STATISTICAL ANALYSIS PLAN

Study: EP0065

Product: Brivaracetam

A MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF INTRAVENOUS BRIVARACETAM IN SUBJECTS ≥1 MONTH TO <16 YEARS OF AGE WITH EPILEPSY

SAP/Amendment Number	Date
Final SAP 1.0	26 Mar 2018
Final SAP 2.0	28 Mar 2018
Final SAP 3.0	26 Sep 2019
Final SAP 4.0	19 May 2020
Final SAP 5.0	25 Sep 2020

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bid	twice daily
BMI	body mass index
BP	blood pressure
BRV	brivaracetam
CDISC	Clinical Data Interchange Standards Consortium
COVID-19	Coronavirus Disease 2019
CS	clinically significant
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
DBP	diastolic blood pressure
DOB	Date of birth
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ER	emergency room
h	hour
IIB	initiating iv BRV
Inf	infusion
IOB	initiating Oral BRV
IPD	Important protocol deviation
iv	intravenous
LOQ	limit of quantification
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
NCS	not clinically significant
OLB	open-label BRV
PCS	Possibly clinically significant
PCST	possibly clinically significant treatment-emergent
PDILI	Potential Drug Induced Liver Injury
PK	pharmacokinetics
PK-PPS	Pharmacokinetic Per Protocol Set
PQ/PR interval	time from the beginning of the P wave until the beginning of the QRS complex
PT	preferred term
PTAE	pre-treatment adverse event

QRS duration	duration of the combination of three of the graphical deflections seen on ECG
QT interval	time between the start of the Q wave and the end of the T wave in ECG
QTcB	QT interval corrected for heart rate (Bazett's formula)
QTcF	QT interval corrected for heart rate (Fridericia's formula)
RR	respiratory rate
RR-interval	time between successive Rs in ECG
RxB	Prescribed-BRV
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	Standard deviation
SOC	system organ class
SS	Safety Set
SS-iv	Safety Set-iv
TC	Telephone contact
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VNS	Vagus Nerve Stimulation
WHODD	World Health Organization drug dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) defines the scope of statistical analyses and provides a detailed description of statistical methodology for the statistical analyses to support the final clinical study report for EP0065. This SAP is based upon the following documents: Final Protocol Amendment 1.0: 19 Jun 2019.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objectives

The primary objective of this study is to evaluate the pharmacokinetics (PK), safety, and tolerability of brivaracetam (BRV) administered as a 15-minute iv infusion and iv bolus (up to 2-minute infusion) in subjects ≥1 month to <16 years of age with epilepsy.

2.2 Study variables

2.2.1 Pharmacokinetic variables

- Plasma concentration of BRV (parent compound only) before, during, and after iv BRV administration.

2.2.2 Safety variables

2.2.2.1 Primary safety variables

- Adverse events (AEs) throughout the study
- Subject withdrawals due to AEs

2.2.2.2 Other safety variables

- 12-lead ECG values before, during, and after each iv BRV administration
- Blood pressure (BP), pulse rate, respiratory rate (RR), and temperature values before, during, and after each iv BRV administration
- Clinical laboratory parameters (hematology, chemistry, and endocrinology) pre and post treatment
- Urinalysis parameters pre and post treatment

Post treatment parameters will be only available for subjects who down titrate and perform Visit 13 assessments.

2.3 Study design and conduct

EP0065 is a Phase 2 multicenter, open-label study to evaluate the PK, safety, and tolerability of iv BRV administered as a 15-minute iv infusion and an iv bolus (up to 2-minute infusion) in subjects ≥1 month to <16 years of age with epilepsy.

Study medication is defined by iv infusion of BRV administered as a 15-minute iv infusion or an iv bolus (up to 2-minute infusion). Oral BRV can be administered during EP0065 but will not be considered as study medication for EP0065.

Approximately 50 enrolled subjects will receive iv BRV in the following age-based cohorts (approximately 12 subjects/cohort):

- Cohort 1: ≥12 to <16 years
- Cohort 2: ≥6 years to <12 years
- Cohort 3: ≥2 to <6 years
- Cohort 4: ≥1 month to <2 years

The age at Screening Visit will be the determining factor for age cohort assignment. Each age cohort will have approximately 50% of subjects with iv BRV infusion and 50% with bolus BRV.

The following subjects will be eligible for enrollment in EP0065:

- Open-label BRV (OLB) subjects: currently receiving oral BRV as participants in a long-term, open-label study
- Prescribed BRV (RxB) subjects: currently receiving prescribed oral BRV from commercial supply
- Initiating Oral BRV (IOB) subjects: not currently receiving BRV; first dose of BRV in EP0065 will be oral tablet or solution
- Initiating iv BRV (IIB) subjects: not currently receiving BRV; first dose of BRV in EP0065 will be by iv Infusion

For OLB and RxB subjects, the maximum BRV dose is 5mg/kg/day (rounded). For IOB and IIB subjects, the maximum BRV dose is 4mg/kg/day. Throughout the study, no subject may receive a dose greater than BRV 200mg/day. Subjects will receive oral BRV (tablets or oral solution) in equally divided doses; BRV oral solution may be given by enteric administration (eg, by feeding tube) based on subject need.

The EP0065 study periods and visits are described below. The PK assessments will be made during the iv PK Period only and safety data will be collected throughout the study, with intensive collection of safety data with each iv BRV dose administered. A Schedule of Study Assessments is provided in the protocol for the Screening through iv PK Periods and for the Down-Titration Period and Safety (BRV-free) Periods (for subjects not continuing BRV).

- Screening Period (1 to 10 days)

During the Screening Period, the OLB and RxB subjects will continue treatment with oral BRV using their assigned open-label study supply or prescribed commercial supply, respectively. The IOB and IIB subjects will not receive BRV during this period.

The OLB subjects will temporarily discontinue assessments in their long-term, open-label study when they enter EP0065. As such, all assessments for these subjects during the Screening Period (and subsequent periods of EP0065) will be recorded in the EP0065 Case Report form (CRF) until they return to a long-term, open-label study or discontinue BRV treatment.

- IOB Treatment Period (2 to 10 days of oral BRV treatment; for IOB subjects only)

Only IOB subjects who meet all eligibility criteria may participate in the IOB Treatment Period. No other subjects may participate in this period.

During the IOB Treatment Period, IOB subjects will initiate treatment with oral BRV 2mg/kg/day not to exceed 100mg/day for subjects with body weights ≥50kg and must have, at minimum, 2 days of treatment with oral BRV before entry into the iv PK Period. Subjects who do not enter the iv PK Period will not be eligible for the long-term, open-label study.

The Investigator is permitted to adjust the oral BRV dose during the IOB Treatment Period in accordance with medical judgment (with a maximum dose of 4mg/kg/day, not to exceed 200mg/day for subjects with body weights ≥50kg); however, subjects must have no change in the oral BRV dose for the 2 days prior to entry into the iv PK Period.

- iv PK Period (1 to 6 days, with Day 1 defined as the initial day of iv BRV infusion)

During the iv PK Period, iv BRV will be administered every 12 hours ±2 hours (q12h ± 2h). All subjects are to receive 1 to 2 consecutive doses of BRV; however, based on medical need, subjects may receive up to 10 consecutive doses of iv BRV. The PK sampling will occur with the first iv BRV administration and with 1 other iv BRV administration.

The first dose of iv BRV will be as follows:

- OLB, RxB, and IOB subjects: mg-to-mg equivalent of the oral BRV dose immediately prior to the iv PK Period; administered q12h ±2h after prior oral dose
- IIB subjects: 1mg/kg not to exceed a maximum of 50mg for subjects ≥50kg

After subjects have completed PK sampling with 2 iv BRV infusions, the Investigator may adjust the BRV dose, but the adjusted dose must not exceed 5mg/kg/day (rounded) for OLB and RxB subjects and 4mg/kg/day for IOB and IIB subjects (with the maximums not to exceed 200mg/day). During the iv PK Period, BRV may only be administered intravenously. Enrollment will be sequential by descending age beginning with age-based Cohort 1. For each age cohort, the first half will receive the 15-minute infusion. The Data Monitoring Committee (DMC) will then meet to review safety and, as available, PK data. After the DMC safety review, the remaining half in that age cohort will receive iv BRV as a bolus (up to 2-minute infusion) and the next age cohort may begin the 15-minute infusion. Subjects may receive bolus infusions only after subjects in the preceding age cohort have completed bolus infusions and the DMC have reviewed these data. The DMC will meet no less than approximately every 6 months commensurate with enrollment.

Telephone contact (TC)-1 will occur 1 to 3 days after completing the final iv BRV dose in the iv PK Period to facilitate reporting of infusion-site related AEs.

- Down-Titration Period (up to 4 weeks) and Safety (BRV-free) Period (2 weeks)

Subjects who receive ≥4 doses of BRV during either the IOB Treatment Period or the iv PK Period and who do not plan to continue treatment with BRV or who discontinue from the study will enter a Down-Titration Period. Subjects who have received <4 doses of BRV may have BRV down titrated at the discretion of the Investigator. During the Down-Titration Period, subjects will have their BRV dose reduced by a maximum of half the dose every week for a maximum of 4 weeks until a dose of 1mg/kg/day (50mg/day for subjects with body weights ≥50kg) is reached. Subjects not able to receive oral BRV for down titration, may receive iv BRV for down titration. In the latter circumstance, the subjects may receive more than 10 consecutive doses of iv BRV in accordance with the Investigator's discretion. A 2-week Safety (BRV-free)

Period will follow the final dose of BRV. In this SAP, the Down-Titration period is considered part of the Follow-Up period, which is described more in Section 3.2.4.

Safety assessments will be collected throughout these periods.

2.4 Determination of sample size

The primary objective of the study is to evaluate the PK, safety, and tolerability of BRV given intravenously. The plan for approximately 50 enrolled subjects (4 age cohorts of approximately 12 subjects each) to receive iv BRV was deemed clinically appropriate for the evaluation of the PK, safety, and tolerability of iv BRV administration in subjects ≥1 month to <16 years of age with epilepsy. No formal sample size calculation has been performed.

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. All summaries will be descriptive; no statistical hypothesis testing is planned. All tables and listings will use Courier New font size 9.

Tables, figures and listings (TFL) will be displayed for the defined analysis sets. If the Safety Set (SS) and the Safety Set-iv (SS-iv) consist of the same number of subjects, TFLs will only be presented for the SS-iv.

For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purpose of the analysis. 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%.

For continuous parameters, descriptive statistics will include number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum, unless otherwise stated.

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

- "n" will be an integer
- Mean, SD, geometric mean, and median will use 1 additional decimal place compared to the original data
- CV [%] will be presented with 1 decimal place
- Minimum and maximum will have the same number of decimal places as the original value

However, the maximum number of decimals displayed will not exceed 4.

All summaries, unless otherwise stated, will be presented overall for all subjects, by age cohorts (Cohort 1: ≥12 to <16 years, Cohort 2: ≥6 years to <12 years, Cohort 3: ≥2 to <6 years, Cohort 4: ≥1 month to <2 years), and by infusion duration (15-minute iv infusion and iv bolus (up to 2-minute infusion)). Selected tables will be provided in addition by subject groups (OLB, RxB and IOB combined, and IIB), or by scheduled assessment timepoints as defined in Section 4.8 .

Selected summaries will be repeated by the country of enrollment (Hungary and rest of the World).

A complete set of listings containing all documented data and relevant derived data (eg, change from Baseline) will be generated. Summary tables will only contain data from subjects and visits which have been foreseen by the protocol, eg. in the event data will be captured after TC-1 when it is not required, this data will only be listed and not summarized.

3.2 Analysis time points

3.2.1 First and last dose of iv BRV

Unless otherwise noted, all references to the first dose of iv BRV in this SAP refer to the first dose of iv BRV during EP0065.

Unless otherwise noted, all references to the last dose of iv BRV in this SAP refer to the last dose of iv BRV in this study.

3.2.2 First and last dose of oral BRV

Unless otherwise noted, all references to the first dose of oral tablet or solution BRV in this SAP refer to the first dose of oral tablet or solution of BRV dispensed during EP0065.

Unless otherwise noted, all references to the last dose of oral tablet or solution BRV in this SAP refer to the last dose of oral tablet or solution of BRV dispensed during EP0065.

3.2.3 Relative day and time

Relative Day is defined as the day relative to the first infusion of BRV. Relative day will not be calculated for partial dates.

If the current date occurred on or after the day of first dose of iv BRV and prior to or on the day of last iv BRV dose, the relative day will be calculated as the current date minus the date of first dose of iv BRV plus 1 (eg, the day of first dose of iv BRV will be Day 1).

If the current date occurred prior to the first dose of iv BRV, the relative day will be calculated as date of first dose of iv BRV minus the current date (eg, the day prior to first dose of iv BRV will be Day -1).

If the current date occurred after the last dose of iv BRV, the relative day will be calculated as the current date minus the date of last dose of iv BRV including a "+" to denote post-treatment days (eg, the day after the last dose of iv BRV will be Day +1).

In order to have a better insight into the times of AEs, laboratory samples, ECG and vital signs collections relative to the administration of BRV, the relative time will be calculated, by subtracting the time of first iv BRV administration from the start time of the event. The relative time will be displayed in hours and minutes for relative times ≤24 hours before and after the first iv BRV administration. For relative times >24 hours the relative times will be calculated in days as described above.

3.2.4 Relative time from previous iv infusion

Relative time from previous iv infusion initiation will be derived for AE listings. It will be displayed in hours and minutes and will be calculated using the following formula:

relative time from previous iv infusion initiation
= *AE start time* – previous infusion start time

3.2.5 Analysis periods

This study consists of a Screening Period, an IOB Treatment Period, an iv PK Period, a Follow-up Period and a Safety (BRV-free) Period, see Section 2.3 for more details on these periods.

Start of Screening Period is defined as the date of enrollment and end of Screening Period is defined as immediately before first allocated BRV treatment.

Start of IOB Treatment Period is defined as the date of first allocated oral BRV treatment and end of IOB Treatment Period is defined as immediately before first iv BRV treatment.

Start of iv PK Period is defined as the date and time of first allocated iv BRV treatment and end of iv PK Period is defined as 12 hours after start of last iv BRV treatment.

Start of Follow-up Period is defined as 12 hours after start of last iv BRV treatment and end of Follow-up Period is defined for the following scenarios:

- Subjects who transition study: as TC-1
- Subjects who do not transition and do not down-titrate: as end of study
- Subjects who down-titrate: as 12 hours after start of last down-titration treatment.

Only subjects who down-titrate have a Safety (BRV-free) Period. Start of Safety Period is defined as immediately after the end of Follow-up Period (>12 hours after start of last down-titration treatment) and end is defined as end of study.

3.2.6 Exposure duration

In EP0065 study medication is defined as iv BRV.

The date and time of first study medication is defined as the start of first iv BRV infusion date and time according to the standard CRF page. The date and time of last study medication is defined as the start of last iv BRV infusion reported on the standard trial termination eCRF.

Days with unknown or zero dosing for the respective BRV formulation (iv, tablet, oral solution, oral, all) which occur between the start and end date of the respective BRV formulation will be included in the exposure calculation. For example, a day with missing or zero dosing between the first and last iv BRV dose will be included in the iv BRV exposure duration (days) and iv BRV exposure duration (hours) calculation.

The iv BRV exposure duration will be calculated separately in hours and days. Duration of iv BRV exposure in days will be calculated using the following formula:

iv BRV exposure duration (days)
= start date and time of the last iv BRV
− start date and time of the first iv BRV + 1 day

Duration of iv BRV exposure in hours will be calculated using the following formula:

iv BRV exposure duration (hours)
= start date and time of the last iv BRV
− start date and time of the first iv BRV + 1 hour

The duration of oral BRV exposure will be calculated in days only by administration method (tablets or oral solution) and over both administration methods separately for the IOB Treatment Period and Follow-up Period. The duration of oral BRV will be calculated separately for each period using the following formulas:

Oral BRV exposure duration from tablets during period (days)
= end date of last BRV tablet during period
− start date of first BRV tablet during period + 1 day

Oral BRV exposure duration from oral solution during period (days)
= end date of last oral solution BRV during period
− start date of first oral solution BRV during period + 1 day

Overall Oral BRV exposure duration during period (days)
= end date of last oral BRV during period
− start date of first oral BRV during period + 1 day

The overall BRV duration (oral BRV and iv BRV exposure) in days will be calculated using the following formula:

Overall BRV exposure duration (days)
= end date of latest BRV (either oral or iv)
− start date of first BRV (either oral or iv) + 1 day

3.2.7 Age and age at first diagnosis

The age at Screening Visit will be the determining factor for age cohort assignment (see Section 2.3 and Section 3.7). For subjects aged 2 years and above, age will be displayed in years, otherwise age will be displayed in months. The age at first diagnosis of epilepsy will be calculated in years and months for all subjects, and will be derived applying all rules for missing data imputation (Section 4.2). Age at first diagnosis in years will be calculated with the following formula:

Age at first diagnosis (years)
= (Date of first diagnosis of epilepsy − Date of birth) / 365.25

For the calculation of age at first diagnosis in months consider 1 month = (365.25/12) days:

Age at first diagnosis (months)
= (Date of first diagnosis of epilepsy − Date of birth) / (365.25/12)

3.2.8 Duration of epilepsy

Duration of epilepsy will be calculated in years and months, and will be derived applying all rules for missing data imputation (Section 4.2).

Duration of epilepsy in years will be calculated with the following formula:

Duration of epilepsy (years)
= (Date of informed consent − Date of first diagnosis of epilepsy)
/ 365.25

For the calculation of the duration of epilepsy in months consider 1 month = (365.25/12) days:

$$\text{Duration of epilepsy (months)} = (\text{Date of informed consent} - \text{Date of first diagnosis of epilepsy}) / (365.25/12)$$

Summary statistics for both durations will be calculated and displayed to 2 decimal places.

3.2.9 Amount of Time and number of days of each PCST prior to TEAE onset

The definition of PCST for ECG, Laboratory values and vital signs are described in the relevant sub-sections in Section 10. PCSTs are described in Appendix 12.2. The definition of TEAE is in Section 10.2

For each TEAE with at least one PCST value at the time of or prior to the adverse event, the number of days and where possible time prior to each TEAE onset relative to each observed PCST will be calculated and displayed. Time prior to each TEAE will only be calculated in days, hours and minutes where the time and date of the TEAE and PCST is available. Imputed AE times will not be used for missing AE times. When the time is missing for the PCST and/or TEAE, but the date of the TEAE is the same or later than the PCST, the TEAE will be assumed to have occurred after the PCST, and only number of days prior to TEAE onset will be calculated.

The formula for time prior to TEAE onset is as follows:

$$\text{Time prior to TEAE onset} = \text{TEAE start day and time} - \text{start day and time of PCST}$$

The formula for number of days prior to TEAE onset is as follows:

$$\text{Number of days prior to TEAE onset} = \text{TEAE start day} - \text{PCST start day}$$

3.3 Body mass index (BMI)

BMI will be calculated using weight and height at Screening Visit with the following formula:

$$\text{BMI (kg/m}^2) = \frac{weight\ (kg)}{[height\ (m)]^2}$$

3.4 Definition of Baseline values

Baseline for laboratory variables (blood chemistry, hematology, and endocrinology), vital signs, body weight, and quantitative electrocardiography (ECG) variables is defined as the latest assessment prior to the first infusion of iv BRV. Both scheduled and unscheduled assessments from the central laboratory are considered.

3.5 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on the primary outcomes for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. Important deviations will be identified and documented prior to database lock to confirm exclusion from the Pharmacokinetic Per-protocol Set (see Section 3.6.3).

3.6 Analysis sets

3.6.1 Safety Set iv (SS-iv)

The Safety Set iv (SS-iv) will include subjects who received at least 1 dose of iv BRV. The SS-iv will be the primary analysis set for the analysis of safety data.

3.6.2 Safety Set (SS)

The Safety Set (SS) will include subjects who received at least 1 dose of BRV (oral or iv). Selected safety summaries will be presented for the SS (see also Section 3.1).

3.6.3 Pharmacokinetic Per-protocol Set

The Pharmacokinetic Per-protocol Set (PK-PPS) will include all subjects in the SS-iv having provided at least 1 measurable post-dose plasma sample (with recorded sampling time) during the iv PK Period with documented iv BRV infusion times and without important protocol deviations impacting the interpretability of the PK analyses.

3.7 Treatment assignment and treatment groups

This is an open-label study with a single treatment arm. The age at Screening Visit will be the determining factor for age cohort assignment. Subjects are summarized in the following age based cohorts (approximately 12 subjects/cohort):

- Cohort 1: ≥ 12 to < 16 years
- Cohort 2: ≥ 6 years to < 12 years
- Cohort 3: ≥ 2 to < 6 years
- Cohort 4: ≥ 1 month to < 2 years

3.8 Center pooling strategy

The expected number of subjects for most sites is low. In general, it will not be feasible to adjust statistical analysis for site effect and there are no plans to present any study outcomes by site. No pooling strategy is defined for this study.

3.9 Coding dictionaries

Medical history and 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 (WHODD) version Sep 2017. Medical procedures are not coded.

3.10 Changes to protocol-defined analysis

As iv BRV is defined as the study medication the following parts of the PK-PPS definition were further clarified: "subjects in the SS-iv" instead of "subjects in the SS" and "infusion times" instead of "intake times". Furthermore, the term “without important protocol deviations impacting the interpretability of the PK analyses” was added to the definition of PK-PPS.

Vital sign and ECG summary tables will summarize the subject data for each timepoint but not as stated in the protocol (pre-bolus/infusion period, the bolus/infusion period, the period immediately post-bolus/infusion, and period between each subsequent bolus/infusion). Adverse events tables will not summarize the subject data as specified in the protocol (pre-bolus/infusion period, the bolus/infusion period, the period immediately post-bolus/infusion, and period between each subsequent bolus/infusion). Instead AEs will be summarized by time relative to most recent bolus/infusion start time (≤5 minutes, >5 to ≤15 minutes, >15 to ≤60 minutes, >60 minutes to ≤12 hours and >12 hours).

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

No statistical testing is planned; therefore, this section is not applicable for this study.

4.2 Handling of dropouts or missing data

No imputation of missing values is planned unless otherwise noted. Imputations for missing or partial dates for AEs and concomitant medications will be applied to determine if an event/medication is to be considered treatment-emergent or concomitant. Such imputations will only be performed for classifications and calculations; in the listings all data will be shown as recorded on the eCRF. Across PK, only reported data will be used.

4.2.1 General imputation rule for incomplete dates

Where necessary for the calculation of derived variables, partial dates will be completed using the earliest calendar date based on the partial date provided. This rule is valid for all partial dates with the exception of the following:

- Date of birth (DOB)
- Start and stop dates of concomitant medication
- Start and stop date of adverse events
- Start and stop dates of study medication
- Date of epilepsy diagnosis

Completely missing dates will not be replaced and the corresponding derived variables will be set to missing.

4.2.2 Handling of partial date of birth

Date of birth (DOB) will not be collected in full form from all subjects due to country differences. The SDTM interpretation guide notes that partial ages should be imputed by using 1 Jan and the provided year, or 1st of the month when month/year is provided. However, in pediatric studies this could be problematic when calculating age at diagnosis or time since diagnosis. Since in the eCRF age as well as DOB will be captured, partial DOB will be imputed by using the enrollment date and the age to back calculate the DOB; using 1st of the month for the day. That is, if a subject is 3 months old and was enrolled in Jun 2018, it will not be imputed as DOB = 1 Jan 2018. In this case it will be imputed as DOB = 1 Mar 2018, providing an age of approximately 3 months.

4.2.3 Handling of prior and concomitant medications with partial or missing date

Any medications with incomplete start and end dates 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 eCRF.

Imputation of Partial Start Dates

- If only the month and year are specified and the month and year of first dose of iv BRV 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 of iv BRV is the same as the month and year of the start, then use the date of first dose of iv BRV.
- If only the year is specified, and the year of first dose of iv BRV is not the same as the year of the start date, then use 1 Jan of the year of the start date.
- If only the year is specified, and the year of first dose of iv BRV is the same as the year of the start date, then use the date of first dose of iv BRV.
- If the start date is completely unknown and the stop date is unknown or not prior to the date of first dose of iv BRV, then use the date of first dose of iv BRV.

Imputation of Partial Stop 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 31 Dec of that year.
- If the stop date is completely unknown, do not impute the stop date.

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.

4.2.4 Handling of adverse events with partial or missing date

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.

Imputation of Partial AE Onset Dates

- If only the month and year are specified and the month and year of first dose of iv BRV or oral BRV from IOB Treatment Period is not the same as the month and year of AE onset, then use the 1st of the month of onset.
- If only the month and year are specified and the month and year of first dose of iv BRV is the same as the month and year of AE onset, then use the date/time of first dose of iv BRV.
- If only the month and year are specified and the month and year of first dose of iv BRV is not the same as the month and year of AE onset, but the month and year of first dose of oral BRV during the IOB Treatment Period is the same then use the date/time of first dose of oral BRV.
- If only the year is specified, and the year of first dose of iv BRV or oral BRV from IOB Treatment Period is not the same as the year of AE onset, then use 1 Jan of the year of onset.
- If only the year is specified, and the year of first dose of iv BRV is the same as the year of AE onset, then use the date/time of first dose of iv BRV.
- If only the year is specified and the year of first dose of iv BRV is not the same as the year of AE onset, but the year of first dose of oral BRV during the IOB Treatment Period is the same then use the date/time of first dose of oral BRV.
- If the AE onset date is completely unknown, then use the date\time of first dose of iv BRV.
- If the AE onset time of the event is unknown, impute it as 00:00 unless the known part of the AE onset date is the same as the date of first iv BRV dose; in this case impute the time of first dose of iv BRV dose.

Imputation of Partial AE 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 31 Dec of that year.
- If the AE resolved and the resolution date is completely unknown, then do not impute the resolution date.

In the event of ambiguity or incomplete data which makes it impossible to determine whether an AE was treatment emergent or not, the AE will be considered as treatment emergent.

With respect to AEs, events with missing intensity will be assumed to be severe. Events with missing relationship to iv BRV per the investigator will be assumed to be related.

Data handling for worsened AEs is provided below. The standard AE eCRF has the outcome of "worsened" to be used when there is an increase in the intensity of an AE. The definition of "worsened" is when the AE is still present but at a heightened intensity. The eCRF instructions dictate to complete a new AE screen with the event term of the worsened event.

Note that the outcome of "worsened" is not allowed terminology within the CDISC standards. In the SDTM.AE, the data is mapped to the outcome "Not Recovered/Not Resolved". The outcome of "Worsened" will be kept in SDTM.SUPPAE. For subject data listings, the convention will be used to map SDTM terminology of "Not Recovered/Not Resolved".

4.2.5 Handling of study medication with partial or missing date

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 earliest of the last day of the month or the date of last contact reported on the trial termination eCRF; if day and month are both missing (only year available), impute the last dose date as the earliest of the last day of the year or the date of last contact on the trial termination eCRF.
- If a subject died and has a partial or missing last dose date, the last dose date is to be 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 according to the study termination eCRF. 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.

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).

4.2.6 Handling of epilepsy diagnosis with missing date

Imputation methods should be applied for missing or partial epilepsy diagnosis date.

- If the month and year are available, the diagnosis date will be imputed as the later of the following dates: the first day of the month or the subject's birthdate (imputed DOB if only partial DOB is captured).
- If only a year is available, the later of the following dates will be imputed: 1 Jan of the year or the subject's birthdate (imputed DOB if only partial DOB is captured).
- Completely missing dates will not be replaced, and the corresponding derived variables will be set to missing.

4.2.7 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 30th May 2020, an additional eCRF page will be foreseen. Sites will complete this page in case a subject was impacted by coronavirus during the study. The COVID-19 Impact eCRF page will include the timing and impact of COVID-19, and relationship to COVID-19 (i.e. whether the subject has confirmed/suspected COVID-19 infection, or whether its general circumstances around COVID-19 without infection).

4.3 Interim analyses and data monitoring

4.3.1 DMC meetings

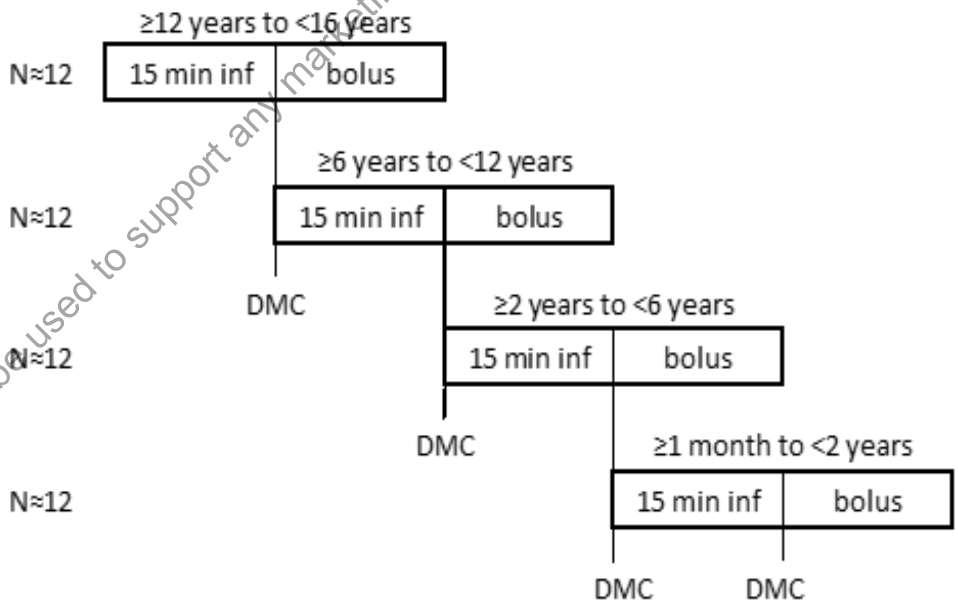
Data will be presented to and reviewed by a DMC during the course of the study. For the first age cohort, after the first half of the subjects receive the 15-minute infusion(s), the DMC will meet to review safety (as indicated in the DMC charter) and, as available, PK data. For subsequent cohorts, the DMC will review data for bolus infusions of the previous cohort and the 15-minute infusions of the current cohort. The DMC will meet no less than approximately every 6 months commensurate with enrollment. The DMC members will be defined in the DMC charter.

At each DMC meeting, the DMC will make recommendations regarding study aspects including:

- Continuation of the study as planned
- Modification of the study or particular expansion cohort(s)
- Suspension of the study or particular expansion cohort(s)

Age cohorts for enrollment are detailed in the schematic in Figure 5-1. Notably, the schematic of sequential cohort enrollment (Figure 5-1) differs from the one provided in the protocol. Ages were changed from "≥12 years to ≤16 years" to "≥12 years to <16 years", "≥6 years to ≤12 years" to "≥6 years to <12 years" and "≥2 years to ≤6 years" to "≥2 years to <6 years". This difference is because the protocol has age boundaries of sequential cohort enrollment defined differently in the schematic to the text, but in practice sites have enrolled using the text.

Figure 5-1: Schematic of sequential cohort enrollment during the iv PK Period



DMC=Data Monitoring Commitee; inf=infusion; iv=intravenous; PK=pharmacokinetic

4.3.2 Interim analysis

No formal interim analysis was planned in this study. The last planned DMC occurred after all subjects aged 2 to <6 years had completed the study, and all subjects aged 1 month to <2 years on 15-minute infusion had completed the study, and the recommendation was to continue the study. However, enrollment was temporarily stopped due to the impact of COVID-19. Therefore, all outputs will be delivered twice, firstly an interim CSR using all data from subjects aged 2 to <6 years and subjects aged 1m to <2 years on 15-min infusion to support ongoing submission work, and secondly a final CSR using all subjects.

4.4 Multicenter studies

Analysis will not be assessed for individual investigator sites due to the low expected number for enrollment within each investigator site.

4.5 Multiple comparisons/multiplicity

No statistical testing is planned; therefore, this section is not applicable for this study.

4.6 Use of an efficacy subset of subjects

No efficacy data are collected; therefore, this section is not applicable for this study.

4.7 Examination of subgroups

There is no subgroup analysis planned. However, the majority of summaries will be presented for all subjects, and separately by age cohort, by infusion duration and by subject group. In addition, selected summaries of Important protocol deviations (IPDs), AEs, vital signs and ECG findings and parameters will be provided by country of enrollment (Hungary and rest of the World).

4.8 Time points by infusion duration

The time points relative to infusion initiation for respective assessments will be as follows:
In case value of blood pressure at the "≤1 hr pre-infusion with low PCS BP" time point is low PCS, the additional timepoint will be listed only and not included in summary tables.

- Vital signs time points for 15 min infusion:
  - ≤ 1 hr before initiation of iv BRV
  - 5 min after initiation of iv BRV
  - 10 min after initiation of iv BRV
  - 15 min after initiation of iv BRV
  - 30 min after initiation of iv BRV
  - 60 min after initiation of iv BRV.
  - 2 hr after initiation of iv BRV, only SBP and DBP will be collected.
- Vital Signs time points for Bolus:
  - ≤ 1 hr before initiation of iv BRV
  - ≤ 2 min after initiation of iv BRV

  - 5 min after initiation of iv BRV
  - 15 min after initiation of iv BRV
  - 30 min after initiation of iv BRV
  - 60 min after initiation of iv BRV
  - 2 hr after initiation of iv BRV, only SBP and DBP will be collected.
- Electrocardiogram time points for 15 min infusion:
  - ≤ 1 hr before initiation of iv BRV
  - 5 min after initiation of iv BRV
  - 10 min after initiation of iv BRV
  - 15 min after initiation of iv BRV
  - 30 min after initiation of iv BRV
  - 60 min after initiation of iv BRV
  - 2 hr after initiation of iv BRV
- Electrocardiogram time points for Bolus:
  - ≤ 1 hr before initiation of iv BRV
  - ≤ 2 min after initiation of iv BRV
  - 5 min after initiation of iv BRV
  - 15 min after initiation of iv BRV
  - 30 min after initiation of iv BRV
  - 60 min after initiation of iv BRV
  - 2 hr after initiation of iv BRV
- Pharmacokinetic time points for 15 min infusion and Bolus:
  - ≤ 1 hr before initiation of iv BRV
  - 15 min after initiation of iv BRV
  - 3 hr after initiation of iv BRV.

4.9 Handling of data from open-label study

Medical and procedural history, AEs, and prior and concomitant medication data for subjects coming from open-label study will only be documented within the open-label study and will be transferred into EP0065.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

Subjects who were screen failures, broken down by primary reason for screening failure, will be presented overall for all subjects screened.

A summary of disposition of subjects will be provided for all screened subjects. The date of first subject in (date of first Screening Visit), date of last subject out (date of last contact), number of subjects screened, number of subjects in each analysis set (SS-iv, SS and PK-PPS), number of subjects in the SS-iv receiving 15 minutes infusion and number of subjects in the SS-iv receiving bolus infusion will be summarized overall, by country and by investigator site. Subjects who transferred sites will be summarized according to their original site.

A summary of disposition of analysis sets will be provided for the SS including the number and percentage of subjects receiving 15 minutes infusion / bolus in each analysis set:

- The number and percentage of subjects in the SS
- The number and percentage of subjects in the SS-iv
- The number and percentage of subjects in the PK-PPS

A summary of disposition and discontinuation reasons will be presented overall for the SS-iv and the SS. The following information is included:

- The number and percentage of subjects starting the study, defined as having signed an informed consent.
- The number and percentage of subjects completing the study, defined as having received at least 1 iv BRV dose and completed at least one assessment at TC-1. This definition differs to the completed subjects from the eCRF.
- The overall number and percentage of subjects discontinuing the study early, and the number and percentage of subjects discontinuing by primary reason for discontinuation
- The number and percentage of subjects starting the Screening Period
- The number and percentage of subjects completing the Screening Period
  - Complete is defined as a non-missing informed consent date.
- The reasons for discontinuing during the Screening Period
- The number and percentage of subjects starting the IOB treatment Period
  - Start is defined by attending Visit 2.
- The number and percentage of subjects completing the IOB treatment Period
  - Complete is defined as receiving oral BRV for at least 2 days during the IOB treatment period.
- The reasons for discontinuing during the IOB treatment period
- The number and percentage of subjects starting the iv PK Period

  - Start is defined by attending Visit 3.
- The number and percentage of subjects completing the iv PK Period
  - Completed is receiving at least one iv BRV dose during the iv PK Period.
- The reasons for discontinuing during the iv PK Period.
- The number and percentage of subjects starting down-titration (Follow-up Period)
  - Start is defined by having at least one down-titration BRV treatment.
- The number and percentage of subjects starting the Safety Period
  - A subject is considered as starting the Safety Period if their date of study termination is at least 12 hours after the last BRV treatment received during down-titration.

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

The following listings will be provided for all subjects screened: subjects who did not meet study eligibility criteria, subject disposition, subject analysis sets, subjects excluded from at least one analysis set, study discontinuation, and visit dates.

5.2 Protocol deviations

IPDs defined in the IPD specification document, and additionally identified at the data evaluation meetings, will be listed. In addition, the number and percentage of subjects with at least one important protocol deviation will be summarized overall and by category of important protocol deviation for the SS-iv and the SS. The number and percentage of subjects with no important protocol deviations will also be summarized. These summaries will be presented overall and by age group for all subjects, and by infusion duration. A separate summary will be presented by country of enrollment (Hungary and rest of the World) for all subjects and by infusion duration.

All completed COVID-19 Impact eCRF pages, and other IPDs will be discussed in important protocol deviation 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.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics and other Baseline Characteristics

Demographic variables will be presented for the SS-iv and the SS. The variables to be presented are:

- Age at entry into EP0065 (in years for subjects aged >2 years at study entry, in months for subjects aged <= 2 years at study entry)
- Age at first diagnosis (in years and in months) (as defined in Section 3.2.7)

- Duration of epilepsy (in years and in months) (as defined in Section 3.2.8)
- Categorized age at entry into EP0065:
  - EudraCT age categories: ≥1 month to <24 months, ≥24 months to <12 years, ≥12 to <16 years
  - Age categories for submission: ≥1 month to <4 years, ≥4 to <16 years
- Gender (male, female)
- Subject group (OLB, RxB, IOB, and IIB)
- Weight at Screening (kg)
- Weight at baseline (kg)
- Weight group at baseline (<50 kg, ≥50 kg)
- Height at Screening (cm)
- BMI at Screening (kg/m^2) (as defined in Section 3.3)
- Racial group (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed)
- Ethnicity (Hispanic or Latino or Not Hispanic or Latino)
- Country (Countries may include Czech Republic, France, Germany, Hungary, Italy, Ireland, Mexico, Poland, Spain, USA)
- VNS Status (VNS not used, VNS used; if used: VNS active, VNS not active)

The following listings will be provided by age cohort for all subjects screened:

- demographics at Screening
- childbearing potential at Screening
- historical seizure count (describing the type and number of seizures experienced in the 3 weeks prior to Screening)
- diagnosis of epilepsy (describing the primary disease, date of first epilepsy diagnosis and history of status epilepticus prior to the 1-month period before Screening)
- vagus nerve stimulation status at Screening
- family medical history (family medical history is only collected for subjects with potential drug-induced liver injury and will describe the medical conditions including start and stop dates)
- lifestyle (lifestyle information is only collected for subjects with potential drug-induced liver injury and will describe the alcohol- and illicit drug use within past 6 months)

6.2 Medical history and ongoing diseases

The number and percentage of subjects with a medical history condition, including both previous and ongoing conditions at the time of study entry (Screening), are summarized separately overall

and by MedDRA primary system organ class (SOC) and preferred term (PT) for the SS-iv. Additionally, the number and percentage of subjects with ongoing medical conditions are summarized overall (i.e. any ongoing medical conditions at Screening) and by primary SOC and PT. A subject data listing for the previous and ongoing medical history conditions will be provided for the SS together with the medical history glossary.

6.3 Prior and concomitant medications

Prior medications include any medications that started prior to the date of first dose of iv BRV. Only prior medication which is ongoing or has an end date in the 2 weeks prior to screening will be included in summaries. Prior medication with an end date prior to the 2 weeks before screening will be listed only. Concomitant medications are medications taken on at least one day in common with the iv PK Treatment Period. Medications may be both prior and concomitant. Medications which started after the day of the last iv BRV treatment will be categorized as follow-up medications.

For OLB subjects only medication which started during the EP0065 study will be recorded in the EP0065 study. Information of medication which started before EP0065 study start will come from the respective OLB study. Only medications with a stop date < 14 days prior to start date of EP0065 will be summarized in EP0065.

Antiepileptic drugs (AED) will be identified using an internal UCB AED list (file: AEDs_ATCs_SEP2017_FINAL_benzo_groups_23JUL2019.xls).

Subject data listings for prior, concomitant and follow-up AEDs, and prior, concomitant and follow-up non-AEDs will be provided separately together with a listing of medication glossary including all reported medications.

6.3.1 Summaries for non-AEDs

The number and percentage of subjects taking non-AED medications prior to first iv BRV and concomitantly with iv BRV will be summarized separately overall, and by anatomical main group (Anatomical Therapeutic Chemical [ATC] classification level 1), therapeutic subgroup (ATC classification level 2), and preferred drug name for the SS-iv. Subjects reporting multiple medications within an ATC class are counted once per medication and class.

6.3.2 Summaries for AEDs

The number and percentage of subjects taking AED medications prior to first iv BRV and concomitantly with iv BRV will be summarized separately overall, and by WHODD preferred drug name for the SS-iv.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Information reported on the eCRF drug accountability (iv formulation) will be listed. The data from the eCRF Drug Accountability (oral solution and tablets) will also be listed. No summaries of drug accountability are planned.

BRV iv and oral dosing compliance will be evaluated through the review of important protocol deviations.

8 EFFICACY

This section is not applicable for this study.

9 PHARMACOKINETICS

9.1 Pharmacokinetics

Plasma concentration of BRV (parent compound only) before, during and after iv BRV administration will be summarized and listed for the PK-PPS.

Descriptive statistics will be calculated for each timepoint by infusion duration, visit and age cohort. These statistics will also be repeated by visit and weight group (<50 kg, ≥50 kg) and by visit and subject group (OLB, RxB and IOB combined, and IIB separately). Descriptive statistics will include: the number of observed values, geometric mean, 95% confidence interval for geometric mean, geometric CV, mean, SD, median, minimum value and maximum value. Values below LOQ will be set to LOQ for all calculations.

Box plots of plasma concentration of BRV at each timepoint (15 minutes and 3 hours) will be produced for each age cohort by visit. Infusion duration will be marked using different symbols.

Box plots of plasma concentration of BRV at each timepoint (15 minutes and 3 hours) will be produced for each infusion duration by visit. Age groups will be marked using different symbols.

A listing for plasma sample collection times and concentrations of BRV will be provided.

9.2 Pharmacodynamics

This section is not applicable for this study.

10 SAFETY ANALYSIS

All analyses for extent of exposure and safety are performed for the SS-iv. Selected tables will be performed on the SS.

Inferential statistical tests are not planned for the safety variables.

10.1 Extent of exposure

The duration of iv BRV exposure, as defined in Section 3.2.6, will be summarized as continuous parameters (once in hours and once in days) for the iv PK Period on the SS-iv. The number and percentage of subjects who received 0, 1, 2, 3, …, 10 BRV infusions will be displayed for the SS-iv. Handling of missing study medication data is described in Section 4.2.5. Mean iv BRV dose (mg/kg) will be summarized as continuous parameters for the iv PK Period for the SS-iv. This table will be presented by age groups for all subjects, by infusion duration and by weight (<50kg and ≥50kg).

The duration of overall oral BRV exposure, oral BRV exposure from tables and oral BRV exposure from oral solution as defined in Section 3.2.6, will be summarized as continuous parameters (in days) separately for the IOB Treatment Period and the Follow-up Period for the SS.

The overall BRV duration (oral BRV and iv BRV exposure), as defined in Section 3.2.6, will be summarized as a continuous parameter (in days) for the SS-iv and SS respectively.

The following listings will be provided for the SS unless otherwise stated:

- study medication administration, which displays relevant information about the BRV iv dosing including the start and stop time of each infusion, the target dose and whether the target dose was delivered.
- BRV exposure, which displays relevant information about the BRV iv and oral dosing including the number of infusions received, and the total BRV exposure.
- Oral BRV dosing during study
- Oral BRV administration from oral solution
- Oral BRV administration from tablets

10.2 Adverse Events

All adverse events (AEs) occurring during EP0065 (ie, after signing of the ICF) must be reported. For subjects who transition to study N01266, any AEs which began after the first dose of BRV in N01266 but prior to TC-1 of EP0065 will be considered as during EP0065 and N01266. Pre-treatment adverse events (PTAEs) are defined as AEs that had onset strictly prior to the date/time of the first BRV medication taken during EP0065. For OLB subjects, where the AE started prior to EP0065 enrollment, information will come from the respective OLB study.

Treatment-emergent adverse events (TEAEs) are defined as those events which started on or after the first BRV medication taken during the EP0065 study. Subjects who began the study on BRV treatment (OLB and RxB subjects) will be assumed to have taken BRV treatment on the first day of screening. Timing of an AE being treatment emergent varies by subject group: all AEs are treatment emergent for RxB and OLB subjects; all AEs on or after the IOB Treatment Period are treatment emergent for IOB subjects; all AEs on or after the iv PK Period are treatment emergent for IIB subjects.

Data handling rules for management of missing or partial start or stop dates for adverse events should follow those defined in the Section 4.2.4. The classification of TEAE will be done after imputation of any partial start dates.

10.2.1 AE summaries

All AE tables will be summarized separately over all AEs and by MedDRA SOC and MedDRA PT. The number and percentage of subjects experiencing each event at least once will be summarized. All summaries will be sorted alphabetically by SOC and by frequency of events within PTs, starting with the most frequent event overall. All summaries are for all study periods combined (Screening, IOB treatment, iv-PK, Follow-up, and Safety (BRV free) Period) unless otherwise indicated. Only the first occurrence of a TEAE of a particular PT will be included in incidence calculations, but all occurrences of TEAEs of the same PT will be included in counts of TEAEs. For summaries by study period, AEs are assigned only to the period on which they began. TEAEs of interest is a selection of TEAEs identified by UCB to be of interest to BRV.

The following summaries will be produced overall and by age cohort, for all subjects and separately by infusion duration, and subject group for the SS-iv:

- Incidence of AEs – Overview (number and percentage of subjects with at least one: AE, TEAE, serious TEAE, non-serious TEAE, TEAE of interest, TEAE requiring dose change,

drug-related TEAE, drug-related serious TEAE, and severe TEAE, as well as the number and percentage of subjects who discontinued due to a TEAE, had permanent withdrawal of BRV due to a TEAE, had an AE leading to death, and had a TEAE leading to death)

- Incidence of TEAEs
- Incidence of TEAEs Leading to Study Discontinuation
- Incidence of Serious TEAEs

The following AE summaries will be produced overall and by age cohort, for all subjects and separately by infusion duration for the SS-iv:

- Incidence of PTAEs
- 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 TEAEs by Maximum Relationship
  Drug-related AEs are AEs for which the relationship to trial medication is specified as related or AEs for which relationship is not specified.
- Incidence of TEAEs of Interest
- Incidence of Non-serious TEAEs Occurring in at least 5% of Subjects
- Incidence of Serious TEAEs by Relationship to BRV
- Incidence of Fatal TEAEs by Relationship to BRV

The following summaries will also be produced by country of enrollment (Hungary and rest of the World) for all subjects, by infusion duration and by subject group for the SS-iv:

- Incidence of AEs – Overview
- Incidence of TEAEs

The following summary will also be produced by country of enrollment (Hungary and rest of the World) for all subjects and by infusion duration for the SS-iv:

- Incidence of TEAEs by Maximum Intensity

The following summaries will be produced overall and by age cohort and study period, for all subjects and separately by infusion duration and subject group for the SS:

- Incidence of TEAEs by Study Period
- Incidence of TEAEs Leading to Study Discontinuation by Study Period
- Incidence of Serious TEAEs by Study Period

The following summaries will be produced overall and by age cohort and study period, for all subjects and by infusion duration for the SS:

- Incidence of TEAEs by Maximum Intensity by Study Period

- Incidence of TEAEs by Maximum Relationship by Study Period

The following TEAE summaries will be produced overall and by age cohort for the SS:

- Incidence of Serious TEAEs - Subject Numbers
- Incidence of TEAEs Leading to Study Discontinuation - Subject Numbers

Additionally, incidence of TEAEs will be summarized by categorized relative time infusion for all subjects, and by age cohort for the SS-iv. The time of each AE relative to the start of the previous iv infusion will be calculated as described in Section 3.2.4 and categorized into 0-<=5 minutes, >5 -<=15 minutes, >15 to <=60 minutes, >60 - <=12 hours and >12 hours.

10.2.2 AE Listings

All AEs reported during the study will be provided in subject data listings for the SS. These listings will include, but is not limited to AE onset date and time, relationship to study medication and whether the AE is of special interest. AE's of special interest are a selection of adverse events, of particularly interest for this study chosen prior to first subject in, and are captured in the CRF.

The following AE listings will be provided:

- Glossary table for all AEs, where the terms included on the table should match those presented in other AE displays
- All AEs
- All serious AEs
- All AEs leading to study discontinuation
- Listing of all deaths
- TEAEs of interest
- All AEs which worsened during the study (The definition of "worsened" is when the AE is still present but at a heightened intensity.)
- TEAEs in relation to previous PCSTs (Listing will contain PCST of each type that occurred from vital signs, ECG and laboratory values in relation to the time prior to the onset of each AE which occurred after the respective PCST (see Section 3.2.9)).

Should it occur, any uncoded AEs should be designated as "UNCODED CLASS" at all MedDRA levels, and such AEs should be included in summary tables and subject data listings based on this classification (eg, SOC and PT set to UNCODED CLASS).

10.3 Medical procedures

Medical procedures prior to study entry and during the study will be listed separately.

10.4 Clinical laboratory evaluations

10.4.1 Hematology, Chemistry and Urinalysis Parameters

Laboratory values will be collected according to the protocol schedule of study assessments. In case a laboratory test is repeated at one visit, the latest measurement will be used for summary

tables. For continuous laboratory variables (including hematology and chemistry) summary statistics of Baseline values, Visit 13 values, and change from Baseline will be presented overall and by age cohort, for all subjects, and by infusion duration at each study visit for the SS-iv. For categorial urinalysis laboratory variables summary statistics of Visit 1 and Visit 13 values will be presented overall and by age cohort, for all subjects, and by infusion duration for the SS-iv.

Shifts from Baseline to Visit 13 based on the normal range (ie, low, normal, high, and missing) for each hematology, and chemistry lab parameter will be presented for subjects who have a Baseline and Visit 13 measurement overall and by age cohort, for all subjects and by infusion duration for the SS-iv. Shifts from Baseline to Visit 13 based on the categorization of each urinalysis lab parameter will be presented for subjects who had done a Baseline and Visit 13 measurement, overall and by age cohort, for all subjects and by infusion duration for the SS-iv.

The number and percentage of subjects with possibly clinically significant treatment-emergent (PCST) for each laboratory variable (i.e. PCST low value, PCST high value) for hematology, biochemistry (including Thyroxine (T4)) and urinalysis will be summarized overall and by age cohort, for all subjects, and by infusion duration. The criteria for a laboratory value to be PCST is defined in Appendix 12.2, but note, only laboratory variables that meet PCST criteria at Visit 13, but not Baseline will be considered as PCST.

The number of occurrences of each unique PCST type will be tabulated by timepoint within each visit within each subject, and include relevant criterion: gender, age, race, timepoint, visit, subject group and infusion duration. In addition, the number of subjects with at least one PCST will be displayed for each age cohort.

The following listings will be provided: all laboratory results of clinical chemistry, hematology, urinalysis including an indicator as to which met the criteria for PCST. A separate listing will contain all additional laboratory tests performed and sample takes.

10.4.2 Potential Drug Induced Liver Injury

A summary of the number and percentage of subjects who met PDILI criteria at any visit and at Visit 13 will be summarized overall, and by age cohort for all subjects and by infusion group. Results from local laboratory should be included, if applicable. Subjects who meet one or more of the criteria for potential drug-induced liver injury (PDILI) at Visit 1 or Visit 13 will be listed. The listing will display only visits for which at least one of the criteria for PDILI (see Appendix 12.3) was fulfilled for a given subject, and will display all results obtained at that visit for the specified variables associated with PDILI. Potential Hy's law cases will be flagged.

All potential drug-induced liver injury (PDILI) events require immediate action, testing, and monitoring (see Appendix 12.3). 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.

10.5 Vital signs, physical findings, and other observations related to safety

10.5.1 Vital signs and body weight

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], respiratory rate [RR], temperature, pulse rate) and body weight will be collected according to the protocol schedule of study assessments.

Observed values of body weight will be summarized for each visit by infusion duration, and by subject group for the SS-iv.

Observed values of SBP, DBP, RR, temperature and pulse rate will be summarized for each time point (as defined in Section 4.8) within each visit. Change from Baseline for SBP, DBP, RR, temperature, and pulse rate will be summarized for all post-Baseline time points within each visit. Tables will be provided overall and by age cohort, for all subjects and by infusion duration, and by subject group for the SS-iv. Observed values for SBP, DBP, RR, temperature, and pulse rate at each timepoint will be plotted as a line for each subject in line graphs by visit (Visit 1 to 3, then for each visit individually i.e. Visit 4, 5, etc), age cohort and infusion duration. Abnormal values defined by the PCST criteria will be marked using symbols.

Vital signs PCS/PCST definitions are located in Appendix 12.2.4. Vital signs PCST events (i.e. Treatment-emergent vital signs PCS) are defined as events which started on or after the first BRV medication taken during the EP0065 study that meet PCS criteria. Subjects who began the study on BRV treatment (OLB and RxB subjects) will be assumed to have taken BRV treatment on the first day of screening. Therefore, timing of a PCS being treatment emergent (i.e. a PCST) varies by subject group: all PCS are treatment emergent for RxB and OLB subjects; all PCS on or after the IOB Treatment Period are treatment emergent for IOB subjects; all PCS on or after the iv PK Period are treatment emergent for IIB subjects.

All vital signs measurements (scheduled and unscheduled) which are taken after the first BRV medication during the EP0065 study will be assessed to determine if they meet PCST criteria. The number and percentage of subjects that meet the criteria for any PCST value, a high PCST value and a low PCST value at each timepoint and visit will be presented for each variable individually overall and by age cohort for all subjects and by infusion duration. A separate summary will be presented by country of enrollment (Hungary and rest of the World) for all subjects and by infusion duration. Percentages will be relative to the number of subjects with a value at each corresponding timepoint or visit.

The number of occurrences of each unique PCST type will be tabulated by timepoint within each visit for each subject, and include relevant criteria: gender, age, race, timepoint, visit, subject group and infusion duration. In addition, the number of subjects with at least one PCST will be displayed for each age cohort.

A subject data listing of all vital sign values will be presented. The listing will contain columns indicating which values met the criteria for PCS and PCST. All body weight values will be listed and will contain a column indicating the PCS and PCST criteria.

10.5.2 Electrocardiograms (ECGs)

Standard 12-lead ECGs (heart rate, RR-interval, PQ/PR interval, QRS duration, QT interval, QTcB interval) will be performed throughout the study, according to the protocol schedule of assessments. The QTcF interval will be calculated using the following formula:

$$QTcF = \frac{\mathrm{QT}}{\sqrt[3]{\mathrm{RR}}}$$

Observed values of ECG parameters will be summarized for each timepoint within each visit. Change from Baseline for ECG parameters will be summarized for all post-Baseline timepoints within each visit. Tables will be provided overall, and by age cohort for all subjects, and by infusion duration, and subject subgroup for the SS-iv. Values for all ECG parameters at each timepoint will be plotted as a line for each subject in line graphs by visit (Visit 1 to 3, then for each visit individually i.e. Visit 4, 5 etc.), age cohort, and infusion duration. Abnormal values are defined by the PCS/PCST criteria (see Appendix 12.2.5) and will be displayed using symbols. ECG PCST events (i.e. Treatment-emergent ECG PCS) are defined as events which started on or after the first BRV medication taken during the EP0065 study that meet PCS criteria. In subjects who begun the study on BRV treatment (OLB and RxB subjects), they will be assumed to have taken BRV treatment on the first day of screening. Therefore, timing of a PCS being treatment emergent (i.e. a PCST) varies by subject group: all PCS are treatment emergent for RxB and OLB subjects; all PCS on or after the IOB Treatment Period are treatment emergent for IOB subjects; all PCS on or after the iv PK Period are treatment emergent for IIB subjects.

All ECG parameter measurements (scheduled and unscheduled) which are taken after the first BRV medication during the EP0065 study will be assessed to determine if they meet PCST criteria. The number and percentage of subjects that meet the criteria for PCST at each timepoint and visit will be presented for each variable individually overall and by age cohort for all subjects and by infusion duration. A separate summary will be presented by country of enrollment (Hungary and rest of the World) for all subjects and by infusion duration. Percentages will be relative to the number of subjects with a value at each corresponding timepoint or visit.

The number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG findings, as assessed by the investigator, will be summarized for all timepoints within visits overall and by age cohort for all subjects and by infusion duration.

Shift tables will display the number and percentage of subjects having the same and different ECG finding (normal/abnormal not clinically significant/abnormal clinically significant) at each post-iv timepoint compared to their pre-iv ECG finding in the same visit, for all subjects and by age cohort, by infusion duration. Therefore, for subjects on bolus the shift from pre -iv BRV to ≤2, 5, 15, 30, 60 minutes and 2 hr after initiation of iv BRV result will be displayed, and for subjects on 15 minutes infusion the shift from pre -iv BRV to 5, 10, 15, 30, 60 minutes and 2 hr after initiation of iv BRV result will be displayed.

A subject data listing will be provided for 12-lead ECG results and will contain a column indicating the PCS and PCST criteria if a subject had abnormal ECG value. A separate listing will be provided, displaying the 12-lead ECG findings including a record of whether each finding was clinically significant or not.

10.5.3 Medical Resource Use

Hospitalization and emergency room visits will be listed for the SS. The listing will describe the event, date, period of onset, ward and reason for the hospitalization or emergency room visit. No summary of hospitalization or emergency room visits are planned.

10.5.4 Health Care Provider Consultations Not Foreseen by the Protocol

Subject data listing will be provided for subjects who consult a health care provider not foreseen by the protocol.

10.5.5 Physical examination

Complete physical examinations will be conducted at Visit 1. Brief physical examinations should be conducted at other designated visits.

Clinically new or worsened physical examination findings will be reported as AEs.

A listing of physical examinations conducted at Visit 1 will be provided; no summaries of physical examination are planned.

10.5.6 Tanner Stage

Tanner Stage will be assessed at Visit 3 prior to iv BRV. A Listing of Tanner Stage will be provided for subjects who are selected for evaluation of Tanner Stage (ie, those subjects who are pubescent).

10.5.7 Neurological examination

Complete neurological examination will be conducted at Visit 1. Brief neurological examination should be conducted at other designated visits.

Clinically new or worsened neurological examination findings will be reported as AEs.

A listing of neurological examinations conducted at Visit 1 will be provided; no summaries of neurological examination are planned.

10.5.8 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia-Suicide Severity Rating Scale). This will be completed according to the protocol schedule of study assessments.

For subjects ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. All subjects who are ≥6 years of age will complete the "Baseline/Screening" version of the C-SSRS at Visit 1 and will complete the "Since Last Visit" version at subsequent visits. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and use the "Since Last Visit" version at subsequent visits.

The C-SSRS is not validated for subjects <6 years of age and will not be used for this population but signs and symptoms of depression will be assessed at each visit.

Subject data listings of the data for the C-SSRS will be provided. No summaries of these results are planned.

11 REFERENCES

This section is not applicable for this study.

12 APPENDICES

12.1 Laboratory parameters

Table 12–1: Laboratory parameters

Hematology	**Chemistry**	**Urinalysis[a]**	**Endocrinology**	**Pregnancy[b]**
WBC	Glucose	Glucose	FSH	β-hCG (urine)
RBC	Sodium	Ketones	LH	
Hemoglobin	Potassium	Occult blood	TSH	
Hematocrit	Calcium	Protein	T_3	
Platelet count	Chloride	Nitrites	T_4	
Lymphocytes (number, %)	Bicarbonate	Leukocytes		
Monocytes (number, %)	Phosphorus (inorganic)	Microscopic examination[c]		
Neutrophils (number, %)	Total protein			
Eosinophils (number, %)	Albumin			
Basophils (number, %)	Total bilirubin			
MCH	ALP			
MCHC	AST			
MCV	ALT			
	GGT			
	Uric acid			
	Urea			
	Creatinine			
	Triglycerides			
	Cholesterol			

Table 12–1: Laboratory parameters

Hematology	Chemistry	Urinalysis[a]	Endocrinology	Pregnancy[b]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=beta-human chorionic gonadotropin; FSH=follicle-stimulating hormone; GGT=gamma-glutamyltransferase; LH=luteinizing hormone; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV= mean corpuscular volume; RBC=red blood cell; T_3=triiodothyronine; T_4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell

[a] Urinalysis will be performed in subjects for whom urine sample collection is feasible.

[b] For female subjects of childbearing potential only.

[c] Includes bacteria, cells, casts, and crystals for all samples.

12.2 PCS criteria

In this section the criteria for laboratory, vital signs and ECG parameters to be considered PCS is described. PCST is a treatment emergent PCS event. The definition of PCST for laboratory parameters is described in Section 10.4, for vital signs in Section 10.5.1 and ECG is in Section 10.5.2.

12.2.1 Hematology

Parameter	Age Range	UNIT (conventional)	PCS Criteria (conventional)	unit (standard)	PCS Criteria (standard)
Hematocrit	<2y	%	≤27 >45	%	≤27 >45
	2y - <18y		≤29 >47		≤29 >47
	≥18y		≤85% of LLN ≥115% of ULN)		≤85% of LLN ≥115% of ULN
Hemoglobin	<2y	g/dL	≤9.0 >15.0	g/L	≤90 >150
	2y - <18y		≤9.5 >16.0		≤95 >160
	≥18y		≤85% of LLN		≤85% of LLN

Parameter	Age Range	UNIT (conventional)	PCS Criteria (conventional)	unit (standard)	PCS Criteria (standard)
			≥115% of ULN		≥115% of ULN
WBC/ Leukocytes	<12y	109/L	<3.5 >15.0	G/L	<3.5 >15.0
	≥12y		<3.0 >12.0		<3.0 >12.0
Neutrophils Absolute	>1m	109/L	<1.5	G/L	<1.5
Lymphocytes	<6m	%	≤30.0	%	≤30.0
	6m - <6y		≤22.0		≤22.0
	6y - <18y		≤12.0 ≥80.0		≤12.0 ≥80.0
	≥18y		≤10.0 ≥80.0		≤10.0 ≥80.0
Basophils	>1m	%	≥3.0	%	≥3.0
Eosinophils	>1m	%	≥10.0	%	≥10.0
Monocytes	>1m	%	≥20.0	%	≥20.0
Platelets	>1m	109/L	≤100 >600	G/L	≤100 >600
RBC/ Erythrocytes	<2y	1012/L	<3.0	T/L	<3.0
	≥2y		<3.5		<3.5

Abbreviations: ANC = absolute neutrophil count; m =month, y = year. A month is defined as 30 days; a year is defined as 365.25 days.

12.2.2 Biochemistry

Parameter	Age Range	UNIT (conventional)	PCS Criteria (conventional)	unit (standard)	PCS Criteria (standard)
AST (SGOT)	<14y	U/L	>180	U/L	>180
	≥14y		>144		>144
ALT (SGPT)	1y - <18y	U/L	>90	U/L	>90
	≥18y		>123		>123
Alkaline Phosphatase	<4y	U/L	>690	U/L	>690
	4y - <10y		>834		>834
	10y - <18y		>1174		>1174
	≥18y		>432 (F) >933 (M)		>432 (F) >933 (M)
GGT	<6m	U/L	>522	U/L	>522
	6m - <1y		>279		>279
	1y - <13y		>66		>66
	13y - <18y		>126		>126
	≥18y		>255		>255
Total Bilirubin	≥1m	mg/dL	≥1.5	umol/L	≥25.656
Total Protein	2m-<1y	g/dL	<3.0 >10.0	g/L	<30 >100
	≥1y		<4.3 >10.0		<43 >100
Albumin	<1y	g/dL	<1.6 >6.0	g/L	<16 >60
	≥1y		<2.4		<24

Parameter	Age Range	UNIT (conventional)	PCS Criteria (conventional)	unit (standard)	PCS Criteria (standard)
			>7.0		>70
BUN	<1y	mg/dL	>21	mmol/L	>7.497
	≥1y		>30		>10.71
Urea	<1y	mg/dL	>42	mmol/L	>7.014
	≥1y		>60		>10.02
Creatinine	1y - <10y	mg/dL	>0.9	umol/L	>79.56
	10y - <16y		>1.4		>123.76
	≥16y		>1.6		>141.44
Creatinine Clearance*	All	mL/min	<70	mL/s	<1.169
Calcium	<1y	mg/dL	<6.9 >12.2	mmol/L	<1.725 >3.05
	1y - <18y		<7.4 >11.7		<1.85 >2.925
	≥18y		<7.9 >11.1		≤1.975 ≥2.775
Phosphorous	<1y	mg/dL	<1.8 >8.2	mmol/L	<0.5814 >2.6486
	≥1y		<1.8 >7.4		<0.5814 >2.3902
Potassium	<1y	mEq/L	<3.0 >6.5	mmol/L	<3.0 >6.5
	≥1y		<3.0 >5.8		<3.0 >5.8

Parameter	Age Range	UNIT (conventional)	PCS Criteria (conventional)	unit (standard)	PCS Criteria (standard)
Sodium	>1m	mEq/L	≤130 ≥150	mmol/L	≤130 ≥150
Glucose	>1m	mg/dL	<50 >180	mmol/L	<2.775 >9.99
Total Cholesterol	1y - <18y	mg/dL	>250	mmol/L	>6.475
	≥18y		>300		>7.77
LDL (calculated)	1y - <18y	mg/dL	>140	mmol/L	>3.626
	≥18y		>200		>5.18
HDL	≤2y	mg/dL	<10	mmol/L	<0.259
	>2y		<20		<0.518
Triglycerides	<1y	mg/dL	>750	mmol/L	>8.475
	≥1y		>250		>2.825
Uric Acid	<1y	mg/dL	>7.7	umol/L	>457.996
	1y - <13y		>6.5		>386.62
	13y - <18y		>8.6		>511.528
	≥18y		>6.8 (F) >9.6 (M)		>404.464 (F) >571.008 (M)
Thyroxine (T4)	<1y	ug/dL	≤4.3 ≥18.4	nmol/L	≤55.3453 ≥236.8264
	≥1y		≤3.8 ≥13.5		≤48.9098 ≥173.7585
Globulin	<1y	g/dL	<1.0 >3.8	g/L	<10 >38

Parameter	Age Range	UNIT (conventional)	PCS Criteria (conventional)	unit (standard)	PCS Criteria (standard)
	≥1y		<1.2 >4.4		<12 >44

Abbreviations: ALT= alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; dL = deciliter; GGT: gamma-glutamyltransferase; HDL = high density lipoprotein; LDL = low density lipoprotein; L = liter; m = month (a month is defined as 30 days) mg = milligram; mmol = millimoles; µg = microgram; U = unit; ULN = upper limit of normal; y = years (a year is defined as 365.25 days)

*Schwartz equation (subjects <12): Cr Cl ml/min = [Height (cm) * 0.55] / serum creatinine

Cockroft equation (subjects >12): Male: Cr Cl ml/min = [(140-age) x body weight (kg)] / (72 x serum creatinine); Female: Cr Cl ml/min = [(140-age) x body weight (kg)] / (72 x serum creatinine)] x 0.85.

Thyroxine (T4) is an Endocrinology parameter.

12.2.3 Urinalysis

Qualitative urine parameters are generally reported by a descriptive score, which differs among laboratories. For data analysis purpose, a four-point scale is used. Five-point, six-point, or seven-point scales will be collapsed into a four-point scale first. A value is considered possibly clinically significant treatment-emergent abnormal if an upward shift of at least 2 degrees from the baseline occurs under investigational treatment. To collapse the results in a five-point scale into a four-point scale, the lowest 2 positive results will be combined (see example below).

Table 12.2: Conversion of results in a five-point scale into a four-point scale

Original Five-point Scale	Four-point Scale
Negative/None	Negative/None
Trace/Rare/Mild/A Few	Trace/1+/Rare/Mild/A Few
1+	
2+/Mod	2+/Mod
3+/Sev	3+/Sev

The original scale and four-point scale for PCST of each urinalysis parameter is described in the table below.

Table 12.3: Urinalysis 4-point scales for PCS criteria

	Four-point Scale			
PARAMETER	**Negative**	**1+**	**2+**	**3+**
Protein	Negative	Trace, 30 mg/dL	100 mg/dL	≥300 mg/dL, ≥1000 mg/dL

	Four-point Scale			
PARAMETER	**Negative**	**1+**	**2+**	**3+**
Glucose	Negative	100 mg/dL, 250 mg/dL	500 mg/dL	≥1000 mg/dL
Ketones	Negative	Trace, 15 mg/dL	40 mg/dL	≥80 mg/dL, ≥160 mg/dL
Hemoglobin (Occult blood)	Negative	Trace, Small	Moderate	Large
Leukocyte Esterase	Negative	Trace, Small	Moderate	Large
Erythrocytes	1-5 6-10	11-20	21-25	>25
Leukocytes	1-5 6-10	11-20	21-25	>25

For parameters which cannot have negative values their lowest two positive values will be at Negative point. For parameters which can have negative values their lowest two positive values will be at point 1+.

12.2.4 Vital Signs

Parameter	Age Range	PCS Criteria
Pulse Rate (beats/minute)	<6m	<100 >180
	6m - <3y	<90 >150
	3y - <12y	<60 >130
	12y - <17y	<50 >120
	≥17y	<50 and a decrease from Baseline of ≥15 >120 and an increase from Baseline of ≥15
Systolic Blood Pressure (mmHg)	<6m	<60 >100

Parameter	Age Range	PCS Criteria
	6m - <3y	<70 >120
	3y - <12y	<80 >140
	12y - <17y	<90 >160
	≥17y	≤ 90 and a decrease from Baseline of ≥20 ≥ 180 and an increase from Baseline of ≥20
Diastolic Blood Pressure (mmHg)	<6m	<40 >65
	6m - <3y	<45 >75
	3y - <12y	<50 >80
	12y - <17y	<50 >105
	≥17y	<50 and a decrease from Baseline of ≥15 >105 and an increase from Baseline of ≥ 15
Respiratory Rate (breaths/minute)	<6m	<25 >55
	6m - <3y	<20 >45
	3y - <12y	<15 >35
	≥12y	<10 >25

Parameter	Age Range	PCS Criteria
Temperature	>1m	>101 0F (38.3 0C)
Body Weight	1m - <17y	Outside of <3% to >97% percentile of the normal body weight based on gender and the age of subject on date of weight assessment[a]
	≥17y	≥ 10% change from Baseline (an increase or a decrease)[a]

Abbreviations: m = month, y = year. A month is defined as 30 days; a year is defined as 365.25 days.

[a] source: http://www.cdc.gov/growthcharts/

12.2.5 ECG

Parameter	PCST Criteria
QT interval	For ≥ 17 y: ≥ 500 ms or ≥ 15% increase from baseline
QTc interval	For < 17y: ≥ 440 ms or ≥ 15% increase from baseline For ≥ 17 y: ≥ 450 ms or ≥ 60 ms increase from baseline
PR interval	For 1 m to < 6 m: ≥ 145 ms or ≥ 25% increase from baseline For 6 m to < 3 y: ≥ 155 ms or ≥ 25% increase from baseline For 3 y to < 11 y: ≥ 170 ms or ≥ 25% increase from baseline For 11 y to < 17 y: ≥ 175 ms or ≥ 25% increase from baseline For ≥ 17 y: ≥ 200 ms or ≥ 25% increase from baseline
QRS interval	For 1 m to < 7y: ≥ 78 ms or ≥ 25% increase from baseline For 7 y to < 17 y: ≥ 88 ms or ≥ 25% increase from baseline For ≥ 17 y: ≥ 100 ms or ≥ 25% increase from baseline
HR	For 1 m to < 12 m: ≤ 110 bpm and a decrease of ≥ 20 bpm from baseline or ≥ 180 bpm and an increase of ≥ 20 bpm from baseline For 12 m to < 3 y: ≤ 90 bpm and a decrease of ≥ 20 bpm from baseline or ≥ 150 bpm and an increase of ≥ 20 bpm from baseline For 3 y to < 12 y: ≤ 65 bpm and a decrease of ≥ 20 bpm from baseline or ≥ 130 bpm and an increase of ≥ 20 bpm from baseline For 12 y to < 17 y: ≤ 60 bpm and a decrease of ≥ 20 bpm from baseline or ≥ 120 bpm and an increase of ≥ 20 bpm from baseline For ≥ 17 y: ≤ 50 bpm and a decrease of 20% from baseline or ≥ 120 bpm and an increase of 20% from baseline

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) (IF APPLICABLE)

13.1 Changes in SAP from final version 1.0 to final version 2.0

SAP final version 1.0 had a not accepted track change visible, which was accepted and resulted in final version 2.0.

13.2 Changes in SAP from final version 2.0 to final version 3.0

- list of abbreviations was updated
- Section 1 : Updated reference to latest protocol version
- Section 2.3:
  - Clarification added that oral BRV can be applied during EP0065 but will not considered as study medication
  - Added sentence: Each cohort will have approximately 50% of subjects with iv BRV infusion and 50% with bolus BRV.
  - Clarification added that the Down-Titration Period is considered part of the Follow-Up Period
- Section 3.1:
  - Moved following sentence from Section 3.6.2 to Section 3.1: If the Safety Set (SS) and the Safety Set-iv (SS-iv) consist of the same number of subjects, TFLs will only be presented for the SS-iv.
  - Removed summary statistics for PK from this overview section
  - Removed summary statistics by infusion periods
  - Added clarity on which data to summarize and which only be listed
- Section 3.2.2: Removed the word ‘study’ before BRV as the wording ‘study BRV’ is not used anywhere else
- Section 3.2.3: Added definition of Relative time.
- Section 3.2.4: Added new section for explanation of derivation of relative time from previous iv infusion
- Section 3.2.5: Corrected grammatical error and added definition for each of the study periods
- Section 3.2.6: Corrected grammatical errors and added formulas for iv BRV exposure duration (days), iv BRV exposure duration (hours), oral BRV exposure duration from tablets, oral BRV exposure from oral solution and overall BRV exposure duration (days).
- Sections about hospital stays and emergency room visits were removed from Section 3 as no derivations are planned
- Section 3.2.7: Added formulas for age at first diagnosis in years and months
- Section 3.2.8: Added formulas for duration of epilepsy in years and months

- Section 3.2.9: Added new section for explanation of derivation of time prior to AE onset
- Section 3.3: Added 'weight and height at Screening Visit' to make clear which variables to use for calculation
- Section 3.4: Wording of definition of Baseline values updated to ' latest assessment prior to the first infusion of iv BRV'
- Section 3.6.2: Moved second sentence to Section 3.1
- Section 3.10: Added clarification that for vital sign and ECG summary statistics will be conducted for each timepoint only i.e. not summarized for the pre-bolus/infusion period, the bolus/infusion period, the period immediately post-bolus/infusion, and period between each subsequent bolus/infusion as stated in the protocol
- Section 4.2: Reordered sentences for clarity and add that imputations will only be done for classification and calculations and not listed
- Section 4.2.4: Updated imputation rules for partial AE onset date
- Section 4.2.5: Replaced 'minimum' with 'earliest' in 'minimum of the last day…'
- Section 4.7: Updated section to: There is no subgroup analysis planned. However the majority of summaries will be analyzed for all subjects, and separately by age cohort, by infusion duration and by subject group.
- Section 4.8: Renamed section from 'Infusion periods and time points' to ' time points by infusion duration', removed infusion periods and added additional time point of BP assessment
- Section 5.1:
  - Updated wording to be more accurate on which table will be provided by which subgroups, analysis sets and overall
  - Added number and percentage for each of the periods for disposition and reason for discontinuation summary table
- Section 6.1:
  - Added variables and clarification which variables will be presented in summary table
  - Added listings on family medical history and lifestyle, and added descriptions where required
- Section 6.2:
  - Replaced 'concomitant' with 'ongoing'
  - Added analysis set
- Section 6.3:
  - Added definition of follow-up medications
  - Updated section of AED identification and added new reference listing

- Section 6.3.1 and Section 6.3.2:
  - Replaced wording of ‘at the time of study entry’ with ‘prior to first iv BRV’ and ‘subjects taking concomitant AED medications’ with ‘concomitantly with iv BRV’
  - Added overall summary
- Section 7: Added oral dosing, as both iv and oral BRV will be evaluated through the review of IPDs
- Section 9.1:
  - Removed ‘during administration’ as PK sample will only be taken prior and after iv BRV
  - Added summary table by visit and subject group (OLB, RxB, IOB, and IIB)
  - Reworded paragraph and aligned summary statistics to the ones defined in standard mock shells
- Section 10.1:
  - Corrected grammatical errors
  - Added clarity on summary tables for overall oral BRV exposure, oral BRV exposure from tablets, oral BRV exposure from oral solution and overall BRV duration of oral and iv exposure
  - Added summary table of overall BRV duration of oral and iv exposure for the SS
  - Completed list of listings and added information on which variables will be described
- Section 10.2 :
  - Reordered AE section and added separate sections for AE summary tables and AE listings
  - Updated definition of TEAE
  - Added clarity to different kind of AE tables and listings
  - Added summary tables for incidence of TEAEs by relative time from bolus/15 minutes infusion start time
  - Replaced ‘TEAE’ with ‘AE’ as glossary table will include all AEs not only TEAEs
  - Added listing of timing of TEAE onset in relation to start time of previous iv treatment
  - Added listing of timing of TEAE onset in relation to previous PCSTs
- Section 10.3: Updated section to make clear medical procedures will be listed only
- Section 10.4.1:
  - Removed endocrinology as those parameters are not separately categorized in CDISC standards
  - Added clarification about which result to use when repeated values are measured at one visit

  - Added analysis set for continuous lab parameters
  - Added summary table for categorial urinalysis parameters at each visit where urinalysis is supposed to be collected for the SS-iv
  - Added clarification about the urinalysis shift table
  - Added clarification for laboratory PCST data listing
  - Added listing for all additional laboratory test performed
- Section 10.4.2: Clarified what will be presented for PDILI
- Section 10.5.1:
  - Added summary table for body weight by infusion duration, and by subject group for the SS-iv
  - Reworded summary tables to clarify that each timepoint will be summarized within each visit by infusion duration, and by subject group for the SS-iv
  - Updated wording of line graphs
  - Updated PCST vital sign values as PCST values which occur on or after first administration of oral or iv BRV through the end of the study
  - Updated wording of summary table for subject that meets the criteria for any PCST value
  - Added column for PCST to the vital sign listings
- Section 10.5.2:
  - Added QTcF interval and formulation
  - Reworded vital sign summary tables for continuous and categorical variables to clarify that each timepoint will be summarized within each visit by infusion duration, and by subject group for the SS-iv
  - Updated wording of line graphs
  - Included all post initiation time points to the shift tables
  - Added ECG listing including a column for PCST
- Section 10.5.3:
  - Combined the two section for hospital stays and emergency room visits to one section
  - Updated to listings only
- Section 10.5.5 and Section 10.5.7: Added clarity that listings will provide examination conducted at Visit 1
- Appendix 12.2.3: Added table for conversion of urinalysis four-point scale for PCST criteria
- Appendix 12.2.4: Updated wording of abnormality criterion for body weight

13.3 Changes in SAP from final version 3.0 to final version 4.0

- Section 2.3: Removed "application" for better wording in following sentence: "Oral BRV application can be applied during EP0065 but will not considered as study medication for EP0065"
- Section 3.2.3: Concomitant medications relative time excluded from this section as unable to derive as start and stop time not collected of concomitant medications.
- Section 3.3: BMI formula rewritten in terms of meters rather than cm
- Section 3.2.9: Added clarification on calculating time prior to AE onset, and added calculation for number of days prior to TEAE onset.
- Section 3.10: Clarified that AEs will not be summarized the periods specified in the protocol, but will be summarized relative to most recent bolus/infusion start time. Slightly reworded for clarity.
- Section 4.2.7: 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:
  - Added clarification on the difference between the sequential cohort enrollment schematic diagram between the SAP and protocol. Spilt into two sections (Section 4.3.1 which discusses sequential cohort enrollment, where text some has been modified for clarity and Section 4.3.2 which has added text on how analysis will be conducted twice due to COVID-19, once using all subjects aged 2 to <16 years and 1m to < 2years on 15 -minute infusion, and once using all subjects.
- Section 5.2: Information added to describe how subjects with a completed COVID-19 eCRF Impact page will be assessed, and displayed.
- Section 6.3 Clarification added to describe how prior concomitant medications will be listed only if they finish 2 weeks or more prior to screening.
- Section 9.1: Text added to text to explain that PK summary tables will also be produced by infusion duration. Clarification added to explain that the summary tables will be produced by the combination of OLB, RxB and IOB groups, and separately for the IIB group.
- Section 10.1: Additional text added to explain the groups that the exposure table will be presented by (all subjects, infusion duration and weight).
- Section 10.2: Described how an AE occurring after first dose in N1266 but prior to TC-1 will be reported in both studies.
- Section 10.2.1: Clarifications added for study periods and incidence definition.
- Section 10.5.1:
  - PCST definition modified, so all PCS occurrences in subjects who enter the study on BRV (RxB/OLB) are considered treatment-emergent (PCST).
  - Added PCS definition
  - Added column for PCS to vital sign listings
- Section 10.5.2:

- Slightly reworded which values will be plotted.
- PCST definition modified, so all PCS occurrences in subjects who enter the study on BRV (RxB/OLB) are considered treatment-emergent (PCST).
- Added PCS definition
- Added column for PCS to ECG listings

- Section 12.2: Clarification added to describe the difference between PCS and PCST.
- Section 12.2.3: Table 12.3 was updated to reflect consistency within 4-point scale derivation.

13.4 Changes in SAP from final version 4.0 to final version 5.0

- Section 3.1: Additional text added to describe how selected summaries will be repeated by the country of enrollment (Hungary and rest of the World).
- Section 4.7: Additional text added to describe how some summaries will be analyzed by country of enrollment (Hungary and rest of the World).
- Section 5.2: Added IPD table by country of enrollment.
- Section 9.1: Added box plots of plasma concentration of BRV for each age cohort at each timepoint by visit. Added box plots of plasma concentration of BRV for each infusion duration at each timepoint by visit.
- Section 10.2.1: Added AE tables which will be produced by country of enrollment.
- Section 10.5.1: Added PCST table which will be produced by country of enrollment.
- Section 10.5.2: Added ECG PCST tables.
- Section 12.2.3: Urinalysis 4-point scales for PCS criteria were changed from “1”, ”2”, ”3”, ”4” to “Negative”, “1+”, ”2+”, “3+”.

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: ep0065-sap-amend-4

Version: 2.0

Document Number: CLIN-000161592

Title: EP0065-Statistical Analysis Plan Amendment 4

Approved Date: 28 Sep 2020

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Qualified Person Date of Signature: 28-Sep-2020 10:01:05 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 28-Sep-2020 10:45:11 GMT+0000