STATISTICAL ANALYSIS PLAN

AMENDMENT 1

Study: EP0101

Product: Brivaracetam

AN OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE PHARMACOKINETICS AND SAFETY OF A SINGLE AND MULTIPLE ORAL DOSES OF BRIVARACETAM IN HEALTHY ADULT CHINESE SUBJECTS

PHASE 1

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VERSION HISTORY

SAP Version	Approval Date	Change	Rationale
1.0	<24 May 2021>	Not Applicable	Original version
Amendment 1	<27 Aug 2021>	1. Definition of ECG baseline (Section 5.6.3.3) 2. Summary tables of Urinalysis (Section 5.6.3.1.2) 3. Handling of BLQ values in individual concentration figures (Section 5.7.1.1)	1. To be consistent with the study protocol 2. To clarify the different summary tables for different data type of urinalysis and urine sediment forms 3. To comply with the UCB NCA data handling rules

LIST OF ABBREVIATIONS

Ae	amount of drug excreted in the urine
AE	adverse event
AUC	area under the curve from 0 to infinite time
$AUC_{(0\text{-}12),ss}$	area under the curve from 0 to 12 hours at steady state
$AUC_{(0\text{-}t)}$	area under the plasma concentration-time curve from zero to the time of the last measured concentration above the limit of quantification
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
BRV	brivaracetam
$C_{av,ss}$	average plasma concentration at steady state
CI	confidence interval
CL/F	apparent total body clearance
CL_R	renal clearance
CL_{ss}/F	apparent total body clearance at steady state
C_{max}	maximum plasma concentration
$C_{max,ss}$	maximum plasma concentration at steady state
$C_{min,ss}$	minimum plasma concentration at steady state

CSR	clinical study report
CV	coefficient of variation
DEM	Data Evaluation Meeting
ECG	electrocardiogram
ES	Enrolled Set
fe	fraction of the dose excreted in the urine
IPD	Important protocol deviation
λ_z	rate constant of elimination
LLOQ	lower limit of quantification
MedDRA®	Medical Dictionary for Regulatory Activities
MRT	mean residence time
PCST	possibly clinically significant treatment-emergent
PD	pharmacodynamic
PK	pharmacokinetic
PK-PPS	Pharmacokinetic Per Protocol Set
PTF	peak trough fluctuation
R_{AUC}	accumulation ratio calculated from AUC at steady state and AUC after single dose
R_{max}	accumulation ratio calculated from C_{max} at steady state and C_{max} after single dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SFU	safety follow-up
SPD	Specification of Protocol Deviations
SS	Safety Set
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to reach maximum plasma concentration
Vz/F	apparent volume of distribution
WHO-DRL	World Health Organization Drug Reference List

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 (CSR) for study EP0101. The SAP is based on the following study document: Protocol Amendment 2, 08 Jan 2021.

1.1 Objectives and Endpoints

Table 1–1: Objectives and Endpoints

Objectives	Endpoints
To assess the pharmacokinetics (PK), safety, and tolerability of BRV after a single dose and multiple doses of 100mg for 6 days in healthy adult Chinese participants (male and female).	**Primary PK Endpoints:** • Concentrations of BRV and 3 metabolites (ucb-42145, ucb-100406-1, and ucb107092-1) in plasma • For the single dose: o $AUC_{(0-t)}$ of BRV o C_{max} of BRV • For the multiple dose: o $AUC_{(0-12),ss}$ of BRV o $C_{max,ss}$ of BRV **Secondary PK Endpoints:** • For the single dose: o t_{max}, $t_{1/2}$, λ_z, MRT, AUC, CL/F, and V_z/F of BRV in plasma o C_{max}, t_{max}, $t_{½}$, λ_z, $AUC_{(0-t)}$, and AUC of metabolites in plasma • For the multiple dose: o t_{max}, $t_{½}$, λ_z, $C_{min,ss}$, $C_{av,ss}$, CL_{ss}/F, and Vz/F of BRV in plasma o t_{max}, $t_{½}$, λ_z, $C_{max,ss}$, and $AUC_{(0-12),ss}$ of metabolites in plasma o PTF of BRV in steady-state o R_{AUC} and R_{max} of BRV

Table 1–1: Objectives and Endpoints

Objectives	Endpoints
	Primary Safety Endpoints: • Incidence of treatment-emergent AEs (TEAEs) **Other Safety Endpoints:** • Changes in vital signs (SBP, DBP, pulse rate, respiratory rate, and body temperature) • Standard 12-lead ECGs parameters and findings • Changes in clinical laboratory test parameters (hematology, blood chemistry, and urinalysis)

1.2 Study design

This is a Phase 1, single site, open-label, single and multiple dose PK study of BRV tablets in healthy male and female Chinese participants. Participants are confined to the clinical trial unit from Day -1 (the day prior to first administration of BRV) until Day 13.

A total of 12 participants (6 males and 6 females) who have signed the informed consent form and fulfilled all inclusion and none of the exclusion criteria are planned to be enrolled and will start the Single-Dose Period. In the Single-Dose Period, each subject receives a single dose of BRV 100mg. In the Multiple-Dose Period, the multiple-dose PK and safety of BRV 200mg/day (100 mg every 12h ± 15 min) are evaluated in the same participants as in the Single-Dose Period.

In the Single-Dose Period, participants will receive a single dose of BRV under fasting conditions with 200mL water. Blood samples will be taken for the determination of the PK profile of BRV and its metabolites (ucb-42145, ucb-100406-1, and ucb107092-1) at predose, and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, and 72h after investigational medicinal product (IMP) administration (Table 1–2).

Table 1–2: Single-Dose Period: schedule for ECGs, vital signs, and PK sampling

	Time relative to BRV administration															
		Postdose (h)														
	Day 1											Day 2			Day 3	Day 4
Assessment	Predose	0.25	0.5	1	1.5	2	3	4	6	9	12	16	24	36	48	72
12-lead ECG	X[a]	--	--	X	--	X	--	X	--	--	--	--	--	--	--	X
Vital signs [b]	X	--	--	X	--	X	--	X	--	--	--	--	--	--	--	X
Blood samples for PK	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BRV=brivaracetam; DBP=diastolic blood pressure; ECG=electrocardiogram; PK=pharmacokinetics; SBP=systolic blood pressure
a. Three ECGs to be performed at 15min (±5min) intervals within 24h prior to BRV dosing on Day 1 to provide a representative baseline
b. Vital sign assessments include SBP, DBP, pulse rate, respiratory rate, and body temperature.

In the Multiple-Dose Period, participants will receive BRV 200mg/day (100mg every 12h ±15min). Participants will receive BRV under fasting conditions with 200mL water. Blood samples will be taken for the determination of the PK profile of BRV and its metabolites (ucb-42145, ucb-100406-1, and ucb107092-1) predose prior to the morning dose administration on Day 5 to Day 9, and at predosing and at the following time points after the last administration of the IMP on Day 10: 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, and 72h (Table 1–3).

Table 1–3: Multiple-Dose Period: schedule for ECGs, vital signs, and PK sampling

Assessment	Day																			
	5	6	7	8	9	10										11			12	13
	Pre	Pre	Pre	Pre	Pre	Pre	Postdose (h)													
							0.25	0.5	1	1.5	2	3	4	6	9	12	16	24	36	48	72
12-lead ECG	--	--	X[a]	--	--	X	--	--	X	--	X	--	X	--	--	--	--	--	--	--	X
Vital signs[b]	--	--	X[a]	--	--	X	--	--	X	--	X	--	X	--	--	--	--	--	--	--	X
Blood samples for PK	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

DBP=diastolic blood pressure; ECG=electrocardiogram; Pre=predose; SBP=systolic blood pressure
[a] To be performed predose on the morning of Day 7.
[b] Vital sign assessments include SBP, DBP, pulse rate, respiratory rate, and body temperature
[c] To be collected predose in the morning.

Participants will be discharged from confinement in the morning of Day 13, approximately 72h after the final administration of IMP, provided there are no medical objections.

Safety and tolerability of BRV will be assessed throughout the study by monitoring of AEs, collecting blood and urine samples for the evaluation of safety laboratory parameters, measuring vital signs (SBP, DBP, pulse rate, respiratory rate, and body temperature), and ECG.

A Safety Follow-up (SFU) Visit will be performed after the final administration of the IMP. The assessments performed for the SFU will also be performed for early withdrawals.

The anticipated maximum study duration per participant is 43 days (approximately 6 weeks), including the Screening Period (up to 28 days), confinement during the Single-Dose and Multiple-Dose Periods (13 days), and follow-up examination (2 days after clinic discharge).

The end of the study is defined as the date of the final visit of the final participant in the study.

2 STATISTICAL HYPOTHESES

No statistical comparisons with hypothetical inference are planned for the primary analysis of the pharmacokinetic variables.

3 SAMPLE SIZE DETERMINATION

A total of 12 healthy (6 male and 6 female) participants is planned to be enrolled at one site in China and allocated to the treatment.

Due to the primary objective of the study being related to PK and safety, no power calculation of the study sample size is performed.

4 POPULATIONS FOR ANALYSIS

PK variables are summarized using the Pharmacokinetic Per-Protocol Set (PK-PPS), and safety variables are summarized using the Safety Set (SS).

Subject data listings are prepared for participants with available data (Enrolled Set [ES], SS, or PK-PPS), depending on the domain.

The reasons for exclusion of participants from either of the analysis sets will be listed.

4.1 Enrolled Set

The ES consists of all participants who gave informed consent including screen failures. This analysis set is also referred to as "All Participants Screened."

4.2 Safety Set

The SS consists of all participants who received at least 1 dose of IMP.

4.3 Pharmacokinetic Per-Protocol Set

The PK-PPS consists of all participants who are included in the SS and also have a sufficient number of bioanalytical assessments to calculate reliable estimates for the primary PK parameters.

5 STATISTICAL ANALYSES

5.1 General Considerations

Statistical analysis and generation of tables, figures, subject data listings, and statistical outputs are performed using SAS version 9.3 or higher. Calculations of PK parameters are made with Phoenix® WinNonlin® version 8.2 or higher. All tables and listings use Courier New font size 9.

Descriptive statistics are displayed to provide an overview of the study results. For categorical parameters, the number and percentage of participants in each category are presented. The denominator for percentages is based on the number of participants appropriate for the purpose

of analysis. Unless otherwise noted, all percentages are displayed to 1 decimal place. No percentage is displayed for zero counts, and no decimals are presented when the percentage is 100%. For continuous parameters, descriptive statistics include number of participants/observations with available measurements (n), mean, standard deviation (SD), median, minimum, and maximum unless otherwise specified.

For decimal places for descriptive statistics, the following rules are applied unless otherwise stated:

- "n" is an integer.
- (Arithmetic or geometric) mean, SD, and median use 1 additional decimal place compared to the original data.
- Minimum and maximum have the same number of decimal places as the original value.
- Coefficient of variance (CV) [%] is presented with 1 decimal place.
- Confidence interval (CI) has the same number of decimal place as the corresponding point estimate.

A set of data listings containing all documented data and all calculated data (eg, change from Baseline) is to be provided.

5.1.1 General study level definitions

5.1.1.1 Analysis Time Points

5.1.1.1.1 Relative day

Relative day is calculated as the current date minus the date of first dose of IMP for days prior to the first dose of IMP, and the current date minus the date of first dose of IMP plus 1 for days on or after the first dose of IMP (eg, the day of first dose is Day 1 and the day prior to first dose is Day -1). Day 1 is composed of predose and postdose portions. Relative day is not calculated for partial dates, which will be presented as '--' in the relevant participants data listing.

5.1.1.1.2 End date of the Treatment Period

The end date of the Treatment Period (ie, Single-Dose Period + Multi-Dose Period) is either the date of Day 13 for participants completing the Treatment Period, or the date of the withdrawal for participants who discontinue during the Treatment Period.

5.1.1.1.3 Study periods and visits

The following study periods/visits are defined for the classification by study period/visits:

- Screening Visit: Day -28 to Day -2
- Treatment Period: Day -1 to Day 13 (14 in-house days)
- Single-Dose Period: Day -1 to Day 4
- Multiple-Dose Period: Day 5 to Day 13
- SFU Visit: Day 15 (2 days after discharge)

5.1.1.1.4 Definition of Baseline values

Baseline for safety outcomes (ie, laboratory variables [blood chemistry, hematology, urinalysis], vital signs, and body weight) is defined as the last non-missing value prior to the first dose of IMP.

Baseline should be determined separately for each individual laboratory variable and each individual vital sign variable. An exception is blood pressure, where a complete set of both systolic and diastolic blood pressure should be selected from the same assessment for Baseline.

5.1.1.2 Protocol Deviations

Important protocol deviations (IPDs) are deviations from the protocol which potentially could have a meaningful impact on the key safety or PK outcomes or on study conduct for an individual subject.

The criteria for identifying important protocol deviations and the classification of important protocol deviations are defined within the protocol-specific document, Specification of Protocol Deviations (SPD). To the extent feasible, rules for identifying protocol deviations are defined without review of the data and without consideration of the frequency of occurrence of such deviations. They are identified from various sources such as programmed edit checks, programmed listings, and monitoring reports, and finalized in the SPD during the Data Evaluation Meeting (DEM) prior to database lock.

Any samples that are obtained outside the tolerance window permitted at the specified timepoint will be discussed at the DEM and any possible exclusion from analysis will be documented accordingly.

The categories (eg, inclusion/exclusion criteria, withdrawal criteria, Prohibited concomitant medication use, treatment/procedure non compliance, and incorrect treatment or dose) are not fixed and can be adapted, extended, or reduced according to the needs of the study.

Time deviation of blood sampling for determination of PK parameters

Unless otherwise indicated, any sample taken earlier or later than scheduled is considered a time deviation even if the deviation is pharmacokinetically irrelevant.

The maximum deviations from scheduled sampling times for PK are defined as follows:

- 0h (predose): within 30min before dosing
- 0.25h: ±1min
- 0.5h: ±2min
- 1 to 4h: ±3min
- 6 to 9h: ±6min
- 12 to 16h: ±12min
- ≥24h: ±20min

5.1.1.3 Treatment assignment and treatment groups

As this is a single-arm study, data are summarized only as a whole.

5.1.1.4 Center pooling strategy

As this is a single-center study, pooling of centers is not applicable.

5.1.1.5 Coding dictionaries

Medical history and AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. Medications are be coded using the World Health Organization Drug Reference List (WHO-DRL) 201709(B3 format). Medical procedures are not coded.

5.2 Participant Dispositions

A study participant is considered to have completed the study if all periods of the study have been completed, including the last scheduled procedure shown in the Schedule of activities in the protocol.

The number of participants screened and screen failures and the primary reason for screen failure are summarized for all participants screened (ES).

The number and percentage of participants who started study (will be defined as participants with dose), participants who completed or prematurely discontinued the study, as well as the reason for discontinuation will be summarized based on the SS.

The number and percentage of participants who discontinued due to AEs will be separately summarized based on the SS.

The following listings will be presented:

- Participants who did not meet study eligibility criteria (ES)
- Participants disposition (ES)
- Study discontinuation (SS)
- Visit dates (SS)
- Participants analysis sets (ES)

The listing of participant disposition will include the date of informed consent, date and time of first and last dose of IMP, date of premature termination and primary reason (if applicable), and date of final contact.

The listing of study discontinuation will include the reason for discontinuation and the number of days on IMP.

The number of days on IMP will be calculated as the actual days that the participant received at least one dose of IMP.

5.3 Primary Endpoint(s) Analysis

The primary analysis for this study is the PK analysis, outlined in Section 5.7.1.1.

5.4 Secondary Endpoint(s) Analysis

The secondary analysis for this study is the safety analysis, outlined in Section 5.6.

5.5 Tertiary/Exploratory Endpoint(s) Analysis

Not applicable.

5.6 Safety Analyses

All safety analyses are conducted for the SS. Safety measurements are summarized at each scheduled time point.

5.6.1 Extent of Exposure

All IMP administration details including actual date-time at dosing and dose will be listed by dose period and participant.

5.6.2 Adverse Events

Adverse events are coded using the MedDRA and are classified as either pre-treatment or treatment- emergent. Pre-treatment AEs are defined as AEs which have onset prior to the first dose of IMP. Treatment-emergent adverse events (TEAEs) are defined as AEs which have onset or worsening severity (relative to pre-treatment) after the first dose of IMP.

Summaries of TEAEs will include the following:

- Incidence of TEAEs - overview (including number and percentage of participants with any TEAEs, serious TEAEs, discontinuations due to TEAEs, drug-related TEAEs, severe TEAEs, TEAEs leading to death, TEAE of special interest, and TEAE related to COVID-19 vaccination; event counts will also be included)
- Incidence of TEAEs
- Incidence of serious TEAEs
- Incidence of TEAEs of special interest
- Incidence of TEAEs by maximum relationship
- Incidence of TEAEs by maximum intensity
- Incidence of TEAEs leading to discontinuation by relationship

- Incidence of fatal TEAEs by relationship
- Incidence of serious TEAEs by relationship
- Incidence of non-serious TEAEs above reporting threshold of 5% of participants
- Incidence of TEAEs related to COVID-19 vaccination

For overview of TEAE and incidence of TEAE tables, AEs will be attributed to the dose period in which they start. Thus, all AEs starting after the first intake of BRV and before the intake of Day 5 will be attributed to Single-Dose Period; all AEs starting after BRV intake on Day 5 and on or before Day 13 will be attributed to the Multiple-Dose Period and AEs starting on or after Day 14 will be attributed to the SFU period.

The number and percentage of participants who experience TEAEs will be summarized by MedDRA SOC and PT. Only overview of TEAE and incidence of TEAE tables will be presented by dose period (Single-Dose, Multiple-Dose, and SFU period) and overall. Other TEAE tables will only be presented overall results.

Summary tables will contain counts of study participants, percentages of study participants in parentheses and the number of events where applicable. A participant who has multiple events in the same SOC or PT will be counted only once in the participant counts but all events will be included.

In summaries including relationship, the following relationships will be summarized: 'Not related', 'Related'. Participants who experience the same event multiple times will be included in the most related category for tabulations by maximum relationship. Events with missing relationship will be considered as 'Related' for summary purpose but recorded as missing in the listings.

In summaries including intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Participants who experience the same event multiple times will be included in the most severe category for tabulations by maximum intensity. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings.

Adverse event summaries will be ordered alphabetically by SOC and decreasing frequency of PT within SOC.

A listing for all AEs will be presented by participant and will include the onset date/time and outcome date/time of the event (including relative days), the AE duration (derived), pattern of event, intensity, relationship, action taken and outcome.

5.6.3 Additional Safety Assessments

5.6.3.1 Clinical laboratory evaluations

Values outside the reference range will be flagged in the listings. Measurements of laboratory data that are below the limit of quantification (BLQ) will be imputed with half of the lower limit of quantification (LLOQ) in the summary tables and will be reported as BLQ in the listings.

Clinical laboratory (hematology, coagulation, blood chemistry, and urinalysis) parameters are assessed at Screening Visit, Day 1-predose, Day 3, and Day 11.

A serum pregnancy test is performed at Screening Visit and urine pregnancy tests are performed at Day -1, Day 3, and Day 13.

5.6.3.1.1 Hematology, coagulation, and blood chemistry parameters

The following parameters are measured:

- Hematology

WBC, RBC, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count, lymphocytes*, monocytes*, neutrophils*, eosinophils*, basophils*, atypical lymphocyte

* Variables are summarized on both absolute value and percentage.

- Coagulation

Prothrombin Time (PT), International Normalized Ratio (INR), and activated Partial Thromboplastin Time (aPTT).

- Blood chemistry

calcium, chloride, creatinine, magnesium, potassium, sodium, glucose, blood urea nitrogen (BUN), aspartate aminotransferase (AST (SGOT)), alkaline phosphatase (ALP), alanine aminotransferase (ALT(SGPT)), gamma-glutamyltransferase (GGT), total bilirubin, lactate dehydrogenase (LDH), total cholesterol, albumin

A summary of the absolute and change from Baseline values for each hematology, coagulation and blood chemistry parameter by scheduled visit will be presented.

Shift from Baseline to the post-Baseline time point (Day 3, Day 11) based on reference range and clinical significance (Normal; Abnormal, Not Clinical Significant; Abnormal, Clinical Significant) is provided for all hematology, coagulation and blood chemistry parameters.

A listing of participants who meet the criteria for potential drug-induced liver injury (PDILI) will be presented together with any additional relevant data collected, including:

- Hy's Law
- ALT
- AST
- Bilirubin
- Symptoms Potentially Associated with Hepatotoxicity: Hepatitis

- Symptoms Potentially Associated with Hepatotoxicity: Hypersensitivity

A figure of time course for serum liver function tests for participants meeting potential Hy's law criteria will be presented.

Hy's law is defined as: ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP on the same visit.

5.6.3.1.2 Urinalysis parameters

The following parameters are measured:

- Urinalysis: pH, bilirubin, glucose, ketones, urobilinogen, protein, nitrite
- Urine Sediment: albumin, bacteria, crystals, RBC, WBC

The number and percentage of participants with each response category for qualitative urinalysis and urine sediment parameters are summarized for the scheduled time points. Percentages are rel ative to the number of participants with a result for each parameter at each time point.

Shift from Baseline to the post-Baseline time point (Day 3, Day 11) for observed values (negative, trace, 1+, 2+, 3+, etc) is summarized for the above qualitative urinalysis parameters (bilirubin, glucose, ketones, urobilinogen, protein, nitrite).

5.6.3.1.3 Pregnancy test

Results of serum and urine pregnancy tests are not summarized but are provided in a subject data listing.

5.6.3.2 Vital Signs

The following parameters are measured:

- systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiratory rate, and body temperature.

Observed values for the vital sign parameters are summarized with descriptive statistics for the scheduled time points. Changes from Baseline (Day1-predose) for each parameter are summarized for all post-Baseline time points.

5.6.3.3 Electrocardiograms

12-lead ECG will be recorded 3 times at 15min [±5min] intervals within 24h before dosing of BRV on Day 1 in order to get representative Baseline. Postdose 12-lead ECG will be recorded 1 time. The individual mean at Baseline will be calculated as raw parameters for descriptive analysis. The definition of Baseline will be the mean of the triplicate measurements predose on Day 1 or Day -1. If there are less than three replicates at Day 1 or Day -1 predose, the mean of the available replicates (predose) will be taken as Baseline.

The following parameters are measured:

- Heart rate, RR interval, PR interval, QRS interval, QT, QTcB*, QTcF**

* QT interval corrected for heart rate by Bazett's formula
** QT interval corrected for heart rate by Fridericia's formula

Observed values for the ECG parameters are summarized with descriptive statistics for the scheduled time points. Changes from Baseline for each parameter are summarized for all post-Baseline time points.

For QTcB and QTcF, observed values and their changes from Baseline are summarized based on the classifications of [<450, 450-<480, 480-<500, ≥500 msec] and [<30, 30-<60, ≥60 msec], respectively.

The individual measurements and the mean of the triplicate measurements will be reported in the by-participant listings. The listing will also include the change from Baseline. All ECG findings for the individual measurements will be listed separately.

5.6.3.4 Other safety endpoint(s)

Physical examination

Participants with abnormalities in the physical examination will be listed including details of the abnormality.

Suicidal risk monitoring

Columbia-Suicide Severity Rating Scale (C-SSRS; Posner et al, 2011) data where ideation or suicidal behavior had been reported will be listed. Module of the questionnaire, time point, question and the associated response will be listed.

5.7 Other Analyses

5.7.1 Other endpoints and/or parameters

5.7.1.1 Pharmacokinetics

In general, plasma concentration-time profiles of BRV and its metabolites are summarized by dosing period (single and multiple dose) using PK-PPS and listed by subject for the SS. PK parameters of BRV and its metabolites are summarized by dosing period (single and multiple dose) using the PK-PPS and listed by subject for the SS.

Descriptive statistics for plasma concentrations of BRV and its metabolites are provided for every scheduled time point (see Table 1– and Table 1–3: Multiple-Dose Period: schedule for ECGs, vital signs, and PK sampling 3) by dosing period.

Descriptive statistics include the number of values (n), arithmetic mean, SD, geometric mean, lower and upper limit of the 95% CI for geometric mean, geometric CV [%], median, minimum and maximum values.

Concentrations BLQ are replaced by half of the LLOQ and missing values are excluded for the calculation of descriptive statistics. When the mean includes one or more replaced BLQ values, a

footnote of the table should be added "contains one or more BLQ values replaced by half the LLOQ value". For each specific time point, only minimum and maximum should be calculated in case the number of BLQ and missing values exceed one third of the total; other descriptive statistics should be reported as missing ("-"). If minimum and/or maximum is BLQ, keep minimum or maximum as "BLQ". A minimum of 3 values are required to calculate summary statistics; if only 2 values are available then these should be presented as the minimum and maximum with other descriptive statistics reported as missing ("-").

Listings for individual concentrations of BRV and its metabolites including the actual and nominal sampling times and the deviation between the actual and nominal sampling times are provided. Concentrations that are BLQ are indicated as "BLQ" in the listings. Missing data should be reported as "NV" (no value). Concentrations should be listed to the same number of significant figures supplied by the bioanalytical laboratory.

Geometric mean profiles vs nominal time are displayed (including corresponding lower and upper limit of 95% CI for the linear scale, without CI on the semi-logarithmic scale) superimposing in one plot for all analytes, with one plot for each dosing period. Summary data plotted in the figure will match data presented in summary table, except for missing values prior to C_{max} which will be set to 0 in the figure.

Individual concentration-time profiles vs scheduled time are displayed graphically on a linear scale and semi-logarithmic scale, superimposing in one plot all analytes, and one plot per dosing period and per participant. A Spaghetti plot of individual plasma concentrations vs scheduled time is displayed by dose period. When reporting individual data in figures, BLQ values prior to C_{max} will be set to 0 and BLQ values that occur post-C_{max} will be considered missing.

Primary/secondary pharmacokinetic parameters

Plasma pharmacokinetic parameters as identified above are calculated from the individual drug concentration vs. actual time profiles by dosing period. Parameters are calculated for BRV and metabolites after single and multiple dose as described in Table 5-4.Table 5-4: Primary/Secondary pharmacokinetic parameters

Pre-dose sample time is set to 0 prior to performing parameter derivation. Missing pre-dose concentrations for Single-Dose period will be replaced by 0. For multiple dose period, the analyst should use scientific judgement to assess what action should be taken and a rationale for this action should be recorded in the analysis documentation (eg set to 0 if no accumulation is expected).

Table 5-4: Primary/Secondary pharmacokinetic parameters

Specimen	PK Parameter		BRV		Metabolites[a]	
	Notation	Description	Single	Mult.	Single	Mult.
Plasma	$AUC_{(0-t)}$	area under the plasma concentration-time curve from zero to the time of the last measured concentration above the LOQ	P	–	S	–
	$AUC_{(0-12),ss}$	area under the curve from 0 to 12 hours at steady state	–	P	–	S

	AUC	area under the curve from 0 to infinite time	S	–	S	–
	C_{max}	maximum plasma concentration	P	–	S	–
	$C_{max,ss}$	maximum plasma concentration at steady state	–	P	–	S
	$C_{min,ss}$	minimum plasma concentration at steady state	–	S	–	–
	$C_{av,ss}$	average plasma concentration at steady state	–	S	–	–
	t_{max}	time to reach maximum plasma concentration	S	S	S	S
	$t_{1/2}$	terminal elimination half-life	S	S	S	S
	λ_z	rate constant of elimination	S	S	S	S
	MRT	mean residence time	S	–	–	–
	CL/F	apparent total body clearance	S	–	–	–
	CL_{ss}/F	apparent total body clearance at steady state	–	S	–	–
	Vz/F	apparent volume of distribution	S	S	–	–
	PTF	peak-trough fluctuation	–	S	–	–
	R_{AUC}[b]	accumulation ratio calculated from AUC at steady state and AUC after single dose	S		–	–
	R_{max}	accumulation ratio calculated from $C_{max,ss}$ and C_{max}	S		–	–

[a] metabolites of BRV (ucb-42145, ucb-100406-1, and ucb107092-1)
[b] AUC_{0-12} on Day 1will be derived for the calculation of R_{AUC}.

P: Primary, S: Secondary.

PK parameters in plasma

- AUC parameters ($AUC_{(0-t)}$, $AUC_{(0-12)}$, $AUC_{(0-12),ss}$, AUC) [ng·h/mL]
  - The linear up/log down trapezoidal method is used to calculate the AUC parameters.
  - $AUC_{(t1-t2)} = \int_{t1}^{t2} C(t)dt$
  - AUC: Calculated as $AUC_{(0-t)}+C_{last}/\lambda_z$
    - If the percentage of extrapolated AUC (AUC_{extr}) is more than 20%, the individual result should be excluded from summary statistics along with all parameters dependent on AUC.
- C_{max} parameters (C_{max}, $C_{max,ss}$) [ng/mL]
  - Obtained directly from the concentration vs. time data

- $C_{min,ss}$ [ng/mL]
  - Obtained directly from the concentration vs. time data
- $C_{av,ss}$ [ng/mL]
  - Calculated as $AUC_{(0-12),\ ss}/12$
- t_{max} [h]
  - Obtained directly from the concentration vs. time data as a time at which C_{max} or $C_{max,ss}$ is observed.
- λ_z [1/h]
  - Estimated at terminal phase by linear regression after natural log-transformation of the concentrations. λ_z is calculated over a time interval using the best fit method.
    - The time interval should be equal to at least 2 × $t_{1/2}$ and have at least 3 data-points not including C_{max}. If it is less than 2 half-lives or if there are too few data to calculate λ_z, then the parameter should be excluded from summary statistics (along with all parameters dependent on half-life).
    - In the case that the R^2 for the regression is less than 0.8, the half-life (and all parameters dependent on it) should be excluded from summary statistics.
- $t_{1/2}$ [h]
  - Calculated as ln 2/ λ_z
    - For the parameter, same notation as corresponding λ_z is noted in the listing if the λ_z has the above-mentioned notation.
- MRT [h]
  - Calculated after single dose as AUMC/AUC, where AUMC is the area under the first moment curve from 0 to infinite time
  - $AUMC = AUMC_{(0-t)} + C_{last} \times t_{last}/ \lambda_z + C_{last}/ \lambda_z^2$
  - $AUMC_{(0-t)} = \int_0^{tlast} C(t) \times t\ dt$
- CL/F [L/h]
  - Calculated as dose/AUC
- CL_{ss}/F [L/h]
  - Calculated as $dose/AUC_{(0-12),ss}$
- Vz/F [L]
  - Calculated as CL/F/λ_z
- PTF
  - Calculated as $(C_{max,ss}-C_{min,ss})/C_{av,ss}$

- R (accumulation ratio) (R_{AUC}, R_{max})
  - R_{AUC} is calculated as $AUC_{(0\text{-}12),ss}$ / $AUC_{(0\text{-}12)}$
  - R_{max} is calculated as $C_{max,ss}$ / C_{max}

If any parameter matching an exclusion criterion is included in summary statistics, then the rationale will be provided.

For the determination of the PK parameters, all BLQ values occurring prior to C_{max} are replaced by 0, except for embedded BLQ values (between two measurable data-points) which are treated as missing. Post-C_{max} BLQ values are treated as missing.

The PK parameters are summarized for the PK-PPS by dosing period using descriptive statistics: the number of values (n), geometric mean, lower and upper limit of the 95% CI for geometric mean, geometric CV [%],arithmetic mean, SD, median, minimum and maximum values. For t_{max}, only n, median, minimum and maximum values are be presented.

Descriptive statistics should be reported to 4 significant figures for the mean, median and SD, and to 3 significant figures for all others.

If at least two thirds of the participants have a PK parameter reported then descriptive statistics will be calculated, otherwise only minimum and maximum will be reported for this PK parameter and all other descriptive statistics will be reported as "NE" (not estimable).

Individual PK parameters of BRV and its metabolites are provided together in the summary table. Individual PK parameters will be reported to 3 significant figures. If a parameter cannot be calculated, it will be reported in the listing either as "NE" (in case calculation is not possible due to missing data) or as "NC" (not calculable, in case data were available but the calculation was considered unreliable). Individual PK parameters of BRV and its metabolites for participants excluded from the PK-PPS are listed for SS.

5.7.1.2 Pharmacodynamics

Not applicable.

5.7.1.3 Genomics

Not applicable.

5.8 Subgroup analyses

Not applicable.

5.9 Interim Analyses

Not applicable.

5.10 Data Monitoring Committee (DMC) or Other Review Board

Not applicable.

6 SUPPORTING DOCUMENTATION

6.1 Appendix 1 Non-key analysis specifications

6.1.1 Baseline characteristics and demographics

Unless otherwise specified, demographic and Baseline characteristics are summarized for the SS, and subject data listings for the demographic and Baseline characteristics are provided for the All Subject Screened (ES).

Demographics

Age, gender (male/female), weight (kg), height (cm), body mass index (BMI), ethnicity, and racial group (Asian) are summarized.

The age of each subject is calculated as completed years at the date of informed consent. Weight is summarized from screening visit. BMI is calculated from the weight and the height at screening visit using the following formula:

$$\text{BMI}(\text{kg/m}^2) = \frac{10{,}000 \times \text{weight (kg)}}{[\text{height (cm)}]^2}$$

Other Baseline characteristics

Lifestyle information will be summarized based on the SS and will be listed based on the ES.

Serology, urine drug, and alcohol detection will be listed based on ES. The detailed tests of serology and urine drug are listed below:

- Serology

  Hepatitis B surface antigen, Hepatitis C virus antibody, HIV antibody, and syphilis

- Urine drug

  Morphine, Tetrahydrocannabinolic acid, Methamphetamine, Dimethylenedioxyamphetamine, Ketamine, and Cocaine

6.1.2 Protocol deviations

The number and percentage of participants with at least 1 IPD are summarized for SS, using the categories as defined in the protocol deviation specification.

A listing of all IPDs identified at the DEM will be presented based on the SS and will include the deviation type and description.

Impact of COVID-19 on study visits

The number and percentage of participants with visits impacted by COVID-19 will be summarized by impact categories based on the SS. And a listing of visits impacted by COVID-19 will be presented for all participants based on the ES, including visit, visit date, relative day, impact category, relationship to COVID-19 and narrative of the event.

6.1.3 Medical history

Medical history

The number and percentage of participants with a medical history condition, including both resolved previously and ongoing conditions at the time of study entry, are summarized overall (ie, any previous and ongoing medical history conditions) and by MedDRA primary SOC and PT.

A subject data listing for the previous and ongoing medical history conditions is provided.

Procedure history

Prior medical procedures or surgeries are not to be summarized and are only provided in a by-participant data listing based on the ES.

6.1.4 Prior/concomitant/follow-up medications

Tabulations will be presented for prior and concomitant medications separately which the details are listed below:

Prior and concomitant medications

Medications are categorized as follow:

- Prior medication
  - Prior medications include any medications that started prior to date of the first dose of BRV.
- Concomitant medication
  - starts before first dose of IMP and is ongoing at day of first dose of IMP
  - starts on or after first dose of IMP

A listing of prior and concomitant medications, which includes the reported term, the anatomical therapeutic chemical subgroup (level 1 and 3) in WHO-DRL, is provided.

Concomitant medical procedures

Concomitant medical procedures or surgeries are not to be summarized and are only provided in a by-participant data listing based on the ES.

6.1.5 Data derivation rules

6.1.5.1 Handling of dropouts or missing data

Participants who drop out from the study before completion of study procedures and for any other reason than for safety issues can be replaced with participants of the same gender after consultation with the sponsor.

In general, there will be no imputation of missing data unless otherwise stated below. Handling of missing data for PK results is described in Section 5.7.1.1. Safety laboratory data will be handled as described in Section 5.6.

6.1.5.1.1 Incomplete dates and times

Partial dates may be imputed for the following reasons:

- Classification of AEs as treatment-emergent
- Classification of medications as prior or concomitant

Imputed dates will not be shown in the listings; all dates will be displayed as reported in the database.

The following rules will be applied for partial start dates and time:

- If only the month and year are specified and the month and year of the first dose of IMP is not the same as the month and year of the start date, then use the 1st of the month, or the date of Screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If time is missing this will be imputed as 00:00 h
- If only the month and year are specified and the month and year of the first dose of IMP is the same as the month and year of the start date, then use the date of the first dose of IMP. If this results in an imputed start date that is after the specified end date, then use the 1st of the month, or the date of Screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If the imputed date is the date of dosing then time will be imputed as the start time of the dosing (ie, event will be regarded as treatment-emergent)
- If only the year is specified, and the year of the first dose of IMP is not the same as the year of the start date then January 01 will be used. If time is missing this will be imputed as 00:00 h
- If only the year is specified, and the year of the first dose of IMP is the same as the year of the start date, then the date of the first dose of IMP will be used. If this results in an imputed start date that is after the specified end date, then January 01, or the date of screening if this is later will be used (if the latter imputation results in an end date that is earlier than the start date, then January 01 will be used). If the imputed date is the date of first dose of IMP then time will be imputed as the start time of the study medication intake (ie, event will be regarded as treatment-emergent)
- If the start date is completely unknown, then use the date of dosing. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the end date, or the date of Screening if this is later.

The following rules will be applied for 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 December 31 of the known year
- If the stop date is completely unknown, do not impute the stop date

Missing or partially missing dates and/or times will be imputed as described in Table below. AE duration is computed and reported in day and time format: xx d hh:mm. Duration is not calculated when the outcome date is missing.

Table 5–1: Calculation rules for duration of adverse events

Data availability	Onset date/time	Outcome date/time	Calculation rules
Complete data	D1/T1	D2/T2	Duration = [(D2 – D1)*24 + (T2 – T1)]/24 d
End time missing	D1/T1	D2/--	End time is substituted by time 23:59h (=23.98 in decimal format) Duration = <[(D2 – D1)*24 + (23.98 – T1)]/24 d
Start time missing	D1/--	D2/T2	If D1 is the same date as the date of first dose of IMP, Onset time is substituted by the start time of dosing (T_{dose}). Duration = <[(D2 – D1)*24 + (T2 – T_{dose})]/24 d Otherwise the onset time is substituted by time 00:00h Duration = <[(D2 – D1)*24 + (T2)]/24 d
Start and end time missing	D1/--	D2/--	Duration = <D2 – D1 + 1
Start day and time missing	--/--	D2/T2	Duration = [(D2 – D0)*24 + (T2 – T0)]/24 d For a participant in the SS, D0 and T0 are the date and time of first administration of study medication and for screen failures, D0 is the date of the screening visit and T0 = 00:00h
End day and time missing	D1/T1	--/--	If the stop date and time are missing, duration will not be calculated.
Start and end date missing	--/--	--/--	If the stop date and time are missing, duration will not be calculated.

SS=Safety Set.

6.1.6 AEs of Special Interest

The AEs of special interest include:

• Autoimmune nephritis

• Nephritis

• Nephritis allergic

• Tubulointerstitial nephritis

• Tubulointerstitial nephritis and uveitis syndrome

• Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded).

6.1.7 Compliance

A study participant is considered compliant with treatment if the participant takes the study IMP at all of 12 scheduled time points. Participants who do not take all 12 doses are to be considered non-compliant to treatment and are to be discussed at the DEM. A data listing for treatment compliance is not provided.

6.2 Appendix 3: Changes to Protocol-Planned Analyses

Not applicable.

7 REFERENCES

• Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168:1266 77.