study. Re-screening for screen-failed subjects will be allowed with prior consultation of the Medical Monitor whenever feasible. Subjects can be re-screened only once.

A continuous consent process will be followed. Continuous consent will be documented in the subjects' medical charts and electronic Case Report form (eCRF).

### 2.3.1 Exploratory cohort

For the Exploratory Cohort, at least 6 subjects who do not have adequate seizure control after they received one or more AEDs per SOC for the treatment of ENS (first-line, second-line, or subsequent treatment, which may have started prior to the subject's admission into the study site; choice of treatment, dose and dosing regimen at the Investigator's discretion) will be enrolled. The AED treatment per SOC can be continued when BRV dosing is initiated. Alternatively, another AED treatment (choice of treatment, dose, and dosing regimen at the Investigator's discretion) must be initiated and continue in parallel with BRV treatment.

At any time after AED treatment per SOC for the treatment of ENS (first-line, second-line, or subsequent treatment) was initiated, an initial low dose of BRV (0.5mg/kg [bid]) will be administered at the Investigator´s discretion. After the Exploratory Cohort completes the study, a PK and safety data review will be performed by the DMC. During the review of data from the Exploratory Cohort, the enrollment of subjects will be on hold.

At least 2 subjects undergoing hypothermia treatment will be included. Subjects in the Exploratory Cohort might be replaced due to lack of data, as deemed necessary following the review of PK and safety data by the DMC.

The study periods for the Exploratory Cohort are as follows:

- Screening Period: from signing and dating of the written Informed Consent form (ICF) up to initiation of the first BRV dose.

  The Screening Period starts up to 36 hours prior to the first administration of BRV. Phenobarbital, midazolam (MDZ), phenytoin (PHT), levetiracetam (LEV), or lidocaine (LDC) may have been administered prior to the subject's enrollment into the study and/or at a location other than the study site.

  Subjects will enter the Evaluation Period and start BRV treatment as soon as the occurrence of ENS per inclusion criterion 2a is confirmed by the Investigator based on local EEG. If preferred by the Investigator, the central VEEG reader can be consulted to confirm the required ENS.

- Evaluation Period (48 hours): The first BRV infusion marks the starting point of the Evaluation Period. At any time after AED treatment per SOC for the treatment of ENS (first-line, second-line, or subsequent treatment) was initiated, a low dose of BRV (0.5mg/kg) will be administered as an approximately 15-minute iv infusion; additional 3 doses of BRV (0.5mg/kg) can be administered every 12 hours for 48 hours (at the discretion of the Investigator). The AED treatment per SOC can be continued when BRV dosing is initiated.

Otherwise, another AED treatment (choice of treatment, dose, and dosing regimen at the Investigator´s discretion) must be initiated and continue in parallel with BRV treatment.

Following the first BRV infusion, 3 to 6 PK blood microsamples (60µL/sample) will be collected during the 48-hour Evaluation Period from each subject for the determination of plasma concentrations of BRV and its metabolites. The number of subjects in the Exploratory Cohort may be increased, if deemed necessary following the analysis of PK data.

At the end of the Evaluation Period, subjects who benefit from BRV treatment may enter the BRV Extension Period in accordance with the Investigator's opinion. Subjects not entering the BRV Extension Period will proceed immediately to the Safety Follow-Up Period (a visit will occur 30±3 days after the final BRV administration).

- BRV Extension Period (up to 28 days of postnatal age [+7 days]): Subjects can proceed to the BRV Extension Period if they benefit from BRV treatment during the Evaluation Period, in accordance with the Investigator's opinion. All subjects who participate in the BRV Extension Period must be offered entry into the long-term study, if they meet the eligibility criteria. Subjects will participate in the BRV Extension Period until they reach a stable condition that will allow them to enter the long-term study. The anticipated duration of the BRV Extension Period per subject is up to 28 days of postnatal age (+7 days). Subjects must switch to BRV oral solution before entering the long-term study. The timing of the switch from iv to oral solution will be at the discretion of the Investigator; subjects who are not able to be dosed with BRV oral solution when they reach 28 days of postnatal age may continue in the BRV Extension Period for an additional 7 days; subjects who are not able to be switched to BRV oral solution by the end of the additional 7 days of the BRV Extension Period will not be eligible for enrollment in the long-term study.

  During the BRV Extension Period, subjects may continue receiving the same BRV dose administered at the end of the Evaluation Period (ie, BRV 0.5mg/kg bid); the BRV dose should not be increased but may be decreased at the discretion of the Investigator.

- Safety Follow-Up Period: Subjects will proceed to the Safety Follow-Up Period if they do not enter the BRV Extension Period. The visit will occur 30±3 days after the final administration of BRV.

- A DMC will be in place for the duration of this study. DMC Data Review Meetings to occur after completion of the 6 subjects in the Exploratory Cohort and after completion of each of the 3 Confirmatory Cohorts (12 subjects each), but no later than in intervals of 6 months.

### 2.3.2 Confirmatory Cohorts

For the Confirmatory Cohorts, enrollment will only start after the dosing of BRV is determined based on the PK findings of the Exploratory Cohort and an existing PK model from N01263. A total of at least 36 subjects without adequate seizure control after receiving one or more of the following AEDs prior to or at the time of enrollment: PB, MDZ, PHT, LEV (≤60mg/kg/day), or LDC (first-line, second-line, or subsequent treatment, which may have started prior to the subject's admission into the study site; dose and dosing regimen at the Investigator's discretion) will enter the Confirmatory Cohorts. The AED treatment can be continued if the subject is on a stable dose for at least 1 hour at the time the first BRV infusion is initiated.

Three consecutive Confirmatory Cohorts (n=12 each) are planned; each cohort must have at least 2 subjects undergoing hypothermia treatment. A PK and safety data review will be performed by the DMC after completion of each of the 3 Confirmatory Cohorts (12 subjects each), but no later than intervals of 6 months. During the PK and safety data review of data from the first and second Confirmatory Cohorts, the recruitment of subjects into subsequent cohorts will continue.

The study periods for the Confirmatory Cohorts are as follows:

- Screening Period: from signing and dating of the written ICF up to initiation of the first BRV dose.

  The Screening Period starts up to 36 hours prior to the first administration of BRV. Phenobarbital, MDZ, PHT, LEV (≤ 60mg/kg/day), or LDC may have been administered prior to the subject's enrollment into the study and/or at a location other than the study site.

- Baseline Period (included in the Screening Period):

  – For subjects with **intermittent ENS**: at least 1 hour prior to entering the Evaluation Period.

  – For subjects in status epilepticus: up to 30 minutes prior to entering the Evaluation Period. At least 15 minutes of continuous seizures, or 50% of cumulative seizure activity during a 30-minute interval are to be confirmed on EEG before the administration of BRV can start.
  As soon as subjects are considered to be in status epilepticus, steps required for the preparation of the initial BRV infusion can be initiated (eg, assignment of BRV kits through interactive response technology [IRT] and the dilution of BRV solution for iv infusion), even if the required EEG recording is not completed by that time.
  Status epilepticus in neonates for the purpose of this study is defined as follows:
  15 minutes of continuous or cumulative electrographic or electroclinical seizure within 30 minutes
  The occurrence of ENS during the Baseline Period must be confirmed either by the local or central VEEG reader prior to BRV administration. Preferably, the central VEEG reader should confirm the required ENS. Video-EEGs that are acquired per standard of care prior to consenting and meet study-specific technical and quality requirements (eg, ability for immediate cloud-based central review) can be used as part of the Baseline assessment VEEG.

- Evaluation Period (96 hours): The first administration of BRV marks the starting point of the Evaluation Period. All subjects will receive iv BRV. The BRV dose for subjects in the Confirmatory Cohorts will be determined based on the results of the PK analysis of the Exploratory Cohort (predicted to be approximately the BRV plasma concentrations in the same range as those observed at the highest recommended dose in older children and adults who receive BRV 200mg/day). If subjects do not benefit from BRV treatment after 96 hours of BRV administration, BRV administration will be stopped and replaced by another AED.

  Following the first BRV infusion, 6 PK blood microsamples (60µL/sample) will be collected during the 96-hour Evaluation Period for each subject for the determination of plasma concentrations of BRV and its metabolites.

The AED PK sample should be collected 3 hours after the start of the initial BRV administration. In addition, opportunistic blood samples for the PK analysis may be used at the Investigator's discretion at any time during the Evaluation Period.

At the end of the Evaluation Period, subjects who benefit from BRV treatment may enter the BRV Extension Period in accordance with the Investigator's opinion. Subjects not entering the BRV Extension Period will proceed to the Down-Titration Period.

- BRV Extension Period (up to 28 days of postnatal age [+7 days]): Subjects can proceed to the BRV Extension Period if they benefit from BRV treatment during the Evaluation Period, in accordance with the Investigator's opinion. All subjects who participate in the BRV Extension Period must be offered entry into the long-term study, if they meet the eligibility criteria. Subjects will participate in the BRV Extension Period until they reach a stable condition that will allow them to enter the long-term study, if epilepsy is confirmed. The maximum anticipated duration of the BRV Extension Period per subject is up to 28 days of postnatal age (+7 days). Subjects must switch to BRV oral solution before entering the long-term study. The time point of the switch from iv to oral solution will be at the discretion of the Investigator.

  Subjects who are not able to be dosed with BRV oral solution when they reach 28 days of postnatal age may continue in the BRV Extension Period for an additional 7 days; subjects who are not able to be switched to BRV oral solution by the end of the additional 7 days of the BRV Extension Period will not be eligible for enrollment in the long-term study.

  During the BRV Extension Period, subjects may continue receiving the same BRV dose administered at the end of the Evaluation Period; the BRV dose should not be increased, but may be decreased at the discretion of the Investigator.

- Down-Titration Period (up to 1 week): A Down-Titration Period of up to 1 week is recommended for subjects in the Confirmatory Cohorts who discontinue BRV treatment prior to completion of the Evaluation Period, who do not proceed to the BRV Extension Period, or start the BRV Extension Period but do not enter the long-term study. The Down-Titration steps and duration may be adjusted at the Investigator's discretion.

- Safety Follow-Up Period: Subjects will proceed to the Safety Follow-Up Period once they complete the Down-Titration Period. The visit will occur 30±3 days after the final administration of BRV.

Rescue medication should be given if the following occurs:

- There is no improvement in seizure burden within the first 3 hours after administration of BRV.
- Seizure burden is unacceptable to the Investigator, in which case rescue medication can be given earlier at any time, but ideally not in the first 3 hours after the initial administration of BRV.

Subjects in the Confirmatory Cohorts are allowed to switch over from BRV to another AED (eg, MDZ or PHT), if needed. Subjects discontinuing BRV treatment during the Evaluation Period should start the Down-Titration Period while completing the Evaluation Period in parallel for the full 96 hours. In this case, subjects will complete all study assessments, except the collection of

blood microsamples for the determination of BRV plasma concentrations. Ideally, changing or adding a new treatment should not occur during the first 3 hours after the initial administration of BRV. Subjects who are switched from BRV to another AED will not be eligible to participate either in the BRV Extension Period or the long-term study.

### 2.3.3 Study duration per subject

The maximum study duration per subject will be up to 75 days (Screening Period [including Baseline Period (Confirmatory Cohorts only)], Evaluation Period, BRV Extension Period, Down-Titration Period [Confirmatory Cohorts only], and Safety Follow-Up Period). The individual study duration will be shorter depending on the type of cohort to which subjects will be assigned, the age at enrollment, and the decision to enter the BRV Extension Period.

The maximum BRV exposure per subject will be up to 42 days, which comprises up to 4 days during the Evaluation Period (depending on type of cohort), up to 28 days (+7 days) of postnatal age during the BRV Extension Period, and up to 1 week during the Down-Titration Period for subjects in the Confirmatory Cohorts only.

All subjects who do not continue into the long-term study will proceed to the Safety Follow-Up Period, and a visit will occur 30±3 days after the final dose of BRV.

The end of the study is defined as the date of the last visit of the last subject in the study.

## 2.4 Determination of sample size

At least 42 evaluable subjects will be enrolled in this study, with at least 6 subjects in the Exploratory Cohort and at least 36 subjects will be enrolled in 3 successive Confirmatory Cohorts, each consisting of 12 subjects. At least 2 subjects undergoing hypothermia treatment will be included in the Exploratory Cohort and each of the 3 Confirmatory Cohorts.

Subjects in the Exploratory Cohort might be replaced due to lack of data, as deemed necessary following the review of PK and safety data by the DMC.

No formal sample size calculation has been performed as a single treatment BRV arm is planned for descriptive summary results and for comparison with the 6 subjects from the Exploratory Cohort. The total number of at least 36 subjects in the Confirmatory Cohorts is expected to provide sufficient evidence of tolerability, safety, and efficacy, as well as good precision for the PK profile of BRV in neonates.

Confirmatory Cohort subjects who drop out or are withdrawn from study participation will not be replaced.

# 3 DATA ANALYSIS CONSIDERATIONS

## 3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be carried out using SAS® Version 9.3 or higher.

Descriptive statistics, such as the number of subjects with available measurement (n), mean, standard deviation (SD), median, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, will be provided. Confidence intervals (95% CIs) will be provided for efficacy variables.

Unless otherwise noted, denominator for percentages will generally be based on the set of subjects with at least 1 assessment at the time point or at least 1 assessment during the time interval being summarized.

Decimal places for descriptive statistics will always apply the following rules:

- "n" will be an integer.
- Mean, SD and median will use 1 additional decimal place compared to the original data.
- Minimum and maximum will have the same number of decimal places as the original value.

Unless otherwise noted, all percentages will be displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%.

In general, descriptive summaries will be used to present study results overall (for the Confirmatory Cohorts) and by cohorts (Exploratory Cohort and each individual Confirmatory Cohort).

Subject data listings will be provided and will present source data and key derived variables for statistical analyses.

## 3.2 General study level definitions

### 3.2.1 Analysis time points

#### 3.2.1.1 Relative day and time

For measurements with date and time collected, relative day and time will be calculated.

Relative day and time in 24-h clock will be calculated as current date minus first dose date, current time in hours minus first dose time in hours, current time in minutes minus first dose time in minutes (add 1 minute if the current date and time is the same or after the first dose date and time).

The relative time will be displayed in hours and minutes for relative times ≤24 hours before or after the first BRV administration. For relative times >24 hours the relative day and time will be calculated in days, hours and minutes. If the current date and time is the same as the first dose date and time, the relative time is 1 minute. If the current date and time is prior to the first dose date and time, then the relative day and time will be denoted by "-". If the current date and time is after the last dose date the relative day and time will be displayed with a leading "+".

The relative day and time in the tables and listings will be displayed in days, hours and minutes where applicable.

- Example 1: first dose date and time is 5-Jan-2017: 10:30 am. The current date and time is 5-Jan-2017: 8:45 am. The relative day and time is calculated as 5-Jan-2017 minus 5-Jan-2017=0, 8:00 h – 10:00 h= -2:00 h, 45 min-30 min=15 min. The relative day and time is 0 d 1 h 45 min and will be displayed as -1 h 45 min.
- Example 2: first dose date and time is 5-Jan-2017: 10:30: am. The current date and time is 7-Jan-2017: 8:45 am. The relative day and time is calculated as 7-Jan-2017 minus 5-Jan-2017=2 d (48 h), 8:00 h – 10:00 h= -2:00 h, 45 min-30 min + 1 min=16 min. The relative day and time is 1 d 22 h 16 min.

- Example 3: first dose date and time is 5-Jan-2017: 10:30 am. The current date and time is 3-Jan-2017: 8:45 am. The relative day and time is calculated as 3-Jan-2017 minus 5-Jan-2017= -2 d (-48 h), 8:00 h – 10:00 h= -2:00 h, 45 min-30 min=15 min. The relative day and time is -2 d 1 h 45 min.

Relative day and time will not be calculated for partial dates and times.

#### 3.2.1.2 Relative day

For measurements with only date collected, relative day will be calculated. Relative day will be calculated as the date of first dose of study medication minus the current date for days prior to the first dose of study medication. During treatment (from the day of first study medication dose until the day of last study medication dose), relative day will be calculated as the current date minus the date of first dose of study medication plus 1 (eg, the day of first dose will be Day 1 and the day prior to first dose will be Day -1). For days after the last dose of study medication, relative day will be calculated as the current date minus the date of last study medication dose and will include a '+' to denote post-treatment days (eg, the day after the last dose will be Day +1). Relative day will not be calculated for partial dates.

### 3.2.2 Study periods for analysis

#### 3.2.2.1 Exploratory cohort study periods

##### 3.2.2.1.1 Screening Period

The Screening Period will start on the date of the written informed consent form (ICF) and will end immediately prior to initiating the first BRV dose. The Screening Period starts up to 36 hours prior to the first administration of BRV.

##### 3.2.2.1.2 Evaluation Period

Evaluation Period starts with the first BRV initiation and will end 48 hours after first BRV initiation.

##### 3.2.2.1.3 BRV Extension Period

If it is decided that the subject continues BRV administration after the Evaluation Period, the Extension Period starts after the end of the Evaluation Period. Subjects who will not attend the long term follow-up study, will have no Extension Period.

If the subject will be enrolled in the long term follow up study, the end of the Extension Period is defined as last contact during N01349. In this case the maximum duration of the period will be 35 days.

In case subject attends the Extension Period but then it's decided to stop the BRV administration, the subject will continue with the Safety Follow-up Period and the end of the Extension Period will be defined as the date and time of last BRV administration.

Subjects not entering the BRV Extension Period will proceed immediately to the Safety Follow-Up Period.

The BRV Extension Period may consist of Extension Period Visit 1 (EPV1), Extension Period Visit 2 (EPV2), Unscheduled Visit and Telephone Contact.

#### 3.2.2.1.4 Safety Follow-Up Period

Subjects will proceed to the Safety Follow-Up Period if they do not require further BRV administration. The start of the Safety Follow-up Period will be defined as after the end of the last BRV administration. The end of the Safety Follow-up Period will be defined as last contact to the subject, which will be the Follow-Up visit. This visit will occur 30±3 days after the final administration of BRV.

### 3.2.2.2 Confirmatory Cohorts study periods

#### 3.2.2.2.1 Screening Period

The Screening Period will start on the date of the written ICF and will end prior to initiating the first BRV dose. Screening Period includes Baseline Period described below.

#### 3.2.2.2.2 Baseline Period

Baseline Period (-1h to 0h) begins 1 hour before and ends immediately prior to the first initiation of BRV infusion. The Baseline Period is included in the Screening Period.

#### 3.2.2.2.3 Evaluation Period

Evaluation Period starts when the subject receives first dose of BRV infusion and will last for 96 hours. If subjects do not benefit from BRV treatment after 96 hours of BRV administration, BRV administration will be stopped and replaced by another AED; however, the subject's participation in the study will continue.

#### 3.2.2.2.4 BRV Extension Period

BRV Extension Period starts after the end of the Evaluation Period, subjects who benefit from BRV treatment may enter the BRV Extension Period in accordance with the Investigator's opinion.

If the subject will be enrolled in the long term follow up study, the end of the Extension Period is defined as last contact during N01349. In this case the maximum duration of the period will be 35 days.

In case subject attends the Extension Period but then it's decided to not continue the BRV administration, the subject will continue with the Down Titration Period and the end of the Extension Period will be defined as the date and time of last stable dose of BRV infusion.

Subjects not entering the BRV Extension Period will proceed immediately to the Down-Titration Period.

The BRV Extension Period may consist of Extension Period Visit 1 (EPV1), Extension Period Visit 2 (EPV2), Unscheduled Visit and Telephone Contact.

#### 3.2.2.2.5 Down Titration Period

Down-Titration Period will start after the Evaluation Period or after the BRV Extension Period, can last up to 1 week. The end of the Down-Titration period is defined as day and time of last BRV administration.

#### 3.2.2.2.6 Safety Follow-Up Period

Subjects will proceed to the Safety Follow-Up Period once they complete the Down-Titration Period. The end of the Safety Follow-up Period will be defined as last contact to the subject, which will be the Follow-Up visit. This visit will occur 30±3 days after the final administration of BRV.

### 3.2.3 Mapping of assessments performed at Early Discontinuation Visit

Efficacy and safety assessments at an Early Discontinuation Visit (EDV) that corresponds to a scheduled visit will be summarized at the scheduled visit corresponding to the EDV if the assessment was scheduled to occur at that visit. Such assessments will also be considered for Last Value. In particular, vital signs, body weight, heart rate monitoring, laboratory parameters, PK samples and VEEG assessments are done at different time points of the Evaluation Period. All assessments of these variables at EDVs corresponding to a scheduled visit will be mapped to the corresponding scheduled visit.

### 3.2.4 Definition of completed study

Subjects will be classified as completed the study if they complete the Safety Follow-up Visit or if they complete the Extension Period Visit 2 (EPV2) and continue BRV treatment in the Follow-up study.

## 3.3 Postnatal age (PNA), Gestational age (GA) and Corrected Gestational age (CGA)

PNA at the time of enrollment or the time elapsed after birth in days will be calculated as the date of signed inform consent minus the date of birth.

GA will be calculated in weeks using PNA in weeks and CGA in weeks with the following formula:

$$GA = CGA - PNA$$

PNA in weeks will be calculated as PNA in days divided by 7 and rounded up to the nearest week. The PNA in weeks for subjects 7 days old and younger will be one week, for subjects aged more than 7 days old and less than or equal 14 days will be two weeks and so on.

## 3.4 Definition of Baseline values

In general, baseline value for safety will be defined as the latest value prior to the first dose of BRV infusion, unless otherwise noted for a specific type of data. For almost all variables, this will be the assessment made at the Baseline visit. If a Baseline measurement is missing, and a Screening value available, the Screening value will be utilized as Baseline instead. If a Baseline assessment of biometric parameters (length, weight, head circumference) is taken on the same day as first dose of BRV infusion and assessment time is not known, the latest value at Screening or Baseline visit before or on the date of first dose of BRV infusion will be utilized as Baseline value.

Both scheduled and unscheduled assessments are considered.

Baseline efficacy will be defined in the efficacy analysis section.

## 3.5 Protocol deviations

Important protocol deviations (IPD) are deviations from the protocol that could potentially have a meaningful impact on key PK, efficacy, or safety outcomes for an individual subject. The criteria for identifying important protocol deviations and the classification of IPDs will be documented in a protocol-defined specification document. To the extent feasible, rules for identifying IPDs will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying IPDs will be implemented algorithmically to ensure consistency in the classification of IPDs across all subjects.

Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock to confirm exclusion from the Pharmacokinetic Per-Protocol Set.

## 3.6 Analysis sets

### 3.6.1 Safety Set

The Safety Set (SS) will consist of all enrolled subjects who take at least 1 dose of BRV. All safety analyses will be performed on the SS for the Exploratory Cohort and the Confirmatory Cohort(s).

### 3.6.2 Full Analysis Set

The Full Analysis Set (FAS) will be used for the analysis of seizure data (efficacy) and will consist of all subjects in the SS who have a minimum of 2 hours of interpretable VEEG data from both the Baseline period and the first 3 hours of the post-Baseline period after initial BRV treatment.

### 3.6.3 Pharmacokinetic Per Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) will consist of all subjects who provide at least one measurable post-Baseline plasma sample (with recorded sampling time) on at least 1 post-Baseline visit with documented study medication intake times. This analysis set will be used for the Exploratory Cohort and the Confirmatory Cohort(s). Subjects with important protocol deviations will be excluded from the PK-PPS.

## 3.7 Treatment assignment and treatment groups

Because N01349 is an open-label, single-arm study, subjects will not be randomized to any treatment groups. The first 6 subjects meeting the eligibility criteria will be assigned to the Exploratory Cohort. Subsequent subjects will be assigned to the Confirmatory Cohorts.

## 3.8 Center pooling strategy

There is no differentiation by center in this study, i.e. the data will be analyzed from all centers together.

## 3.9 Coding dictionaries

Medical history (if available) and adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. Medications will be coded using

the World Health Organization Drug Dictionary (WHO-DD) version September 2017. Medical procedures will not be coded.

## 3.10 Changes to protocol-defined analyses

**Table 3.1: Changes to protocol-defined analyses**

| Protocol-defined analyses | New analyses |
|---|---|
| Primary cause of seizure subgroups for the efficacy analysis are changed from the protocol defined:<br>1. HIE, hemorrhage, or infarction<br>2. CNS malformations;<br>3. CNS infections;<br>4. undetermined causes | Primary cause of seizure subgroups based on the eCRF categories:<br>1. HIE<br>2. Ischemic stroke<br>3. Intracranial hemorrhage<br>4. Epileptic encephalopathy/genetic epilepsy<br>5. Intracranial infection<br>6. Brain malformation<br>7. Inborn error of metabolism<br>8. Undetermined cause<br>9. Other |

# 4 STATISTICAL/ANALYTICAL ISSUES

## 4.1 Adjustments for covariates

Not applicable for this study.

## 4.2 Handling of dropouts or missing data

There will be no specific imputation of missing data except for missing dates and/or times for concomitant medication and AE.

The handling of missing dates and times for seizures if applicable will be discussed during the Data Evaluation Meeting (DEM).

### 4.2.1 Handling of prior and concomitant medications with missing data

Any medications with incomplete start and end dates/times will be handled according to the following rules for classification as prior and concomitant and for the calculation of relative study days. Such imputations will only be performed for these classifications and calculations; in the listings all data will be shown as recorded on the electronic Case Report Form (eCRF).

Imputation of Partial Start Dates:

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of the start date, then use the 1st of the month.

- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start date, then use the date of first dose.
- If only the year is specified, and the year of first dose is not the same as the year of the start date, then use January 1 of the year of the start date.
- If only the year is specified, and the year of first dose is the same as the year of the start date, then use the date of first dose.
- If the date is completely unknown, then use the date of first dose.

Imputation of Partial End Dates:

- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then use December 31 of that year.
- If the date is completely unknown, do not impute the stop date.

There will be no imputation of any other missing data.

### 4.2.2 Handling of adverse events with missing data

Any AEs with incomplete onset and outcome (end) dates/times will be handled according to the following rules for classification as treatment-emergent. Such imputations will only be performed for these classifications; in the listings all data will be shown as recorded on the eCRF.

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of onset, then use the 1st of the month.
- If only the month and year are specified and the month and year of first dose is the same as the month and year of onset, then use the date/time of first dose.
- If only the year is specified, and the year of first dose is not the same as the year of onset, then use January 1 of the year of onset.
- If only the year is specified, and the year of first dose is the same as the year of onset, then use the date/time of first dose.
- If the AE onset date is completely unknown, then use the date of first dose.
- Imputations for missing end dates/times will not be performed for classification as treatment-emergent as this is not required.

Adverse events with missing severity or causality will be regarded as ‘severe’ and ‘related’ respectively for the tabulations. There will be no imputation of any other missing data. Any AE with additional missing data that prohibits classification for a given tabulation will be excluded from that tabulation.

In case of uncoded AEs, these AEs should be designated as “UNCODED” at all MedDRA levels, and such AEs will be included in summary tables and subject listings based on this classification.

### 4.2.3 Handling of dropouts or missing efficacy data

For subjects who drop out during the Evaluation Period, the number of hours from the start of the Evaluation Period to the time of withdrawal (in hours) will be considered for analysis. Subjects in the Confirmatory Cohorts who are withdrawn or are switched over to another AED treatment prior to the Evaluation Period or are administered >1 dose of rescue medication (including BZDs) following the first 3 hours after initial BRV treatment started will be considered BRV non-responders.

### 4.2.4 Handling of study medication with missing data

No imputation should be performed for missing study medication start dates. This field on the eCRF should not be partial or missing.

For partial or missing date of last dose of study medication, the following imputation rules will be applied for the purpose of calculating overall exposure:

- If the day is missing (but month and year available), impute the last dose date as the minimum of the last day of the month or the date of last contact reported on the trial termination CRF; if day and month are both missing (only year available), impute the last dose date as the minimum of the last day of the year or the date of last contact on the trial termination CRF.
- If a subject died and has a partial or missing last administration date, the date is to set to the date of death. If there is a partial date of last dose and the month/year are prior to the month and year of the date of death, follow partial date imputation rules.
- If the last dose date is completely missing and no information could be obtained from data cleaning exercises, the last dose date should be imputed as the date of last contact per the study termination CRF. A review of the data for subjects with completely missing last dose dates should be performed to ensure that the imputation does not result in an unrealistic value for duration of exposure.
- If the time is missing, set the time to 00:00

Imputed date of last dose dates should only be used for calculation of the duration of exposure. The date as recorded on the eCRF should be presented in subject data listings (no imputed dates should be included in subject data listings).

### 4.2.5 Potential impact of Coronavirus Disease 2019 on dropouts or missing data

The Coronavirus Disease 2019 (COVID-19) pandemic may cause disruption in the conduct of ongoing clinical trials including treatment and study withdrawals, subjects missing study visits, and/or visits being performed remotely instead of at site. Therefore, for subjects enrolled after 30 May 2020, an additional eCRF page will be foreseen. Sites will complete this page in case a subject was impacted by COVID-19 during the study. The COVID-19 Impact eCRF page will include the timing and impact of COVID-19, and relationship to COVID-19 (ie, whether the subject has confirmed/suspected COVID-19 infection, or whether the impact was related to general circumstances around COVID-19 without infection).

## 4.3 Interim analyses and data monitoring

No formal interim analysis is planned for this study; however, PK and safety data will be presented to and reviewed by a DMC. The DMC will oversee the PK and safety of the study by reviewing the PK and safety data periodically, in order to evaluate the risk-benefit profile in relation to the overall progress of the study. The DMC will make recommendations regarding subject safety and continuance of the study based on the observed risk-benefit of the emerging data; however, no formal statistical stopping rules will be defined.

The DMC will perform interim reviews of the PK and safety data to ensure subject safety. The first DMC meeting to review safety data will occur after the Exploratory Cohort (6 subjects) completed the study. The remaining DMC meetings will take place after completion of each of the 3 Confirmatory Cohorts (12 subjects each) but no later than in intervals of 6 months between meetings.

The DMC or Sponsor can convene an ad hoc DMC meeting to review the data and make recommendations on the continuation or modification of the study. The objectives and procedures for the DMC will be detailed in the DMC Charter. A DMC SAP will be developed and will capture analysis needed for DMC.

## 4.4 Multicenter studies

The results will not be presented by individual center.

## 4.5 Multiple comparisons/multiplicity

Not applicable for this study. The study is not statistically powered, and all analyses are of descriptive nature. No statistical tests will be performed.

## 4.6 Use of an efficacy subset of subjects

The efficacy analysis will be based on the FAS subjects from the Confirmatory Cohorts.

The efficacy evaluation at the end of the Down-Titration Period will be based on the subset of subjects in the Confirmatory Cohorts who enter the Down-Titration Period.

## 4.7 Active-control studies intended to show equivalence

Not applicable for this study.

## 4.8 Examination of subgroups

All efficacy variables will be analyzed by

1. Primary cause of seizure subgroups: HIE, ischemic stroke, intracranial hemorrhage, epileptic encephalopathy/genetic epilepsy, intracranial infection, brain malformation, inborn error of metabolism, undetermined causes, other.
2. Concomitant use of hypothermia subgroups: yes, no.

# 5 STUDY POPULATION CHARACTERISTICS

## 5.1 Subject disposition

The number of screen failures and the primary reason for screen failure will be summarized for all enrolled subjects (ie, all subjects with the signed informed consent).

Disposition of subjects screened will be summarized overall and by sites: the date of first subject in, date of last subject out (latest scheduled or unscheduled visit), and the number of enrolled subjects will be summarized for all study sites and by study site. Additionally, the number of subjects in each of the SS, FAS and PK-PPS will be summarized overall and by cohorts.

*Disposition and Discontinuation Reasons by Periods*

- Subjects started study
- Subjects entered treatment
- Subjects completed study
- Subjects discontinuing the study and primary reason for discontinuation
- Subjects started Screening Period
- Subjects completed Screening Period
- Subjects discontinuing the study during the Screening Period and primary reason for discontinuation
- Subjects started Evaluation Period
- Subjects completed Evaluation Period
- Subjects discontinuing the Evaluation Period and primary reason for discontinuation
- Subjects entering BRV Extension Period
- Subjects switching to Oral Solution prior to entering the BRV Extension Period
- Subjects completed BRV Extension Period
- Subjects qualifying to enter the Long-Term Follow-up study
- Subjects discontinuing during the BRV Extension Period and primary reason for discontinuation
- Subjects entering Safety Follow-Up Period and not entering BRV Extension Period
- Subjects entering Down-Titration Period and not entering BRV Extension Period (Confirmatory Cohorts)
- Subjects completed Down-Titration Period (Confirmatory Cohorts)
- Subjects discontinuing during the Down-Titration Period and primary reason for discontinuation (Confirmatory Cohorts)
- Subjects entering Safety Follow-Up Period after completing Down-Titration Period (Confirmatory Cohorts)

All percentages will be relative to the number of enrolled subjects.

*Discontinuation due to Adverse Events*

A summary of discontinuations due to AEs for the SS will present the number and percentage of subjects who discontinued this study due to AEs overall, and by type of AE.

Listings of study eligibility criteria text, of subjects who did not meet study eligibility criteria, of subject disposition and of subject analysis sets will be provided for all subjects screened.

## 5.2 Protocol deviations

The number and percentage of FAS subjects with no important protocol deviations and at least 1 important protocol deviation will be summarized overall, and by main category of protocol deviation (Inclusion criteria deviation, Exclusion criteria deviation, Withdrawal criteria deviation, Prohibited concomitant medication, use incorrect treatment or dose, Treatment non-compliance, Procedural non-compliance). Additionally, the number and percentage of subjects excluded from the PK-PPS due to important protocol deviations will be summarized overall and by main protocol deviation category for the FAS. Other specific categories of protocol deviations will be defined within the IPD specifications document.

Listing of subjects excluded from PK-PPS will be provided.

Listing of important protocol deviations will be provided for the SS.

All completed COVID-19 Impact eCRF pages and other IPDs will be discussed in IPD meetings, including whether the deviation may have been caused by COVID-19.

All data collected from the COVID-19 Impact eCRF page will be listed only.

# 6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

## 6.1 Demographics

Demographic summaries will be presented for the FAS, PK-PPS and SS overall and by cohorts. The variables to be considered are:

- Corrected gestational age
- Postnatal age (as defined in Section 3.3)
- Gestational age (as defined in Section 3.3)
- Gestational age category (Pre-term <37 weeks vs Full term ≥37 weeks)
- Gender
- Weight (g)
- Length (cm)
- Head circumference (cm)
- Racial group (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, and Other/Mixed)
- Country
- Apgar score (1 minute)

- Apgar score (5 minutes)
- HIE status

The listing of demographics including Apgar score will be provided for all subjects screened.

## 6.2 Medical history and concomitant diseases

The number and percentage of subjects with a medical history (if available) condition including both resolved and ongoing conditions at the time of study entry will be summarized overall and by MedDRA primary system organ class (SOC) and preferred term (PT) for the SS.

Listing of medical history glossary and medical history (if available) will be provided for the SS.

## 6.3 Diagnosis of epilepsy

Listing of diagnosis of epilepsy will be provided for the SS.

## 6.4 Prior and concomitant medications

Each medication recorded on the Prior and Concomitant Medication eCRF will be classified as either an AED or a non-AED medication based on the coded Preferred Drug Name. Medications which pharmacologically can be classified as an AED but which were taken for non-epilepsy indications may also be classified as AEDs. Identification of medications as a non-AED or AED will be done using the UCB file:
AEDs_ATCs_SEP2017_FINAL_benzo_groups_23JUL2019.xls. The classification of such medications will be confirmed prior to database lock. Listing of prior and concomitant medications indicating whether medication is AED or not will be provided for the SS. Glossary of all prior and concomitant medications indicating AED and non-AED medications will be provided for the SS.

For the summarization, similar AEDs are grouped and summarized together. For example: Valproate includes valproate sodium, valproate semisodium, valproate bismuth, valproate magnesium, valpromide, ergenyl chrono, valproic acid; Phenytoin includes phenytoin sodium, phenytoin calcium, mephenytoin, zentronal, metetoin, ethotoin, albutoin, hydantal, phelantin, hydantol D, anirrit, dintoinale, fosphenytoin sodium, phenytoin, fosphenytoin, hydantoin derivatives, hydantoin; Phenobarbital includes phenobarbital sodium, methylphenobarbital, metharbital, alepsal, phenobarbital, kaneuron, epanal, phenobarbital calcium, phenobarbital diethylamine, phenobarbital magnesium, phenobarbital quinine. Benzodiazepine AEDs that can be grouped by Bromazepam, Alprazolam, Cloxazolam, Diazepam group, Chlordiazepoxide, Clonazepam, Clobazam, Lorazepam, Clotiazepam, Temazepam, and Clorazepate are considered the same AED at the group level. Combination AEDs are not considered for grouping.

### 6.4.1 Medications at study entry

Medications with the start date and time prior or equal to the date of signed informed consent are considered medications at study entry.

### 6.4.2 Concomitant medications

Medications that were taken on at least one day in common with the study medication dosing period regardless of the start and stop date and time are defined as concomitant medications. This definition includes 1) medications with the start date and time taken after the first dose of study medication but prior to the last dose of study medication, 2) medications with the start date and

time prior to the date and time of the first dose of study medication but with the stop date and time after the first dose of study medication.

### 6.4.3 Non-AEDs taken at study entry

The number and percentage of subjects taking non-AED medications at the time of study entry will be summarized overall and by WHO-DRL pharmacological group (Anatomical Therapeutic Chemical [ATC] classification level 1), therapeutic subgroup (ATC classification level 2) and preferred drug name for the SS. Subject data listing for non-AED taken at study entry will be provided for the SS.

### 6.4.4 Concomitant Non-AEDs

The number and percentage of subjects taking concomitant non-AEDs will be summarized similar to non-AEDs at study entry for the SS. Subject data listing for concomitant non-AED will be provided for the SS.

### 6.4.5 AEDs taken at study entry

The number and percentage of subjects taking AEDs at the time of study entry will be summarized by WHO-DRL preferred drug name for the SS. Subject data listing for AED taken at study entry will be provided for the SS.

### 6.4.6 Concomitant AEDs

The number and percentage of subjects taking concomitant AEDs will be summarized by WHO-DRL preferred drug name for the SS. Subject data listing for concomitant AED will be provided for the SS.

## 6.5 Procedure history

Listing of procedure history will be provided for the SS.

## 6.6 Concomitant medical procedures

Listing of concomitant medical procedures will be provided for the SS.

## 6.7 Primary cause of seizure

Primary cause of seizure will be summarized by cohorts for SS. The summary analysis of the primary cause of seizure should be based on the latest data collected per subject prior to study completion/termination. Listing of all primary causes of seizure will be provided for the SS.

# 7 MEASUREMENTS OF TREATMENT COMPLIANCE

## 7.1 Drug accountability

Listing of drug accountability for oral solution during the BRV Extension Period will be provided for the SS.

## 7.2 Treatment compliance

Treatment compliance will be analyzed for iv BRV administered during the study Evaluation Period. Treatment compliance will be calculated per subject per infusion for iv BRV. Noncompliance will be recorded for subjects who are administered <80% or >120% of the planned BRV dose.

Compliance will be calculated as 100 times the actual dose given during the infusion at particular time point based on the Study Drug Administration CRF and dividing this quantity by the planned infusion dose at that time point. For the Exploratory Cohort, planned iv BRV dose will be calculated as 0.5 mg times body weight (kg) per subject per infusion per time point. The last weight measurement prior to the first BRV dose will be taken for this calculation.

For the Confirmatory Cohorts, planned iv BRV dose (mg/kg) will be determined based on the evaluation of BRV plasma concentrations from the Exploratory Cohort.

Treatment compliance will also be analyzed for BRV Extension Period, the planned dose for oral BRV is the same dosage administered at the end of the Evaluation Period (i.e., BRV 0.5mg/kg bid for the Exploratory Cohort). The BRV dose should not be increased but can be decreased at the discretion of the Investigator. Therefore, noncompliance will be recorded only for subjects who are administered >120% of the planned oral BRV dose. For the Confirmatory Cohorts, the planned dose will be also the same dosage administered at the end of the Evaluation Period.

Listing of the calculated treatment compliance will be provided for the SS.

# 8 EFFICACY ANALYSES

Efficacy analyses will be performed using FAS subjects from the Confirmatory Cohorts only. Only the Overall Confirmatory Cohort will be used for efficacy interpretations. Efficacy parameters will be summarized descriptively (with 95% CIs) by individual Confirmatory Cohorts and for all combined Confirmatory Cohorts. In addition, all efficacy variables will be analyzed by the latest primary cause of seizure (see categories in Section 4.8) and concomitant use of hypothermia and reported for each subject using data listings.
Seizure efficacy data may also be transformed if needed. The transformation of seizure data to be used (if needed) will be log (x + 1) where x is the neonate seizure count or the seizure burden.

## 8.1 Endpoint definitions and derivations

### 8.1.1 BRV responder and non-responder definitions

A BRV responder is defined as a subject who achieves the following reduction in seizure burden (ENS in minutes per hour) without need for rescue medication, compared to the seizure burden measured during the Baseline Period immediately prior to BRV administration, evaluated for a 2-hour period starting 1 hour after the start of initial BRV treatment:

- At least 80% reduction (≥80 percent change) in non-severe seizure burden

  (Non-severe seizure burden is defined as ≤50% seizure activity on video-electroencephalography (VEEG) in all 30-minute timespans)

OR

- At least 50% reduction (≥50 percent change) in severe seizure burden

(Severe seizure burden is defined as >50% seizure activity on VEEG in any 30-minute timespan. Timespans of 30 minutes refer to the following intervals within the 2-hour period: 0 to ≤30 minutes, >30 to ≤60 minutes, >60 to ≤90 minutes, and >90 to ≤120 minutes.)

Subjects not meeting the BRV responder definition are classified as BRV non-responders. In addition, subjects who drop out due to lack of BRV efficacy, are switched over to another AED treatment, or are administered any rescue medication (any treatment initiation with a new AED, or any increase of dose or frequency of an existing concomitant AED for the treatment of seizures during the Evaluation Period - including BZDs) during the first 3 hours after initiation of BRV treatment will be considered BRV non-responders.

### 8.1.2 Baseline seizure burden

Baseline seizure burden is defined as seizure burden measured on the continuous VEEG (total ENS in minutes per hour) during a period of up to 1 hour immediately prior to the first administration of study medication.

#### 8.1.2.1 Baseline non-severe seizure burden

Baseline non-severe seizure burden is defined as seizure activity (total ENS duration in minutes) for ≤ 15 minutes in all of the following 30-minute time periods: 0-30 and >30-60 minutes during the 1-hour Baseline Period. For example, if total ENS duration of 18 minutes occurred as 9 minutes of ENS duration in each of any two 30-minute time periods or 18 minutes of ENS are distributed over several 30 minute time intervals so that the ENS duration in each interval is ≤15 minutes, then the baseline seizure burden is non-severe.

#### 8.1.2.2 Baseline severe seizure burden

Baseline severe seizure burden is defined as seizure activity (total ENS duration in minutes) for >15 minutes in at least one of the following 30-minute time periods 0-30 and >30-60 minutes during the up to 1-hour Baseline Period. For example, if total ENS duration is 18 minutes and the distribution of ENS duration is 16 minutes in 0-30 minutes time period and 2 minutes in >30-60 minutes time period, then the baseline seizure burden is severe.

### 8.1.3 ENS definition

For this study, an ENS is defined as an electroencephalographic (EEG) seizure lasting for at least 10 seconds on VEEG.

### 8.1.4 Average per hour seizure burden (ENS in minutes per hour)

Average per hour seizure burden per subject (ENS in minutes per hour) is defined as total seizure burden measured over a period of time (in minutes) divided by the number of hours in the given period of time. That is all seizure activity times (durations in minutes) will be added up across the Evaluation Period. It will then be divided by the total duration of the Evaluation Period to calculate a seizure burden value in minutes per hour. Average seizure burden value will be calculated during the Baseline period and the Evaluation Period (and transformed the data by taking log (x +1) for both Baseline and the Evaluation Period if needed).

### 8.1.5 Percent change in baseline seizure burden

Percent change in baseline seizure burden is defined as a difference between average per hour seizure burden at baseline (calculated over the 1-hour baseline period) and average per hour

seizure burden calculated over given period of time after the start of initial BRV treatment divided by the average per hour seizure burden at baseline and multiplied by 100.

If the percent change is ≥80% (reduction in baseline) and baseline seizure burden is non-severe or if the percent change ≥50% (reduction in baseline) and baseline seizure burden is severe then this subject is defined as **BRV responder**. No rounding will be applied, one decimal will be considered for comparison (for example, if the percent change is 79.999%, then consider 1 decimal as 79.9% which is less than 80%).

### 8.1.6 Responder to other treatment

Responder to other treatment is defined as subject who stopped BRV or switched from BRV to act as a rescue medication and achieved at least 80% reduction (≥80 percent change) in non-severe seizure burden from start of other treatment to end of other treatment or at least 50% reduction (≥50 percent change) in severe seizure burden measured from initiation of other treatment to end of other treatment during the 96-hour Evaluation Period. Baseline Period for other treatment is defined as 1 hour prior to starting the other treatment. Other treatment Evaluation Period is from the start to the end of other treatment or to the end of 96-hour Evaluation Period if other treatment end is after the 96-hour Evaluation Period.

## 8.2 Statistical analysis of the secondary efficacy variable

### 8.2.1 Derivations of the main secondary efficacy variable

The main secondary efficacy variable is the proportion of responders to BRV treatment from Baseline to 3 hours after the initial BRV dose. The numerator is the number of BRV responders for main secondary efficacy variable defined in Section 8.1. The denominator is defined as the number of the subjects in the FAS from Confirmatory Cohorts.

### 8.2.2 Analysis of the main secondary efficacy variable

The main secondary efficacy variable will be summarized using descriptive statistics (counts and proportions with the 95% CIs). See Section 3.1 for the details. Subgroup analysis of main secondary efficacy variable will be produced for the latest primary cause of seizure (see categories in Section 4.8) and concomitant use of hypothermia. Listing of main secondary efficacy variable will be provided.

To further evaluate BRV efficacy, a descriptive comparison will be conducted of the main secondary efficacy variable data from N01349 with published responder rates for MDZ (historical control group matched in age and condition) effective for the treatment of neonatal seizures in subjects of similar age (<29 days of postnatal age) and condition (neonatal seizures as noted in N01349 eligibility criteria). A recent study (Weeke et al, 2016) provides response rates for second line MDZ treatment of neonatal seizures in a similar population and with primary endpoints comparable to N01349. Results from this study, as well as results from other studies available in the literature at the time of N01349 completion and with populations and efficacy endpoints comparable to N01349, will be used for these descriptive comparisons.

A listing of main secondary efficacy variable will be provided for the FAS.

### 8.2.3 Sensitivity analysis of the main secondary efficacy variable

The impact of missing data on the assessment of the main secondary efficacy variable will be evaluated with sensitivity analyses. Subjects who drop out for reasons other than due to lack of

BRV efficacy, are switched over to another AED treatment, or are administered any rescue medication (including BZDs) will be excluded from the analysis.

The numerator of the main secondary efficacy variable is defined as the number of responders to BRV treatment from Baseline to 3 hours after the initial BRV dose (see Section 8.1 for the definition of BRV responders). Subjects, who dropped out for reasons other than due to lack of BRV efficacy, are switched over to another AED treatment or received any rescue medication during the first 3 hours after the initiation of BRV treatment will be excluded from the analysis.

The denominator is defined as the number of the FAS subjects in the Confirmatory Cohorts with the following subjects excluded: subjects who dropped out for reasons other than due to the lack of BRV efficacy reasons, are switched to another AED or received any rescue medication (including BZDs) during the first 3 hours after the initiation of BRV treatment.

### 8.2.4 Derivations of the secondary efficacy variables

The following secondary efficacy variables are defined as follows:

- Proportion of subjects with at least 80% reduction in non-severe seizure burden from Baseline to 3 hours after the initial BRV treatment [***derivations:*** see the definition of baseline non-severe seizure burden in Section 8.1.2.1; reduction of at least 80% in non-severe seizure burden from baseline is defined as a ≥80% difference between average per hour seizure burden at baseline (calculated over the 1-hour Baseline Period) and average per hour seizure burden calculated over 3 hours after the start of initial BRV treatment divided by the average per hour seizure burden at baseline and multiplied by 100. The numerator is defined as the number of subjects with the 80% reduction described above. The denominator is defined as the number of subjects in the FAS from Confirmatory Cohorts with baseline non-severe seizure burden.]
- Proportion of subjects with at least 50% reduction in severe seizure burden from Baseline to 3 hours after the initial BRV treatment [***derivations:*** see the definition of baseline severe seizure burden in Section 8.1.2.2; reduction of at least 50% in severe seizure burden from baseline is defined as a ≥50% difference between average per hour seizure burden at baseline (calculated over the 1-hour Baseline Period) and average per hour seizure burden calculated over 3 hours after the start of initial BRV treatment divided by the average per hour seizure burden at baseline and multiplied by 100. The numerator is defined as the number of subjects with the 50% reduction described above. The denominator is defined as the number of subjects in the FAS from Confirmatory Cohorts with baseline severe seizure burden.]
- Absolute reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period [***derivations:*** see the definition of baseline seizure burden and of average per hour seizure burden in Section 8.1, average per hour over 96-hour Evaluation Period seizure burden is calculated as the total seizure burden during the 96-hour Evaluation Period divided by 96, the number of hours in the Evaluation Period, average per hour seizure baseline seizure burden is calculated as the total seizure burden over 1-hour Baseline Period divided by 1. The ***absolute reduction*** in average per hour seizure burden is defined as the average per hour seizure burden at the end of the 96-hour Evaluation Period minus average per hour baseline seizure burden]

- Percentage reduction in average seizure burden measured by continuous VEEG from Baseline to the end of the 96-hour Evaluation Period [***derivations:*** see the definition of baseline seizure burden and of average per hour seizure burden in Section 8.1, average per hour over 96-hour Evaluation Period seizure burden is calculated as the total seizure burden during the 96-hour Evaluation Period divided by 96, the number of hours in the Evaluation Period, average per hour seizure baseline seizure burden is calculated as the total seizure burden over 1-hour Baseline Period divided by 1. The ***percentage reduction*** is defined as the absolute reduction in average per hour seizure burden divided by the average per hour baseline seizure burden and multiplied by 100.]
- Proportion of BRV responders during the 96-hour Evaluation Period (measured at the end of the 96-hour Evaluation Period) [***derivations:*** see the definition of BRV responders for other than main efficacy variable in Section 8.1, the post-baseline seizure burden will be evaluated during the last 1 hour1 of the 96-hour Evaluation Period, the denominator is defined as the number of subjects in the FAS from Confirmatory Cohorts.]
- Proportion of subjects who are seizure-free (100% reduction in seizure burden from Baseline, i.e. those subjects whose seizure burden disappeared) at 24 hours following the start of initial BRV treatment, categorized by subjects with non-severe or severe seizure burden at Baseline [***derivations*:** the numerator is the number of subjects with 100% reduction in seizure burden from Baseline or no ENS during the last 2 hours of the 24-hour time period following the start of initial BRV treatment, see the definition of baseline seizure burden in Section 8.1, the denominator is defined as the number of subjects in the FAS from Confirmatory Cohorts.]
- Time to reduction in seizure burden for BRV responders (defined as the first time point when BRV responder criteria are met ) [***derivations:*** the time to reduction in seizure burden is measured in hours, defined as the first time point (date and time) when BRV responder criteria are met minus the date and time of the first BRV dose, event is defined as response to BRV, subjects will be evaluated for response at the following time points: 3 hours, 4 hours, 5 hours, etc. , 96 hours after the initial BRV dose. Response will be calculated referring to the last 1 hour prior to the time point. Non-responder for the analysis of other than main efficacy variable subjects defined in the Section 8.1 are censored with time to censoring defined as the date and time of the event defining the non-responder status (drop out due to lack of BRV efficacy, switch over to another AED treatment, used >1 dose of rescue medication following the first 3 hours after initiation of BRV treatment) or date and time of the end of the Evaluation Period in case there are no events of response or non-response minus the date and time of first BRV dose; when the time is not collected, use HH:MM=23:59.]
- Seizure freedom at the end of the Down-Titration Period (Confirmatory Cohorts only) [***derivations:*** defined as proportion of subjects who are seizure-free at the end of the Down-Titration Period, the numerator is the number of subjects with seizure-freedom defined as no ENS at the end of the Down-Titration Period, i.e. no ENS during 1 hour of VEEG, the denominator is defined as the number of subjects in the FAS from Confirmatory cohorts with VEEG data at the end of the Down-Titration Period.]
- Rate of at least 50% reduction in ENS frequency per hour from Baseline to the end of the 96-hour Evaluation Period [***derivations:*** the numerator is defined as the number of subjects with the 50% reduction in ENS frequency, i.e. the difference between the average ENS frequency

per hour at Baseline and the average ENS frequency per hour over the 96-hour Evaluation Period divided by the average per hour Baseline ENS frequency and multiplied by 100 should be at least 50%, the denominator is defined as the number of subjects in the FAS from Confirmatory Cohorts. Average per hour ENS frequency at Baseline is calculated as the total number of ENS over 1-hour Baseline Period divided by 1; average per hour ENS frequency at the end of the 96-hour Evaluation Period is defined as the number of ENS over 96-hour Evaluation Period divided by 96.]

- Proportion of subjects who are seizure-free by time interval at 3 hours, at 3-hour intervals thereafter through 24 hours, and every 12 hours to 24 hours following the start of the initial BRV treatment [***derivations:*** the numerator is defined as the number of subjects with no ENS or 100% reduction in seizure burden from Baseline to 3 hours after the first BRV dose and then with no seizure burden at 6, 9, 12, 15, 18, 21, 24, 36, 48, 60, 72, 84, 96 hours after the first BRV dose, the 2 hours of VEEG prior to the defined time point will be evaluated for seizure freedom/ENS absence; the denominator is defined as the number of subjects in the FAS from Confirmatory Cohorts, see the definition of reduction in seizure burden from Baseline in Section 8.1.]
- Absolute difference in clinical seizures (annotated by central reader) at the end of the first 24-hour of the 96-hour Evaluation Period from Baseline for neonates with motor seizures at the time of inclusion [***derivations: absolute difference*** is defined as the difference between the number of clinical seizures observed during the 1-hour Baseline Period and the number of post-baseline clinical seizures observed during the 1 hour prior to the end of the 24-hour Evaluation Period]
- Percent difference in clinical seizures (annotated by central reader) at the end of the first 24 hour of the 96-hour Evaluation Period from Baseline for neonates with motor seizures at The Time of Inclusion [***Derivations: Percent Difference*** is Defined as the Absolute Difference in Clinical Seizures (Defined Above) Divided by the Number of Clinical Seizures During The Baseline Period and Multiplied by 100.]

### 8.2.5 Analysis of the secondary efficacy variables

Categorical secondary efficacy variables will be summarized using descriptive statistics (counts and proportions with the 95% CIs). Continuous key efficacy variables will be analyzed descriptively as described in Section 3.1.

Time to reduction in seizure burden will be summarized descriptively by individual Confirmatory Cohorts and for all combined Confirmatory Cohorts, the cumulative number of events (response to BRV), Kaplan-Meier estimates at each hour during the Evaluation Period and median time to seizure burden reduction with 95% confidence interval will be provided. Also, graphical displays of Kaplan-Meier curves will be provided for each cohort separately.

A listing of secondary efficacy variables will be provided for the FAS.

## 8.3 Statistical analysis of other efficacy variables

### 8.3.1 Derivations of other efficacy variables

The other efficacy variables are defined as follows:

- Absolute and percentage reduction from Baseline in seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment [***derivations:*** see the definition of baseline seizure burden and of average per hour seizure burden in Section 8.1, the ***absolute reduction*** is defined as the difference between the baseline average per hour seizure burden and average per hour seizure burden at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment. The ***percentage reduction*** is defined as the absolute reduction in seizure burden divided by the baseline average per hour seizure burden and multiplied by 100.]
- Categorized percentage reduction from Baseline to the end of the 96-hour Evaluation Period in seizure burden (<-25% [worsening], -25% to <25% [no change], 25% to <50%, 50% to <80%, and ≥80%) [***Derivations:*** The ***percentage reduction*** of seizure burden is defined as the difference between the average per hour baseline seizure burden and the average per hour seizure burden at the end of the 96-hour Evaluation Period divided by the average per hour baseline seizure burden and multiplied by 100. For the definition of the average per hour seizure burden, please see Section 8.1.]
- Proportion of BRV responders by time interval at evaluation periods of 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment [***derivations:*** see the definition of BRV responders in Section 8.1, for the numerator calculate the number of responders during the given above evaluation periods 0-3 hours, >3-6 hours, >6-12 hours, >12-24 hours, >24-36 hours, etc., the denominator is defined as the number of subjects in the FAS from Confirmatory Cohorts.]
- Proportion of subjects who are switched over from BRV to another AED during the 96-hour Evaluation Period [***derivations:*** for the numerator calculate the number of subjects who stopped iv BRV and started another AED during the Evaluation Period, the denominator is defined as the number of subjects in the FAS from Confirmatory Cohorts.]
- Proportion of responders to other treatment during the 96-hour Evaluation Period (including at the end of the 96-hour Evaluation Period, and by time intervals: 0 hours to 3 hours, >3 hours to 6 hours, >6 hours to 12 hours, >12 hours to 24 hours, >24 hours to 36 hours, >36 hours to 48 hours, >48 hours to 72 hours, and >72 hours to 96 hours after the start of initial BRV treatment. [***Derivations:*** only subjects who switched from BRV to other treatment (stopped BRV due to lack of efficacy) during the 96-hour Evaluation Period will be considered for this variable. See the definition of ***responder to other treatment*** in Section 8.1. The numerator for proportion of responders to other treatment at the end of 96-hour Evaluation Period is the number of responders to other treatment as defined in Section 8.1; the denominator is the number of subjects in FAS from Confirmatory Cohorts. The numerator for proportion of responders to other treatment during the time intervals: 0-3 hours, >3-6 hours, >6-12 hours, >12-24 hours, >24-36 hours, >36-48 hours, >48-72 hours, >72-96 hours after the start of initial BRV treatment is defined as the number of responders to other treatment with the other treatment stop date and time during 0-3 hours, >3-6 hours,

>6-12 hours, …, >48-72 hours, >72-96 hours after the start of initial BRV treatment respectively. The denominator is the number of subjects in FAS from Confirmatory Cohorts.]

### 8.3.2 Analysis of other efficacy variables

Categorical other efficacy variables will be analyzed using descriptive statistics (counts and proportions with the 95% CIs). Continuous key efficacy variables will be analyzed descriptively as described in Section 3.1.

A listing of other efficacy variables will be provided for the FAS.

# 9 PHARMACOKINETICS

The PK data, along with the safety data collected from the Exploratory Cohort and the 3 Confirmatory Cohorts, will be reviewed by the DMC. In addition, plasma concentrations of BRV and its metabolites will be monitored and subjected to interpretation on an ongoing basis. The analysis of the PK parameters for the Exploratory and Confirmatory Cohorts will include a sub-analysis for any concomitant use of hypothermia if allowed by the available data.

## 9.1 Pharmacokinetics

Pharmacokinetics summary tables and listings will be produced on PK-PPS. Listings of the PK parameters and plasma concentrations for all cohorts will be provided.

### 9.1.1 Exploratory Cohort

Based on the plasma samples collected for the Exploratory Cohort, PK parameters AUC, $C_{max}$, $t_{1/2}$, volume of distribution, and clearance, will be summarized.

Summary tables will be provided for the PK parameters, for plasma concentrations of BRV, ucb-42145, ucb-100406-1, ucb-107092-1 and of concomitant AEDs (PB and PHT).

The same summary tables for subjects with concomitant hypothermia will be provided.

Individual plots of plasma concentrations over time will be provided.

### 9.1.2 Confirmatory Cohorts

Based on the plasma samples collected for the Confirmatory Cohorts, PK parameters AUC, $C_{max}$, $t_{1/2}$, volume of distribution, and clearance, will be summarized.

Summary tables will be provided for the PK parameters, for plasma concentrations of BRV, ucb-42145, ucb-100406-1, ucb-107092-1 and of concomitant AEDs (PB and PHT) for each Confirmatory Cohort separately and overall for combined Confirmatory Cohorts.

Summary tables for subjects with concomitant hypothermia use will be provided for each Confirmatory Cohort separately and overall for combined Confirmatory Cohorts.

Individual plots of plasma concentrations over time will be provided for each Confirmatory Cohort separately and overall for combined Confirmatory Cohorts.

# 10 SAFETY ANALYSES

All safety analyses will be presented for the SS. Descriptive summaries will be presented overall and by cohorts for

- AEs,

- SAEs,
- physical and neurological examination assessments,
- laboratory results,
- vital signs, (SBP, DBP, respiration rate, heart rate, temperature and oxygen saturation)
- body weight, and
- head circumference.

Following subject characteristics related to safety will also be summarized descriptively:

- cooling status variables (target low body temperature, age since birth when cooling began, duration of cooling [date and start and stop time of cooling], and timing of cooling in relation to first dose of BRV),
- rewarming status variables (duration of rewarming [date and start and stop time of rewarming] and timing of rewarming in relation to first dose of BRV),
- the mother's use of AEDs (including BZD and opiates) at childbirth,
- N-PASS score,
- Thompson score,
- the primary cause of seizure (HIE, hemorrhage, or infarction; CNS malformations; CNS infections; undetermined causes), and
- EEG parameters for the assessment of sedation.

## 10.1 Extent of exposure

The duration of BRV exposure, is defined as the start date and time of last administration of study medication (BRV) minus the start date and time of first administration of study medication (BRV) plus duration of dosing interval (12 hours, however the dosing interval may be adjusted if results point into that).

The duration of iv BRV exposure during the Evaluation Period will be displayed in hours. The duration of exposure of iv BRV and oral BRV solution during the BRV Extension Period will be displayed in days.

The date and time of last administration of study medication is the maximum date and time from the CRFs "Study Medication Administration (Infusion)" and "Study Medication Administration (Oral Solution)".

Exposure as categorical parameter will be summarized as number of doses received (1 dose, > 1 dose) and continuous parameter (in hours or days). For the continuous parameter, descriptive statistics for the duration of exposure to study medication in hours or days will be presented. For the number of doses, the number and percentage of subjects who received 1 dose and >1 doses will be summarized. Handling of study medication missing data is described in Section 4.2.4.

Exposure as a continuous parameter will be categorized (>0-12 hours, >12-24 hours, >24-48 hours, >48-72 hours, >72-96 hours, >96 hours – 14 days, >14 days) by study periods for

Exploratory, individual Confirmatory Cohorts and for overall combined Confirmatory Cohorts for the SS.

The following listings will be provided:

- study medication administration,
- exposure to study medication BRV infusion, and
- exposure to study medication BRV oral solution.

## 10.2 Adverse events

Treatment-emergent adverse events (TEAEs) are defined as AEs which have onset on or after the start date and time of initial study medication (BRV) administration.

### 10.2.1 General summaries of AEs

A table with overall summary of AEs will be provided separately for Evaluation Period, Extension Period, Down-Titration Period, Safety Follow-up Period and for the entire study, the table will include:

- the numbers and percentages of subjects with at least one TEAE
- the number and percentage of subjects with serious TEAEs
- the number and percentage of subjects with non-serious TEAEs
- the number and percentage of subjects with a TEAE that led to permanent discontinuation of study medication
- the number and percentage of subjects with a drug-related TEAE
- the number and percentage of subjects with a drug-related serious TEAE
- the number and percentage of subjects with a severe TEAE
- the number and percentage of subjects with AE leading to death
- the number and percentage of subjects with TEAEs leading to death
- the number and percentage of subjects who died prior to the first BRV dose

The following summary tables of AEs/TEAEs will be provided by primary SOC and PT. Summaries will be presented by Exploratory Cohort and individual Confirmatory Cohorts and for overall combined Confirmatory Cohorts for the SS.

- Incidence of pre-treatment AEs

  Pre-treatment AEs are defined as AEs that had onset strictly prior to the date/time of the first dose of BRV
- Incidence of TEAEs (for Evaluation Period, Extension Period, Down-Titration Period, Safety Follow-up Period and for the entire study)
- Incidence of serious TEAEs
- Incidence of non-serious TEAEs

- Incidence of TEAEs by maximum intensity
  Each subject will be counted at most once per primary SOC or PT according to the maximum intensity of all AEs within that SOC or PT. Severe intensity will be assumed for AEs for which intensity is not specified.
- Incidence of drug-related TEAEs
  Drug-related AEs are AEs for which the relationship to study medication is specified by the Investigator as Related or AEs for which relationship is not specified.
- Incidence of drug-related serious TEAEs
  Drug-related AEs are AEs for which the relationship to study medication is specified by the Investigator as Related or AEs for which relationship is not specified.
- Incidence of TEAEs by relationship
- Incidence of non-serious TEAEs by relationship
- Incidence of serious TEAEs by relationship
- Incidence of fatal TEAEs by relationship
- Incidence of TEAEs leading to permanent discontinuation of study medication
- Incidence of TEAEs leading to death
- Incidence of non-serious TEAEs above reporting threshold of 5% of subjects in any cohort
- Incidence of non-serious TEAEs above reporting threshold of 5% of subjects by relationship
- Incidence of TEAEs of Interest
  Defines as a selection of TEAEs identified by UCB to be of interest to BRV. These are identified using an UCB Excel file.

For the incidence of serious TEAE, TEAEs leading to permanent discontinuation of study medication and TEAEs of interest, the summary of subject numbers will be reported.

Listings AE Glossary and all adverse events will be provided for all subjects screened.

## 10.3 Clinical laboratory evaluations

### 10.3.1 Hematology, Chemistry and Urinalysis Parameters

Mandatory and optional clinical laboratory parameters are listed in Section 12.1. Continuous laboratory variables summary statistics of actual values and change from Baseline will be presented by Exploratory Cohort, individual Confirmatory Cohorts and for overall combined Confirmatory Cohorts for the SS at each study visit and time point to the end of the Evaluation Period.

The number and percentage of subjects with possibly clinically significant treatment-emergent (PCST) value, PCST low values, and PCST high values will be summarized by individual Confirmatory Cohorts and for overall combined Confirmatory Cohorts for the SS. The summary of subject numbers will be reported as well. PCST criteria are included in the Appendices in the Section 12.1.

The following listings will be provided:

- a separate subject data listing for PCST (all laboratory assessments for subjects with PCST values are to be included in the listing),
- all laboratory results of clinical chemistry, hematology and urinalysis laboratory tests.

### 10.3.2 Potential Drug Induced Liver Injury

A summary of the number and percentage of subjects who met PDILI criteria at any point in time will be summarized overall, and by cohort for all subjects. Results from local laboratory testing should be included, if applicable. Subjects who meet one or more of the criteria for potential drug-induced liver injury (PDILI) at any point in time will be listed. The listing will display all assessments for which at least one of the criteria for PDILI (see Appendix **Error! Reference source not found.**) was fulfilled for a given subject, and will display all results obtained at that time for the specified variables associated with PDILI. Potential Hy's law cases will be flagged.

All PDILI events require immediate action, testing, and monitoring. The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are included but not limited to those listed in laboratory measurements.

Additional PDILI information will also be listed. If specific PDILI information collected separately is matching to the entries in the standard eCRF pages collected for all subjects, the specific PDILI information will be added to the corresponding listing for the standard eCRF information. For information collected on top (eg, family history of PDILI, lifestyle) a new listing will be generated.

Suspected hepatic events will be listed for the SS.

## 10.4 Vital signs, physical findings, and other observations related to safety

Vital signs SBP (systolic blood pressure), DBP (diastolic blood pressure), respiration rate, temperature, oxygen saturation including apnea and heart rate are assessed throughout the study. Physical and neurological assessments include Sarnat scale for subjects with HIE, psychometric parameter N-PASS, and EEG.

### 10.4.1 Vital signs

Observed values for SBP, DBP, respiration rate, heart rate, temperature and oxygen saturation will be summarized for each visit and time points. Changes from Baseline for SBP, DBP, heart rate, respiration rate, temperature, and oxygen saturation will be summarized for post-baseline visits and time points. Similar summaries will be provided for body weight.

Line graph plots of observed vital sign parameters mean values and change from baseline in vital sign parameters mean values will be presented by visit and time point.

The numbers and percentages of subjects with a PCST (possibly clinically significant treatment emergent) value, PCST low values, and PCST high value will be summarized for SBP, DBP, heart rate, and respiration rate by individual Exploratory Cohort, individual Confirmatory Cohorts and for overall combined Confirmatory Cohorts for SS. PCST criteria are based on FDA

Division of Neuropharmacologic Drug Products guidelines with some UCB-defined additions and are included in the Appendices in the Section 12.1.

A listing of vital signs will be provided for the SS.

### 10.4.2 Hypothermia treatment

Listing of hypothermia treatment will be provided for the SS. It will include information if subject received hypothermia treatment, age since birth, age since birth when cooling began, target low body temperature, date and time cooling began, date and time cooling ended, duration of cooling (in days, hours and minutes, date and time cooling ended minus date and time cooling started plus 1 minute), timing of cooling in relation to first BRV dose (in hours, relative day and time), date and time rewarming began, date and time rewarming ended, duration of rewarming (in days, hours and minutes, date and time of end of rewarming minus date and time of start of rewarming plus 1 minute) and timing of rewarming in relation to first dose of BRV (in hours, date and time of start of rewarming minus date and time of first BRV dose).

### 10.4.3 Mother's use of AEDs

A listing of mother's use of AEDs (including BZDs and/or opiates) with the information on mother taking AEDs (BZDs and/or opiates) at the time of delivery, taken medication, dose per intake will be provided for the SS.

### 10.4.4 Sarnat scale

The Sarnat grading scale comprises 6 components: alertness, muscle tone, seizures, pupils, respiration, and duration assessed together to provide 3 stages (Grade I [mild]; Grade II [moderate]; Grade III [severe]) of HIE. Summaries of shift from Baseline to 24h, 48h, 72h, 96h (72h and 96h visits are for Confirmatory Cohorts only) and last value (defined as the latest available value) will be provided based on the categories Grade I (Mild), Grade II (Moderate) and Grade III (Severe) by individual cohorts and for overall combined Confirmatory Cohorts for the SS subjects with HIE. A listing of Sarnat scale will be provided.

### 10.4.5 Thompson score

Thompson score ranges from 0 to 22 and is calculated by adding the scores from all 9 aspects of the neurological examination of infants with HIE.

Observed values and changes from Baseline in Thompson score will be summarized for post-baseline visits and time points by individual cohorts and for overall combined Confirmatory Cohorts for the SS subjects with HIE. A listing of Thompson score will be provided for the SS.

### 10.4.6 N-PASS scale

The N-PASS scale was developed as a clinically relevant tool to assess ongoing or acute pain in neonates and infants, as well as sedation levels. The 5 indicators are: (1) crying/irritability (silent cry observed in the intubated infant is scored as a cry), (2) behavior/state, (3) facial expression, (4) extremities/tone, and (5) vital signs. Points are added to the preterm infant's pain score to approximate the normal response of a full-infant. These points were derived from the Premature Infant Pain Profile pain assessment tool (Stevens et al, 1996). Gestational age groups are <28 weeks (3 points), 28 to 31 weeks (2 points), 32 to 35 weeks (1 point), and >35 weeks (0 points). Scores range from 0 to 13. Behavioral state as a modifier was not included in the development of N-PASS, as it was designed initially for ongoing pain assessment (Hummel et al, 2010).

The N-PASS total Sedation score will be calculated as the sum of negative or zero scores of individual indicators (0, -1, -2), the range of sedation score is from 0 to -10. A score of 0 is given if the infant has no signs of sedation, does not under-react. Deep sedation is when the score is from -10 to -5, light sedation is when the score is from -5 to -2.

The N-PASS total Pain/Agitation score is calculated as the sum of positive scores of individual indicators (1, 2). The total pain score ranges from 0 to 11. Add 1 if gestational age is <30 weeks.

Observed values and changes from Baseline in N-PASS total sedation and total pain scores will be summarized for post-baseline visits and time points by individual cohorts and for overall combined Confirmatory Cohorts for SS subjects.

A listing of N-PASS scores will be provided for the SS.

### 10.4.7 EEG parameters

A listing of video EEG monitoring (start date and time, stop date and time, was this temporarily stopped, interim stop time, reason for temporary stop, restart time, was EEG permanently discontinued, reason for discontinuation) for the SS and a listing of reactivity to stimulus on vEEG (change of background activity with auditory stimulus, change of background activity with painful stimulus) will be provided for the SS.

### 10.4.8 Biometric parameters

Biometric parameters are body length, body weight and head circumference. Observed values and changes from Baseline in biometric parameters will be summarized for post-baseline visits and time points by individual cohorts and for overall combined Confirmatory Cohorts for SS subjects. A listing of biometric parameters will be provided for the SS.

### 10.4.9 Mechanical ventilation

Mechanical ventilation variables:

− Number and percentage of subjects requiring mechanical ventilation during the Evaluation Period [***derivations:*** for subjects from the Exploratory Cohort, the numerator is defined as the number of subjects with the mechanical ventilation start date and time after the initial BRV dose and no later than 48 hours after the start date and time of the initial BRV dose. For subjects from the Confirmatory Cohort, the numerator is defined as the number of subjects with the mechanical ventilation start date and time after the initial BRV dose and no later than 96 hours after the start date and time of the initial BRV dose, the denominator is defined as the number of subjects in the FAS].

− Duration of mechanical ventilation during the Evaluation Period [***derivations:*** the duration of mechanical ventilation during the Evaluation Period is defined if the start date and time of the ventilation is after the first BRV dose and not later than 48 hours after the first BRV dose for subjects from the Exploratory Cohort and if the start date and time of the mechanical ventilation is after the first BRV dose and no later than 96 hours after the first BRV dose for subjects from the Confirmatory Cohorts. For subjects from the Exploratory Cohort, the duration is calculated as end date and time of the mechanical ventilation minus the start date and time of the ventilation if the end date and time of the ventilation is no later than 48 hours after the first BRV dose for subjects. If the end date and time of the ventilation is later than 48 hours after the first BRV dose, then the duration is calculated as 48 hours minus start date and time of the ventilation. For

subjects from the Confirmatory Cohorts, the duration is calculated as end date and time of the ventilation minus the start date and time of the ventilation if the end date and time of the mechanical ventilation is no later than 96 hours after the first BRV dose. If the end date and time of the ventilation is later than 96 hours after the first BRV dose, then the duration is calculated as 96 hours minus start date and time of the ventilation. The duration is calculated in hours, i.e. the number of days is multiplied by 24, then the number of hours added, and the number of minutes divided by 60 is added].

Summary table will display the number and percentage of subjects requiring mechanical ventilation during the Evaluation Period and descriptive statistics for the duration of mechanical ventilation during the Evaluation Period. The summary table will be presented by individual cohorts and for overall combined Confirmatory Cohorts for SS subjects.

Listing of mechanical ventilation will be provided for the SS.

### 10.4.10 Bayley-III® score

Neurodevelopmental tests validated for age and language will be done after 1 year for subjects who qualify to enter the long-term follow-up study in countries where a validated translation of the Bayley Scales of Infant and Toddler Development ®, Third Edition (Bayley-III®) score is available.

Listing of Bayley-III score will be provided for the SS.

### 10.4.11 Withdrawal and rebound phenomena

Withdrawal and rebound phenomena will be assessed by observing any AEs experienced by subjects following the cessation of BRV administration. These AEs will be reported by the Investigators, and any AEs relating to BRV withdrawal will be used for the analysis of withdrawal and rebound phenomena. Withdrawal and rebound phenomena, if any, will be captured from data collected at the end of BRV exposure for subjects in Confirmatory Cohorts.

The following summaries will be provided for the SS: incidence of TEAEs with onset during the Down-Titration Period, incidence of TEAEs with onset during the Down-Titration Period and leading to permanent discontinuation of study medication.

A listing of AEs with onset during the Down-Titration Period will be provided for the SS.

## 10.5 AED plasma level monitoring

Listing of AED plasma level monitoring will be provided for the SS.

## 10.6 Drug-Induced Liver Injury (DILI)

Where applicable, the following listings will be provided for the SS: family medical history for suspected DILI cases, hepatic event supplemental medical history, information on potential hepato-toxic medications injury, physical examination for DILI, symptoms of hepatitis and hypersensitivity, most recent study medication administration for DILI, local laboratory tests for DILI and vital signs for DILI.

# 11 REFERENCES

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# 12 APPENDICES

## 12.1 Laboratory Parameters

### Table 12–1: Mandatory laboratory measurements

| Hematology | Biochemistry |
|---|---|
| Basophils | Calcium |
| Eosinophils | Chloride |
| Lymphocytes | Potassium |
| Atypical lymphocytes | Sodium |
| Monocytes | Glucose |
| Neutrophils | Urea/BUN[a] |
| Hematocrit | Creatinine[b] |
| Hemoglobin | Creatine kinase |
| MCH | AST |
| MCHC | ALT |
| MCV | ALP |
| Platelet count | GGT |
| RBC count | LDH |
| WBC count | Total bilirubin |
| | Direct (conjugated) bilirubin |

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma-glutamyltransferase; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell

[a] Urea or BUN to be tested depending on the local lab´s standard panel for neonates.

[b] During the first days of life, creatinine will only be collected if the site assesses this parameter per standard of care.

### Table 12–2: Optional laboratory measurements

| Biochemistry | Urinalysis[b] | Endocrinology[c] |
|---|---|---|
| Total cholesterol[a] | Protein | TSH |
| | Bacteria | $T_4$ |
| | Glucose | |
| | pH | |
| | RBC | |
| | WBC | |

RBC=red blood cell; $T_4$=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell

[a] Total cholesterol to be measured if this is part of the local lab´s standard panel for neonates.

[b] Urinalysis to be performed only if a urine sample was obtained for clinical purposes. A urine dipstick is acceptable.

[c] TSH and $T_4$ to be recorded for the study only if measured for neonatal screening of congenital hypothyroidism prior to or during study participation.

## 12.2 Potentially clinically significant treatment-emergent criteria (PCST) for neonates (postnatal age up to 1 month)

**Introduction**

This document defines rules to be applied in the safety analyses of the UCB Pharma, Inc. clinical development programs in CNS Therapeutic Area. Rules for detecting possibly clinically significant treatment-emergent laboratory values, vital signs, and ECG parameters are considered. The purpose of this document is to bring consistency to reviewing laboratory data without over-riding the Investigator's clinical assessment of these parameters within the clinical context of the study subject.

**POSSIBLY CLINICALLY SIGNIFICANT TREATMENT-EMERGENT (PCST) CRITERIA**

These possibly clinically significant treatment-emergent (PCST) values are based on grade 2 toxicity if appropriate grading is available for age group, based on abnormal values or clinical experience based on discussion with [redacted] (see comments).

### 12.2.1 Blood pressure / vital signs

| Parameter | low | high | Comment |
|---|---|---|---|
| Heart rate | <100 | >200 | Normal range neonates 85-205 PALS/EPLS[1]<br>Grade 2 is defined as Asymptomatic or symptomatic increase or decrease in heart rate, responsive to medical therapy[2]. Values adapted based on discussion with JA. |
| Respiration rate | <30 | >60 | Normal range neonates 30-60 EPLS[1]<br>Grade 2 is considered persistent tachypnea and/or hypoxemia requiring high $FiO_2$ supplementation or CPAP. Associated with other clinical symptoms (nasal flaring, grunting, retractions, pallor, or cyanosis)[2] |
| Systolic BP | <40 mmHg | >100 mmHg | Normal range preterm day 1-7: 48-63 mmHg; term day 1-week 4: 61-95 mmHg[3]<br>Grade 2 is considered symptomatic and persistent decrease in systolic or mean arterial blood pressure ≥15 mm Hg below normal for age and gender (symptomatic and persistent increase of >= 35 mmHg above normal and gender)[2]<br>Per discussion with JA systolic BP below 48 mmHg may occur in preterm infants therefore 40 was chosen. |
| Diastolic BP | <20 mmHg | n/a | Normal range preterm day 1-7: 25-35 mmHg; term day 1-week 4: 30-55 mmHg[3]<br>Per JA diastolic BP <20 would be clinically meaningful. Usually clinical decisions in this setting are made based on MAP rather than systolic and diastolic pressure |



[1]Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; published online March 15. DOI:10.1016/S0140-6736(10)62226-X.

[2] Munoz et al.; Assessment of Safety in Newborns of Mothers Participating in Clinical Trials of Vaccines Administered During Pregnancy; Clinical Infectious Disease 2014; Table 1: Recommended core dataset of AE definitions and Severity grading

[3] Blood pressure disorders - *Victorian Agency for Health Information, Safer Care Victoria* on https://www.bettersafercare.vic.gov.au/resources/clinical-guidance/maternity-and-newborn-clinical-network/blood-pressure-disorders#goto-normal-neonatal-blood-pressure-values

### 12.2.2 Hematology parameters

| Parameter | low | high | Comment |
|---|---|---|---|
| WBC count cells/mm3 | ≤ 7d: <5500<br><br>>7d: <2000 | >50000 | Grade 2 tox criteria[4]<br>No criteria defined for high WBC; definition based on discussion with JA |
| Neutrophils cells/mm3 | ≤ 1d: <2000<br><br>>1d: <1000 | n/a | Grade 2 tox criteria[4]<br>No criteria defined for high neutrophils count<br>Adapted based on discussion with JA |
| Platelets Cells/mm3 | <100.000 | >1000000 | Grade 2 tox criteria[4]<br>No criteria defined for high platelets count; definition based on discussion with JA |
| Hemoglobin g/dL, (mmol/L) | ≤ 7d: <13 (<8.05)<br><br>8-≤21d: <11 (<6.81)<br><br>22-35d: <9.5 (<5.88) | ≤ 7d: > 16 g/dl | Grade 2 tox criteria[4]<br>No criteria defined for high hemoglobin. DMID criteria are more stringent[5]<br>High Hb cutoff added per JA |



[4] U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. Available from: https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf

[5] DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

### 12.2.3 Chemistry (without Bilirubin)

| Parameter | low | high | Comment |
|---|---|---|---|
| Calcium mg/dL (mmol/L) | <7d: <6.5 (<1.63)<br><br>>=7d: <7.8 (<1.95) | <7d: >=12.4 (>=3.1)<br><br>>=7d: >=11.5 (>=2.88) | Grade 2 toxicity based on DAIDS criteria[4] |
| Potassium mEq/L (mmol/L) | <3.0 | >6.0 | Grade 2 toxicity based on DAIDS criteria[4] |
| Sodium mEq/L (mmol/L) | <130 | >=150 | Grade 2 toxicity based on DAIDS criteria[4] |
| Glucose mg/dl (mmol/L) | <50 (<2.22) | >160 (>13.89) | Grade 2 toxicity based on DAIDS criteria[4] |
| AST/ALT/ALP | n/a | >2.5 ULN | Grade 2 toxicity based on DAIDS criteria[4] |

### 12.2.4 Chemistry (Bilirubin)

| Bilirubin mg/dl | | | |
|---|---|---|---|
| **Postnatal Age** | **GA<38** | **GA>=38** | **Comment** |
| ≤12 h | 6 | 8 | Considered PCST if bilirubin values reach cutoff for phototherapy recommendation, considering neonates with risk factors<br>Based on AAP guideline 2004[6] |
| >12 h and ≤ 24 h | 8 | 10 | |
| >24 h and ≤ 48 h | 11 | 13 | |
| >48 h and ≤ 72 h | 13 | 15 | |
| >72 h and ≤ 96 h | 14 | 17 | |
| > 96h | 15 | 18 | |



[6] Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation, AAP, PEDIATRICS Vol. 114 No. 1 July 2004

## 12.3 PDILI

| Laboratory value | |
|---|---|
| **ALT or AST** | **Total bilirubin** |
| ≥3xULN[b] | ≥2xULN[ab] |
| ≥3xULN | NA |
| ≥5xULN (and ≥2x baseline) | <2xULN |
| ≥3xULN (and ≥2x baseline) and <5xULN | <2xULN |

[a] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[b] The criteria of Hy's Law are (ALT or AST ≥ 3×ULN) and total bilirubin ≥ 2×ULN.

# 13 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN (SAP)

## 13.1 Change from Final SAP 26 April 2018 to SAP Amendment 1

- List of abbreviations was updated
- Section 1: updated protocol version
- Section 2.1 and throughput the rest of the SAP: phenobarbital (PB) was replaced by previous antiepileptic drug (AED)
- Section 2.2: aligned the sub-sections to the protocol to stay consistent between the documents
- Section 2.2.1: added endpoint Plasma concentrations of BRV on other occasions
- Section 2.2.2:
  - separate section for main efficacy variable was removed to stay consistent between SAP and protocol
  - endpoints were listed and derivation of endpoints were removed from this section
- Section 0: section was aligned with protocol to define secondary safety variable (AE) and list other safety variables
- Section 2.3:
  - The sentence "N01349 consists of 2 steps including a comparison with a historical control from literature (midazolam (MDZ) treatment from literature of subjects matched in age and condition) for the evaluation of efficacy." was replaced by "N01349 consists of a 2-step design and includes a descriptive comparison with a historical control group (matched in age and condition) from literature treated with AEDs per System Organ Class (SOC) and diagnostic methods."
  - "multiple therapeutic doses of MDZ" was replaced by "AEDs for the treatment of ENS per SOC (first-line, second-line, or subsequent treatment; choice of treatment ".
  - Reference "N01266" as long term study was removed to use a more general wording
- Section 2.3.1 and Section 2.3.2 : Specified information about study periods and cohorts, and reworded for clarification according to protocol amendments.
- Section 2.3.3: Specified periods for the Confirmatory Cohorts
- Section 2.4:
  - Removed "MZD treated"
  - Specified that only subject from Confirmatory Cohort who drop out or withdrawal will not be replaced.
- Section 3.1: 25$^{th}$ and 75$^{th}$ percentile were removed from standard descriptive statistics as there are not foreseen in the standard mock shells.
- Section 3.2.1.2: Corrected typo of "mediation" to "medication"

- Section 3.2.2: Removed all repeated texts from Section 2.3 and defined start and end of each study period for Exploratory Cohort and Confirmatory Cohorts.
- Section 3.2.4: Section added to describe who is classified as completing the study.
- Section 3.3: Sentence "Assessments taken on the date of study medication administration without a reported time will not be considered for baseline assessments (eg, will be assumed to have been taken after the start time of study medication administration)" was removed as this could lead to missing baseline value.
- Section 3.5: Abbreviations were used
- Section 3.6: Enrolled Set was removed as it is not defined in the protocol.
- Section 4.2.5: Section added to describe potential impact of COVID-19 on this study and, how information about this will be captured and used.
- Section 4.3: aligned the DMC meeting occurrence to the DMC Charter to stay consistent between the documents.
- Section 5.2:
  - Main categories of protocol deviations were added.
  - Listing of subjects excluded from FAS will not be needed and is removed. Only subject listing excluded from PK-PPS Set will be provided.
  - Information added to describe how subjects with a completed COVID-19 Impact eCRF page will be assessed, and displayed.
- Section 6.1:
  - Clarified that demographic variables will be presented for FAS, PK-PPS and SS overall and by cohorts.
  - "Gestational age (weeks)" was replaced by "Corrected gestational age".
  - "Postnatal age" was added
  - "HIE status" was added.
- Section 6.2: Listings will be provided for SS instead of ES, which was removed as not defined in protocol.
- Section 6.4.2: Sentence "In the event of ambiguity or incomplete data which makes it impossible to determine whether a medication was concomitant or not, the medication will be considered as concomitant" added for clarity.
- Section 6.4.3, 6.4.4, 6.4.5 and 6.4.6: Subject data listings were added.
- Section 7.1: It was specified that listing for oral solution will be provided during the BRV Extension Period for the SS.
- Section 8:

  - Sentence “Seizure efficacy data may also be transformed if needed. The transformation of seizure data to be used (if needed) will be log (x + 1) where x is the neonate seizure count or the seizure burden” was added for clarification.
  - Section was reordered to have first the endpoint definition and derivation and then section for analysis.
  - Added subsection titles for each definition of endpoints.
- Section 8.1.1 Reworded for clarification.
- Section 8.1.2 Added subsection to explain difference between non-severe and severe baseline seizure burden and derivation of seizure burden.
- Section 8.2: Renamed section to “Statistical analysis of the secondary efficacy variables” to stay align with protocol.
- Section 8.2.1, 8.2.2, 8.2.3 and 8.2.5: Added “secondary” to section titles for clarification.
- Section 8.2.4:
  - Title changed from “Statistical analysis of the key efficacy variables” to “Derivations of the secondary efficacy variables”.
  - Absolute and percentage reduction in absolute seizure burden were split into two passages.
  - Absolute and percent difference in clinical seizures were split into two passages.
- Section 8.2.5 and 8.3.2: FAS analysis set was added to the listing.
- Section 10:
  - SBP, DBP, respiration rate, pulse rate, temperature and oxygen saturation were added to the vital signs.
  - Updated wording for clarification.
- Section 10.1
  - Added “start” to clarify that the start date and time of administration is used for exposure calculation.
  - Removed “Multiply the number of days by 24, add number of hours and number of minutes divided by 60” as this will be not needed.
- Section 10.2: Replaced “Treatment-emergent adverse events (TEAEs) are defined as AEs which have onset on or after the start date and time of study medication administration” with “Treatment-emergent adverse events (TEAEs) are defined as AEs which have onset on or after the start date and time of initial study medication (BRV) administration” for clarification.
- Section 10.2.1:
  - Extension and Safety Follow-up Period was added for Incidence of TEAE by period.
  - Summary for Incidence of TEAEs leading to death was added.

- Section 10.3: Added "Mandatory and optional clinical laboratory parameters are listed in Section 12.1" for clarification.
- Section 10.3.2 Potential Drug Induced Liver Injury was added.
- Section 10.4.2, 10.4.5, 10.4.6, 10.4.7, 10.4.8, 10.4.9 and 10.4.11: Added SS analysis set for listing of hypothermia treatment, listing of Thomson score, listing of N-PASS scores, listing of EEG parameters, listing of biometric parameters, listings of mechanical ventilation and for the summaries and listings of withdrawal and rebound phenomena.
- Section 12.1: Laboratory parameters were added.
- Section 12.2.1: Pulse rate was replaced by heart rate to stay consistent throughout the document.
- Section 12.3: PDILI was added.
- Section 13: Changes to the final SAP 16 April 2018 were added.

## 13.2 Change from SAP Amendment 1 to SAP Amendment 2

- List of abbreviations was updated
- Section 2.2.3.2 and throughput the rest of the SAP: pulse rate was removed
- Section 3.2.1.1: Clarified how the relative day and time will be displayed in listings
- Section 3.3: Section added to describe the relationship among three age indicators and, how each indicator will be calculated.
- Section 3.4: It was specified that if baseline assessment of biometric parameters (length, weight, head circumference) is taken on the same day as first dose of BRV infusion and assessment time is not known, the latest value at Screening or Baseline visit before or on the date of first dose of BRV infusion will be utilized as Baseline value.
- Section 5.1: Clarified what summary will be presented for subjects who discontinued this study due to AEs.
- Section 6.1: Some demographic variables were added.
- Section 6.4:
  - Specified file to be used to identify of non-AED or AED medications.
  - Added paragraph to describe the grouping of similar AED medications.
- Section 6.4.2: "In the event of ambiguity or incomplete data which makes it impossible to determine whether a medication was concomitant or not, the medication will be considered as concomitant." was removed.
- Section 7.2: Updated the definition of treatment noncompliance.
- Section 8.1.2: Removed explanation of how the number of severe and non-severe seizures are standardized.
- Section 8.1.4: Updated wording for clarification how average per hour seizure burden will be calculated
- Section 10.1: Clarified that only duration of iv BRV exposure during the Evaluation Period will be displayed in hours.
- Section 10.2.1:
  - Added the definition of pre-treatment AEs.
  - "the number and percentage of subjects who death prior to the first BRV dose" variable was added
- Section 10.4.1:
  - Removed "Change from baseline in heart rate at 3 hours, 24 hours, 48 hours and 96 hours after the start of initial BRV treatment will be summarized." as this will be not needed.
  - Added clarification for vital sign PCST summary.
- Section 10.4.2: Calculation of the duration of cooling and rewarming was clarified.

- Section 10.4.9: Added descriptive statistics for the duration of mechanical ventilation.
- Section 10.5: Section added to describe the output that must be provided.

# STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

# Approval Signatures

**Name:** n01349-sap-amend-2

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Amendment # 2

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