STATISTICAL ANALYSIS PLAN

AMENDMENT 1

Study: EP0110

Product: Brivaracetam

A SINGLE-DOSE, OPEN-LABEL, RANDOMIZED, 2-WAY CROSS-OVER STUDY TO ASSESS THE BIOEQUIVALENCE BETWEEN BRIVARACETAM TABLET AND DRY SYRUP IN HEALTHY MALE JAPANESE STUDY PARTICIPANTS

A single-dose study to assess the bioequivalence between brivaracetam tablet and dry syrup in healthy Japanese study participants

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Registry	ID
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TABLE OF CONTENTS

VERSION HISTORY

SAP Version	Approval Date	Change	Rationale
Final	02 Mar 2022	Not Applicable	Original version
Amendment 1	08 Jun 2022	Update on front page and CRF version	Clarification of CTN number CRF update

LIST OF ABBREVIATIONS

List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Curve from 0 to Infinity
$AUC_{(0-t)}$	Area under the Curve from 0 to the Time of the Last Quantifiable Concentration
AUC_{extr}	Extrapolated AUC
AUMC	Area under the First Moment Curve from 0 to Infinity
BMI	Body Mass Index
BRV	Brivaracetam
CI	Confidence Interval
CL/F	Total Clearance after Oral Administration
C_{last}	Last Observed (Quantifiable) Concentration
C_{max}	Maximum (Plasma) Concentration
CPStat	Clinical Program Biostatistician
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DEM	Data Evaluation Meeting
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EOS	End of Study
ES	Enrolled Set
geoCV	Geometric Coefficient of Variation

List of Abbreviations

IMP	Investigational Medicinal Product
IPD	Important Protocol Deviation
λ_z	First Order Terminal Elimination Rate Constant
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean Residence Time
PDILI	Potential Drug Induced Liver Injury
PK	Pharmacokinetics
PK-PPS	Pharmacokinetic Per Protocol Set
PT	Preferred Term
QTcF	QT interval corrected with Fridericia's formula
REML	Restricted Maximum Likelihood
RS	Randomized Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SFU	Safety Follow Up
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures and Listings
$t_{1/2}$	Terminal Elimination Half-life
t_{last}	Time of Last Observed (Quantifiable) Concentration
t_{max}	Time of C_{max}
ULN	Upper Limit of Normal
V_z/F	Apparent Volume of Distribution

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of study EP0110. This SAP should be read in conjunction with the study protocol amendment 1.0 that provides all necessary background information and rationale for the current study and its design.

The SAP is based on the following study documents:

- Protocol Amendment 1.0: 11 Jan 2022
- Electronic Case Report Form (eCRF) v2.0: 04 Mar 2022

1.1 Objectives and Endpoints

Table 1-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate the bioequivalence between the BRV 50mg tablet and BRV 50mg as dry syrup after a single oral dose in healthy Japanese male study participants	Primary Endpoints: • C_{max} • $AUC_{(0-t)}$
Secondary	
• To evaluate the safety and tolerability of 2 oral dosage forms of BRV in healthy Japanese male study participants	Secondary endpoints: • Incidence of TEAEs • Incidence of treatment-emergent SAEs
Other	
Other PK Objective: • To evaluate other PK parameters of 2 oral dosage forms of BRV in healthy Japanese male study participants	The other PK endpoints will be calculated: • AUC • AUC_{extr} • CL/F • V_z/F • MRT • t_{max} • $t_{½}$ • λ_z

Table 1-1: Objectives and Endpoints

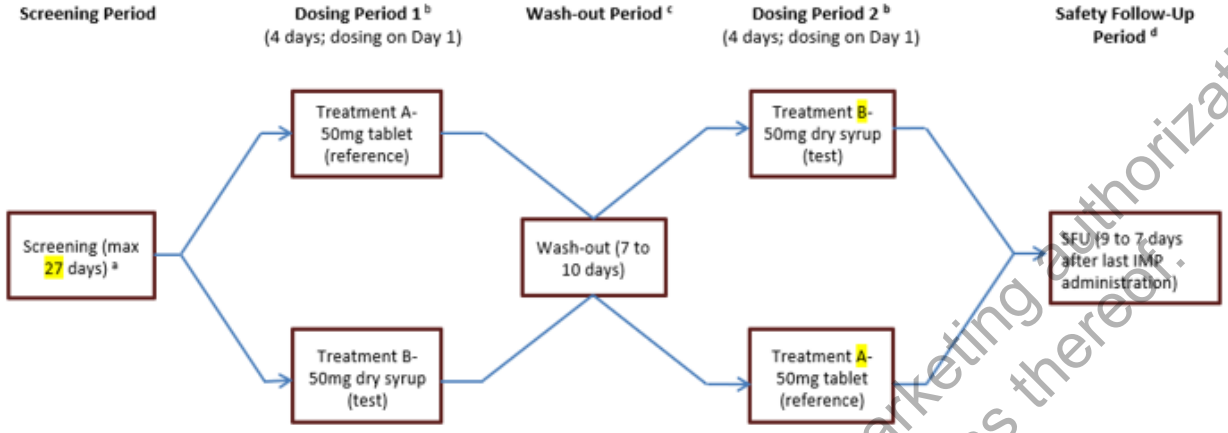
Objectives	Endpoints
Other Safety Objective: • To further evaluate the safety and tolerability of 2 oral dosage forms of BRV in healthy Japanese male study participants	Other safety endpoints will be assessed during the study: • Changes in clinical laboratory test parameters (i.e., hematology, clinical chemistry, and urinalysis) • Changes in vital signs (SBP, DBP, pulse rate, respiratory rate, and body temperature) • 12-lead ECG parameters and findings • Physical examinations

λ_z=first order terminal elimination rate constant; AUC=area under the curve from 0 to infinity; $AUC_{(0-t)}$=area under the curve from 0 to the time of the last quantifiable concentration; AUC_{extr}=extrapolated AUC; BRV=brivaracetam; CL/F=total clearance after oral administration; C_{max}=maximum concentration; DBP=diastolic blood pressure; ECG=electrocardiogram; MRT=mean residence time (i.e., of the unchanged drug in the systemic circulation); PK=pharmacokinetics; SAE=serious adverse event; SBP=systolic blood pressure; $t_{1/2}$=terminal elimination half-life; TEAE=treatment-emergent adverse event; t_{max}=time of C_{max}; Vz/F=apparent volume of distribution

1.2 Study design

EP0110 is a single-center, single-dose, open-label, randomized, 2-way cross-over study designed to assess the bioequivalence between the BRV 50mg tablet and BRV 50mg as dry syrup formulations in healthy Japanese male study participants after oral administration under fasted conditions. In addition, safety and tolerability of BRV will be evaluated.
Study participants will enter a Screening Period (2 to 28 days before administration of investigational medicinal product [IMP]) and eligible study participants will start the Dosing Period 1. The Dosing Period consists of 2 periods (Dosing Period 1 and Dosing Period 2) of 4 days each with a single administration on Day 1 of each Dosing Period. The Dosing Periods will be separated by a Wash-Out Period (at least 7 days and no more than 10 days between the 2 administrations for each study participant) and followed by a Safety Follow-Up (SFU) Visit, 7 to 9 days after the last administration of IMP. Study participants who prematurely discontinue the IMP/study are to return for a Withdrawal Visit, 7 to 9 days after the last IMP administration. Refer to the study schematic in Figure 1-1.

Figure 1-1: Schematic Diagram



BRV=brivaracetam; IMP=investigational medicinal product; SFU=Safety Follow-Up

[a] Following a Screening Period (2 to 28 days before IMP administration), each study participant will be randomly assigned to 1 of 2 treatment sequences (A-B or B-A) before dosing in Dosing Period 1, after all Day -1 assessments have been completed. Treatment A – a single dose of BRV 50mg tablet and Treatment B – a single dose of BRV 50mg as dry syrup (1.25g of granules for oral solution 4% w/w).

[b] Each Dosing Period is 4 days (Day -1 to Day 3) with a single administration of IMP on Day 1 of each Dosing Period. For each Dosing Period, study participants will be admitted to the study site on Day -1 (1 day before dosing). Study participants will receive IMP on Day 1 and will be discharged in the morning of Day 3, approximately 48 hours after the administration of IMP.

[c] The 2 Dosing Periods will be separated by a Wash-Out Period of 7 to 10 days between IMP administrations.

[d] An SFU Visit will occur 7 to 9 days after the last administration of IMP. Study participants who prematurely discontinue the IMP/study will be encouraged to undergo Withdrawal Visit procedures within 7 to 9 days after the last administration of IMP.

On Day 1 of each Dosing Period, the study participants will receive 1 of the following treatments in randomized order under fasting conditions:

- Treatment A − a single dose of BRV 50mg tablet
- Treatment B – a single dose of BRV 50mg as dry syrup (1.25g of granules for oral solution 4% w/w)

1.3 Schedule of Activities

The Schedule of Activities is provided in Table 1-2.

Table 1-2: Schedule of Activities

Procedure	Screening	Dosing Period 1 or 2 [a]				SFU/Withdrawal [b]
	V1	V2 or V3				V4
	2 to 28 days before administration of IMP	Check in Day -1	Day 1	Day 2	Day 3	7 to 9 days after the last administration of IMP
Written informed consent	X					
Demographics, habits, and lifestyle	X					
Verification of inclusion/exclusion criteria	X	X				
Medical/surgical history	X					
Physical examination	X	X			X	X
Height and weight	X					
Viral serology (HBsAg, HCV, HIV, and syphilis)	X					
Urine drug test and alcohol breath test	X	X				
COVID-19 precautions [c]	X	X				X
Vital signs [d]	X		X	X	X	X
Clinical laboratory tests (hematology, clinical chemistry, and urinalysis)	X				X	X
Randomization [e]		X [f]				
12-lead ECG [g]	X		X	X	X	X
IMP administration [h]			X			
Blood sampling for PK [i]			X	X	X	
Recording of prior and concomitant medication and procedures	X	X	X	X	X	X
Recording of AEs	X	X	X	X	X	X
Confinement		X	X	X	X	

AE=adverse event; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IMP=investigational medicinal product; PK=pharmacokinetic(s); SFU=Safety Follow-Up

[a] Each study participant will enter 2 Dosing Periods, separated by a Wash-Out Period of 7 to 10 days between IMP administrations. Dosing Period 2 will start after the Wash-out Period (at least 7 days and no more than 10 days between the 2 IMP administrations).
[b] An SFU visit will occur 7 to 9 days after the last administration of IMP. Study participants who prematurely discontinue the IMP/study should be encouraged to undergo Withdrawal Visit procedures within 7 to 9 days after the last administration of IMP.
[c] COVID-19 precautions as described in Section 2.3.1 and Section 5.3.5 of the protocol.
[d] Vital signs are taken at the Screening Visit, at predose, 4, 8, 24, and 48 hours postdose, and at the SFU Visit/Withdrawal Visit.
[e] Each study participant will be randomly assigned to 1 of 2 treatment sequences (A-B or B-A) before dosing in Period 1, after all Day -1 assessments have been completed.
[f] Randomization occurs only for Dosing Period 1, either on Day -1 or Day 1 before any assessment of Day 1.
[g] 12-lead ECGs are recorded at Screening, at predose, 1, 4, 8, 24, and 48 hours postdose, and at the SFU Visit/Withdrawal Visit. At predose on Day 1 of each Dosing Period, 3 Baselines values will be measured at 2- to 5-minute intervals.
[h] IMP administration: BRV 50mg will be administered as a 50mg tablet (Treatment A [reference]) or as dry syrup (1.25g of BRV granules for oral solution 4% w/w; Treatment B [test]) under fasting conditions.
[i] Blood samples for PK analysis are collected at predose, and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose. Allowable deviations from these scheduled PK sampling times are provided in Table 8-2 of the protocol.

2 STATISTICAL HYPOTHESES

The study is aimed to demonstrate the bioequivalence between BRV 50mg dry syrup (1.25g of granules for oral solution 4% w/w) (test) and BRV 50mg tablet (reference) according to C_{max} and $AUC_{(0-t)}$.

Null hypothesis (H_0): the adjusted test/reference geometric mean ratio is smaller than 80% or larger than 125%.
Alternative hypothesis (H_1): the adjusted test/reference geometric mean ratio is within 80% to 125%.

The 90% confidence intervals (CIs) of the adjusted test/reference geometric mean ratio will be calculated.
Based on the hypotheses, bioequivalence between the test (dry syrup) and reference (tablet) formulations will be concluded if the 90% CI limits for C_{max} and $AUC_{(0-t)}$ fall fully within 80% to 125%.

3 SAMPLE SIZE DETERMINATION

A total of 24 study participants are planned to be randomized and to complete the study; however, additional study participants may be randomized in case some study participants discontinue the study early (not only limited to the COVID-19 circumstances).
Previous BRV PK studies (N01287, N01185, N01118, N01081, and N01075) provide estimates of the intra-participant variability (CV%) approximately ranging from 10% to 23% (median 18%) for C_{max} and from 4% to 12% (median 6%) for AUC.
Provided that the ratio of expected means is equal to 1.00 and assuming a CV% of 20%, 19 study participants in total provide a power of 90%, at the 5% level of significance (one-sided), to declare that the true geometric means ratio is in the range of 80% to 125%.

In the case of the true mean difference of 5% (the ratio of 0.95 or 1.05), a power of 90% would be reached with 24 study participants completing the study.

4 POPULATIONS FOR ANALYSIS

The analysis sets are defined as follows:

4.1 Enrolled Set

All study participants who sign the informed consent form (ICF) will be included in the Enrolled Set (ES).

4.2 Randomized Set

All enrolled study participants who are randomized will be included in the Randomized Set (RS).

4.3 Safety Set

All randomized study participants who receive at least 1 dose of the IMP will be included in the Safety Set (SS).

4.4 Pharmacokinetic Per Protocol Set

All randomized study participants who are included in the SS, have no important protocol deviations (IPDs) that are considered to impact the study participant's data validity for analysis of the primary study objective, and have a sufficient number of bioanalytical assessments to calculate reliable estimates for the primary pharmacokinetic parameters for both treatments will be included in the Pharmacokinetic Per-Protocol Set (PK-PPS).

If a study participant's predose concentration is greater than 5% of the corresponding C_{max} value in both Dosing Periods, the study participant will be excluded from the PK-PPS. If this occurs in 1 of the 2 Dosing Periods, but not in the other Dosing Period, data of the other Dosing Period will be used. Furthermore, since the study participant will be entered as a random effect in the ANOVA, the data of the single Dosing Period can still be used for the bioequivalence assessment.
If vomiting occurs at or before 2 times of the median t_{max} of the study, the study participant will be excluded
from the PK-PPS.

5 STATISTICAL ANALYSES

5.1 General Considerations

Statistical evaluation will be performed by the Sponsor or designee and supervised by the Exploratory Statistics Department of UCB. Statistical analysis and generation of tables, figures, and study participant data listings will be performed using SAS Version 9.3 or higher. The PK noncompartmental analysis (NCA) will be performed using Phoenix WinNonlin® Version 8.2 or higher (Certara L.P., Princeton, NJ, USA) for Pharmacokinetics parameters estimation.

A complete set of listings containing both all documented data and all calculated data will be generated by treatment sequence, unless otherwise specified. Missing data will not be imputed, unless otherwise specified. Outlier detection and statistical analysis of outliers will not be performed.

Descriptive statistics will be displayed to provide an overview of the study results.
For categorical endpoints, the number and percentage of study participants in each category will be presented. The denominator for percentages will be based on the number of study participants appropriate for the purpose of the analysis. For continuous endpoints, descriptive statistics will include number of study participants, mean, standard deviation, median, minimum, and maximum. The descriptive statistics for plasma concentrations and PK parameters will be described in Section 9.1 and Section 9.2.1.
Unless otherwise noted, the denominator for percentages should be based on the number of participants included in the respective analysis set. For summaries of demographics and Baseline characteristics: summarize percentages based on all participants in the analysis set and include a potential "Missing" category (corresponding to participants with missing data at the time of the variable being summarized) as the last row in the list of categories being summarized.

Percentages will be presented to 1 decimal place. If the percentage is 100%, do not present a decimal. If the percentage is 0, do not present the percentage. Typically, the % sign should be presented in the column header, but not with each individual value.
Decimal places for descriptive statistics will always apply the following rules, unless otherwise stated:

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

Derived variables in general will display the mean, SD and median to 1 more decimal place than the variables used in the derivation. If the number of decimal places reported in the raw data is varied then use either the maximum raw number of reported decimal places or 3, whichever is the lowest, as a guide for the descriptive statistics.
If participants have more than one observation for a given time point, the observation closest to the intended time point will be used. If both observations are equidistant from the intended time point, then the later value will be used.

Refer to Appendix 3 (Section 11.3.1 and Section 11.3.2) for standard reporting procedures of PK concentrations and parameters in listings, tables, and figures.

5.1.1 General study level definitions

5.1.1.1 Analysis Time Points

5.1.1.1.1 Relative day

Relative day will be derived with the date of IMP administration in each Dosing Period as reference for that specific Dosing Period.

For days on the day of IMP administration in each Dosing Period

Relative day will be calculated as follows:

Relative day = Current date - Date of IMP administration + 1

i.e., the day of IMP administration in each Dosing Period will have a relative day of '1'.

For days prior to IMP administration in each Dosing Period

Relative day will be prefixed with '-' and calculated as follows:

Relative day = Current date – Date of IMP administration within the same Dosing Period

e.g., the day prior to the IMP administration will have a relative day of '-1'.

For days prior to the first IMP administration in the Screening Period

Relative day will be prefixed with '-' and calculated as follows:

Relative day = Current date – Date of first IMP administration

e.g., Screening Visit that is 7 days prior to the first IMP administration will have a relative day of '-7'.

For days after the day of IMP administration in Dosing Period

Relative day will be prefixed with '+' and will be calculated as follows:

Relative day = Current date - Date of IMP administration within the same Dosing Period

e.g., the day after IMP administration in a Dosing Period will have a relative day of '+1'.

For days after the Dosing Period

Relative day will be prefixed with '+' and calculated as follows:

Relative day = Current date - Date of last IMP administration

e.g., A certain day in a washout period following Dosing Period 1 that is 7 days after IMP administration in Dosing Period 1 will have a relative day of '+7'.

e.g., Safety Follow-Up Visit that is 8 days after the last IMP administration will have a relative day of '+8'.

Relative day will not be calculated for partial dates. Relative day for partial days will be displayed as '--' to distinguish it from missing values which are displayed as blanks.

5.1.1.1.2 End date of the Dosing Period

Dosing Periods are specified in section of study periods.

5.1.1.1.3 Study periods

The total duration of the study for an individual study participant is 17 days to 48 days and will include:

- A Screening Period (2 to 28 days before IMP administration)
- Two Dosing Periods (4 days each, with IMP administration on Day 1 of each Dosing Period)
- A Wash-out Period following Dosing Period 1 (7 to 10 days between the 2 IMP administrations)
- An SFU Visit/Withdrawal Visit (7 to 9 days after the last IMP administration)

Table 5-1: Duration of Each Period

Period	Duration
Screening Period	Prior to the date of first IMP administration (Relative Day -28 to -2)
Dosing Period 1	Defined as Relative Day -1 to 3
Wash-out Period	Defined as Relative Day + 3 to + 6 (~ + 9)
Dosing Period 2	Defined as Relative Day -1 to 3
Safety Follow-Up Period	Defined as Relative Day + 3 to + 6 (~ + 8)

5.1.1.1.4 Mapping of assessments performed at Withdrawal Visit

Safety assessments made at a withdrawal visit that correspond to a scheduled visit will be summarized at the scheduled visit to corresponding to the withdrawal visit if the assessment was scheduled to occur at that visit. Such assessments at the withdrawal visit will also be considered for safety follow up/ withdrawal visit.

5.1.1.1.5 Definition of Baseline values

Baseline will be the last available predose result for each Dosing Period. Each Dosing Period will therefore have its own Baseline, independent of the other Treatment Periods unless the data collection is not scheduled (e.g., clinical laboratory tests). If no predose results are available for Dosing Period 1, then the Screening result will be used as the Baseline result for that Dosing Period.

Table 5-2: Definition of Baseline

Measurement	Definition of Baseline
Vital Signs	Day 1, Pre-dose value in each period. If this value is unavailable, the latest available value before dosing will be imputed. For Dosing Period 1, the latest value in Screening Period and Dosing Period 1 before dosing can be used.

Measurement	Definition of Baseline
	For Dosing Period 2, the latest value in Wash-out Period and Dosing Period 2 before dosing can be used.
12-lead ECG	Day 1, Pre-dose value in each period. If this value is unavailable, the latest available value before dosing will be imputed. For Dosing Period 1, the latest value in Screening Period and Dosing Period 1 before dosing can be used. For Dosing Period 2, the latest value in Wash-out Period and Dosing Period 2 before dosing can be used.
Clinical laboratory tests (hematology, clinical chemistry, and urinalysis)	The Screening value for each period. If this value is unavailable, unscheduled visit closest to and before dosing of the Dosing Period 1 will be imputed for both Dosing Period. For Dosing Period 2, the latest value in Wash-out Period and Dosing Period 2 before dosing can be used if any other baseline value is unavailable.

5.1.1.2 Protocol Deviations

Important protocol deviations (IPDs) will be summarized by treatment sequence, and overall using the SS and PK-PPS. The summary will include the following:

- Number and percentage of participants with no IPDs
- Number and percentage of participants with at least one IPD
- Number and percentage of participants by type of protocol deviation

By-participant listings of IPDs as identified in the Data Cleaning Meeting and DEM will be provided by treatment sequence, period, treatment (tablet or dry syrup) using the SS. This will include deviation type, deviation description, and whether the deviation led to exclusion from the PK-PPS.
Protocol deviations (e.g., missing assessments or visits) related to COVID-19 will be listed separately.

5.1.1.3 Treatment assignment and treatment groups

Treatment assignment for the SS and PK-PPS will be based on the actual treatment received in each Dosing Period.
Listings will be presented by treatment sequence, unless otherwise specified.
Summaries will be presented by treatment sequence or treatment group and overall, where applicable. The following order will be used in the Tables, Figures and Listings (TFLs): tablet, dry syrup and overall, where applicable.

For analysis conducted using the ES, an additional group for participants not randomized may be displayed, as applicable.

5.1.1.4 Center pooling strategy

Not applicable since this study will be conducted at a single site.

5.1.1.5 Coding dictionaries

All AEs and medical history will be coded for analysis according to the Medical Dictionary for Regulatory Activities (MedDRA®) coding dictionary, using the MedDRA version 18.1. Prior and concomitant medications will be coded for analysis using the World Health Organization Drug Dictionary (WHO-DD) version Sep. 2017. Medical procedures will not be coded.

5.1.1.6 Multicenter studies

Not applicable since this study will be conducted at a single site.

5.1.1.7 Handling of dropouts or missing data

Missing data will not be imputed unless otherwise stated. Data from subjects who prematurely discontinue the study will be used to the maximum possible extent.
Partial dates for concomitant medication and AEs will be imputed as described in Section 6.3 and Section 10.2.

5.2 Participant Dispositions

Participant screening and primary reason for screen failure will be summarized using the ES. The summary will include the following:

- Number of participants screened
- Number and proportion of participants with screen failures
- Number and proportion of screen failures by primary reason for screen failure

Disposition of participants screened will be summarized using the ES. The number and percentage of participants in each analysis set by treatment (tablet or dry syrup) will be calculated based on the RS.

Participants who have started the study, completed the study and discontinued the study will be summarized using the RS by treatment sequence. The summary will include the following:

- Number of and proportion of participants who have started the study
- Number of and proportion of participants who have discontinued the study
- Number of and proportion of participants who have completed the study.
- Number of and proportion of participants who have discontinued the study by primary reason.

Participants that started the study are defined as participants that were randomized and dosed.

Participants completing the study are those participants completing all Treatment Periods of the study as well as the SFU assessment.

By-participant listings of participant disposition will be provided by treatment sequence for ES, and will include the following:

- Study termination/completion status
- Date of informed consent
- Date of randomization
- Date and time of IMP administration
- Date of premature study termination for successfully screened participants dropping out of the study
- Date of screen failure for screen failure participants
- Treatment (Period) at discontinuation
- Primary reason for premature study termination, as applicable
- Primary reason for screen failure, as applicable.

By-participant listings of visit dates will be presented by treatment sequence using the RS.
By-participant listings of participant who did not meet study eligibility criteria will be presented overall using the ES.
By-participant listings of participant inclusion in each analysis set will be presented overall using the ES. By-participant listings of participant excluded from each analysis set will be presented by treatment sequence including the reasons for exclusion; the listing will be based on all subjects in the RS.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics and other baseline characteristics

Demographic variables including age, gender, race (Asian), ethnicity (not Hispanic or Latino), height (cm), body weight (kg), and body mass index (BMI: kg/m^2) will be listed by treatment sequence for all participants in the ES. Age will be used as recorded on the electronic case report form (eCRF) and will not be recalculated.

Demographic and the other baseline characteristic variables at Screening will be summarized by treatment (tablet or dry syrup) and overall based on the SS.

The continuous variables will be summarized using descriptive statistics, and the categorical variables will be summarized using frequency counts and percentages.

Age will be summarized in both continuous and categorized (as per clinicaltrials.gov requirements) format.

For the clinicaltrials.gov reporting, the age categories will include:

- ≤ 18 years
- 19 to < 65 years
- ≥ 65 years

By-participant listings of lifestyle data will be provided for the RS.

Viral serology will be listed based on the ES.

6.2 Medical history and concomitant diseases

By-participant listings of previous and ongoing medical history and procedure history will be provided for the RS. Medical history will include MedDRA SOC and PT, reported condition, start date and stop date (or status ongoing, as applicable). Hepatic event supplemental medical history will be listed.

6.3 Prior and concomitant medications

Prior and concomitant medications will be listed by treatment sequence and participant for participants in the RS and will include the reported term, the anatomical therapeutic chemical (ATC) subgroup (level 1 and 3), preferred term, dose and dose unit, frequency, formulation, indication, prior or concomitant classification flag, start and stop dates (including relative day calculated as described in Section 5.1.1.1.1), duration (unit: day, calculated as stop date – start date + 1) and treatments assigned to. A glossary of medication terms including reported term, preferred term, and ATC levels 1 and 3 will also be presented. Data handling will be described in Section 11.1.4.
Prior and concomitant medications will be summarized separately for the SS by treatment (concomitant medications only) and overall, ATC code (level 1 and 3), and preferred term, including the number and percentage of subjects receiving each medication as categorized by the ATC subgroup or preferred term. The denominator for percentages will be the number of subjects in the SS for each treatment group.
In the case of missing dates, the classification of medications as prior or concomitant will be performed after imputation of dates as described below. Imputations of missing dates will be performed prior to calculation of relative days.

The following rules are applied to impute partial start dates for medications:

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

The following rules will be applied for partial stop dates and will be imputed for the calculation of duration of each medication:

- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then use December 31 of that year.

- If the stop date is completely unknown, do not impute the stop date. In this case the medication will be assigned to all Dosing Periods subsequent to the medication start date.

Concomitant medications will be assigned to Dosing Periods, based on the time when the medication is taken. Assignment to Dosing Periods will be done after missing dates have been imputed as described above. Concomitant medications will be assigned to a treatment based on the treatment received in the Dosing Periods as follows:

- Dosing Period 1: the start or end date is on or after IMP administration in Dosing Period 1 and prior to IMP administration in Dosing Period 2
- Dosing Period 2: the start or end date is on or after IMP administration in Dosing Period 2.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Any dosing deviations will be assessed in the Data Evaluation Meeting (DEM) for possible impact on the PK-PPS. No listing will be provided since study participant compliance to treatment will be ensured by the administration of IMP under the Investigator's (or designated site personnel's) supervision.

8 EFFICACY ANALYSES

Not applicable.

9 PHARMACOKINETICS

Pharmacokinetic analyses will be performed on the SS. Statistical analyses will be performed on the PK-PPS.

9.1 Plasma concentration-time profiles

Blood samples will be collected for measurement of plasma concentrations of BRV at predose, and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose. Allowable deviations from these scheduled PK sampling times are provided in Table 8-2 of the protocol.
Individual concentration-time data will be listed for the SS by treatment sequence.
Concentration listings will include nominal PK sampling time, actual sampling times relative to dose administration, deviation from nominal time, and percent deviation from nominal time, and concentrations, day, dosing period and sequence, treatment (tablet or dry syrup).
Percent deviation (%) = (actual time – scheduled time)/scheduled time * 100.
Plasma concentration data will be listed and summarized with the descriptive statistics by treatment (tablet or dry syrup) and scheduled time for the PK-PPS.
Descriptive statistics will include number of study participants (N), number of available observations (n), mean, standard deviation, median, minimum, and maximum, geometric mean, geometric coefficient of variation (CV), and 95% confidence interval (CI) for the geometric mean.
The geoCV will be calculated as $geoCV(\%) = 100 \times \sqrt{\exp\{(lnSD)^2\} - 1}$,

where $\ln SD$ is the standard deviation of the log transformed values.

Graphical displays of individual plasma concentrations by actual time will be presented on semi-logarithmic and linear scales.
Graphical displays of geometric mean concentrations with its corresponding 95% CI (linear scale and semi-logarithmic scale) and zoomed geometric mean concentrations between 0 and 6 hr. will also be presented by treatment (tablet or dry syrup) and scheduled time on semi-logarithmic and linear scales.
Plasma concentrations will be displayed superimposed in a single plot for both treatments.
Spaghetti plots will be presented separately for treatment, with profiles for all participants superimposed on the same graph.

Refer to Appendix 2 (Section 11.3.1) for standard reporting procedures of individual values and descriptive statistics for plasma concentration data in listings, tables, and figures.

9.2 Primary/other pharmacokinetic variables

The primary and other PK parameters distinction is given in Section 9.3.1 and Section 9.4.1.

9.2.1 Derivation of primary/other pharmacokinetic variables and descriptive summaries

Pharmacokinetic parameters will be calculated by non-compartmental analysis methods from the concentration-time data using Phoenix® WinNonlin® (Version 8.2) or higher.

Actual sampling times will be used for deriving the PK parameters. Pharmacokinetic parameters will be estimated according to the guidelines presented in Appendix 4, Section 11.4.

According to the definition of the Pharmacokinetic Per-Protocol Set (PK-PPS) (Section 4.4), all randomized study participants who are included in the SS, have no important protocol deviations that are considered to impact the study participant's data validity for analysis of the primary study objective, and have a sufficient number of bioanalytical assessments to calculate reliable estimates for the primary pharmacokinetic parameters for both treatments will be included in the PK-PPS. If study participant's predose concentration is greater than 5% of the corresponding C_{max} value in both Dosing Periods, the study participant will be excluded from the PK-PPS. If this occurs in 1 of the 2 Dosing Periods, but not in the other Dosing Period, data of the other Dosing Period will be used. If vomiting occurs at or before 2 times of the median t_{max}, the study participant will be excluded from the PK-PPS.

The PK parameters will be listed and summarized with descriptive statistics by treatment (tablet or dry syrup) for the PK-PPS. For individual C_{max}, $AUC_{(0-t)}$ and AUC, ratio of test (dry syrup) versus reference (tablet) will be listed by participant and summarized with descriptive statistics for the PK-PPS. Both the primary and other PK parameters will be listed by treatment (tablet or dry syrup) for subjects excluded from PK-PPS, but included in the SS.

The following descriptive statistics will be calculated: mean, SD, geometric mean, geometric coefficient of variation (CV), minimum, median and maximum and 95% confidence interval (CI)

for the geometric mean. The only exception is t_{max}, for which only median, minimum, and maximum will be reported.

Ping pong plots for individual data in the PK parameters (C_{max}, $AUC_{(0-t)}$ and AUC) will also be displayed for the PK-PPS.

Refer to Appendix 3 (Section 11.3.2) for standard reporting procedures of individual values and descriptive statistics for PK parameters in listings and tables.

9.3 Primary Endpoint(s) Analysis

9.3.1 Definition of endpoint(s)

The primary endpoints are defined as follows:

- Maximum concentration, C_{max}
- Area under the curve from 0 to the time of the last quantifiable concentration, $AUC_{(0-t)}$

9.3.2 Main analytical approach

The bioavailability of BRV dry syrup (1.25g of granules for oral solution 4% w/w, corresponding to 50mg of BRV) (test) will be compared with BRV 50mg dose administered as a 50mg tablet (reference).
The parameters C_{max} and $AUC_{(0-t)}$ will be evaluated according to a univariate model of analysis of variance, adapted to crossover experimental designs. The model will include the treatment (tablet or dry syrup), the dosing period, and treatment sequence as fixed effects. The study participant (nested to the sequence) will be the random effect. The dependent variables will be logarithmically transformed by natural logarithms (ln) prior to statistical testing, following the usual recommendations.

This linear mixed model is represented as:

$log(Y_{ijkl}) = \mu + S_{i(j)} + Q_j + F_k + P_l + e_{ijkl}$, where

- $log(Y_{ijkl})$ is the log transformed PK parameter value of the i-th subject (i=1,2,3,..) in the j-th sequence (j=1,2); for the k-th treatment (k=1,2) in the l-th period (l=1,2),
- μ is the overall mean,
- $S_{i(j)}$ is the random effect of the i-th subjects nested to the j-th sequence,
- Q_j is the fixed effect for the j-th sequence,
- F_k is the fixed effect for the k-th treatment,
- P_l is the fixed effect for the l-th period,
- e_{ijkl} is the (residual) random error in observing $log(Y_{ijkl})$.

The MIXED procedure in SAS software will be used for this analysis.
For estimation based on a linear mixed model, covariance matrix applied to the within-subject error will be estimated by restricted maximum likelihood (REML). The Kenward-Roger

approximation will be used to estimate the degree of freedom. Variance component structure will be used as covariance in this linear mixed model.

The adjusted test/reference geometric mean ratio and its corresponding 90% confidence intervals (CIs) will be calculated. Bioequivalence between the test (dry syrup) and reference (tablet) formulations will be concluded if the 90% CI limits for C_{max} and $AUC_{(0-t)}$ fall fully within 80% to 125%.

Inter-participant and intra-participant variability for each parameter will also be derived from these analyses as geoCVs.

Geometric least squares means and the corresponding 90% CI for each treatment (tablet or dry syrup) will be provided as well.

9.4 Other Endpoint(s) Analysis

9.4.1 Definition of endpoint(s)

The other PK endpoints are defined as follows:

- Area under the curve from 0 to infinity, AUC
- Extrapolated AUC, AUC_{extr}
- Total clearance after oral administration, CL/F
- Apparent volume of distribution, V_z/F
- Mean residence time (i.e., of the unchanged drug in the systemic circulation), MRT
- Time of C_{max}, t_{max}
- Terminal elimination half-life, $t_{½}$
- First order terminal elimination rate constant, λ_z

9.4.2 Main analytical approach

AUC will be analyzed using the same linear mixed model as in primary endpoints (see Section 9.3.2).

The adjusted test/reference geometric mean ratio and the corresponding 90% CI will be calculated.

Inter-participant and intra-participant variability for each parameter will also be derived from analyses using the linear mixed model as geoCVs. Geometric least squares means and the corresponding 90% CI for each treatment (tablet or dry syrup) will be provided as well.
For t_{max}, a distribution-free 90% CI using Hodges-Lehmann's method will be calculated for the median differences (location shift) between each test and the reference. Median and the corresponding 90% CI for each treatment (tablet or dry syrup) will be provided using cumulative

binomial probability. If the exact Hodges-Lehmann confidence limits cannot be calculated, asymmetric limits will be derived instead of symmetric limits.

10 SAFETY ANALYSES

Unless otherwise specified, all summaries will be based on the SS.

10.1 Extent of Exposure

Administration of IMP will be listed by treatment sequence, and Dosing Period for all participants in the SS and will include the following information: IMP formulation, date/ time of IMP administration.

10.2 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and characterized as pretreatment and treatment emergent according to the intake of the IMP.

Adverse events with a start date prior to the first dose of IMP will be defined as pre-treatment AEs. A TEAE is defined as any AE with a start date/time on or after the first dose of IMP or any unresolved event already present before administration of IMP that worsens in intensity following exposure to IMP.
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 (i.e., 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 (i.e., 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 date and/or times will be imputed as described in Table 10-1 for the calculation of duration of each AE. AE duration is computed and reported in day and time format.

Table 10-1: Calculation Rules for Duration of AEs

Data Availability	Onset Date/Time	Outcome Date/Time	Calculation Rules
Complete data	D1/T1	D2/T2	Duration = (D2-D1)*24+(T2-T1)
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)
Start time missing	D1/--	D2/T2	Onset time is substituted by 00:00h. Duration=<(D2-D1)*24+T2
Start and end time missing	D1/--	D2/--	Duration=<[(D2-D1)+1]*24
Start day and time missing	--/--	D2/T2	Duration=<(D2-D0)*24+(T2-T0) For a participant in the SS, D0 and T0 are the date and time of the first administration of study medication and for screen failures, D0 is the date of the Screening Visit date and T0=00:00h.
End day and time missing	D1/T1	--/--	If the stop date is missing, duration will not be calculated.
Start and end date missing	--/--	--/--	If the stop date is missing, duration will not be calculated.

The duration of each AE will be calculated as follows and will be presented in dd:hh:mm format where dd represent days, hh: hours, and mm: minutes:

Duration of AE = End date/time of AE – Start date/time of AE

Adverse events will be assigned to Dosing Periods, based on the onset date/ time of the AE. Assignment to Dosing Periods will be done after missing dates have been imputed as described

above. AE will be assigned to a treatment based on the treatment received in the Dosing Periods as follows:

- Dosing Period 1: the start date is on or after IMP administration in Dosing Period 1 and prior to IMP administration in Dosing Period 2.
- Dosing Period 2: the start date is on or after IMP administration in Dosing Period 2.

10.2.1 Secondary Endpoints

An overview of the occurrence and incidence of TEAEs will be provided by treatment (tablet or dry syrup), and overall. The overview will present individual occurrences as well as number and percentage of (unique) participants experiencing each of the following:

- TEAEs
- Treatment-emergent SAEs

Summaries of the occurrence and incidence of TEAEs and treatment-emergent SAEs will be provided by treatment (tablet or dry syrup) and overall. The summary will present individual occurrences as well as number and percentage of (unique) participants, by SOC and PT. These summaries will be provided for the following:

- Incidence of TEAEs
- Incidence of treatment-emergent SAEs

10.2.2 Other Adverse Events

An overview of the occurrence and incidence of TEAEs will be provided by treatment (tablet or dry syrup), and overall. The overview will present individual occurrences as well as number and percentage of (unique) participants experiencing each of the following:

- TEAEs leading to withdrawal from the study
- Drug-related TEAEs
- Severe TEAEs
- All deaths (AEs leading to death)
- TEAEs leading to death
- TEAEs of special interest

Summaries of the occurrence and incidence of TEAEs will be provided by treatment (tablet or dry syrup) and overall. The summary will present individual occurrences as well as number and percentage of (unique) participants, by primary SOC and PT. These summaries will be provided for the following:

- Incidence of TEAEs leading to withdrawal from the study
- Incidence of Drug-related TEAEs
- Incidence of TEAEs leading to death
- Incidence of TEAEs by maximum severity (intensity)
- Incidence of TEAEs of special interest
- Incidence of non-serious TEAEs above threshold of 5% of participants

For AEs occurred before the first dose of IMP, the summary will present individual occurrences as well as number and percentage of (unique) participants, by primary SOC and PT.

Summaries by maximum severity will count each subject at most once within each MedDRA level based on the maximum severity within that MedDRA level.

Adverse events with missing severity (intensity) will be considered as 'Severe' events for summary purposes but recorded as missing in the listings. Adverse events with missing causal relationship to IMP will be considered as 'Related' for the tabulations but presented as missing in the listings.
For the summary of non-serious TEAEs above threshold of 5% of participants, only TEAEs which are reported in above 5% of participants within a treatment (tablet or dry syrup) will be included.
Adverse event summaries will be ordered by alphabetical SOC and decreasing frequency of PT within SOC in the overall column for tables including event counts. For tables including only number and percentage of participants, summaries will be ordered by alphabetical SOC and decreasing incidence of PT within SOC in the overall column.

A listing will be presented by treatment sequence, period, treatment (tablet or dry syrup) and participant for all AEs for the ES. This will include reported term, SOC, PT, the onset date/time and outcome date/time of the event (including relative days), stop date and time (or ongoing if applicable; relative days), the AE duration, pattern of event, severity, relationship, action taken and outcome. In addition, the listing will flag TEAEs, SAEs and AE of special interest. A glossary of AE terms including reported term, SOC and PT will also be presented.

10.3 Other Safety Assessments

10.3.1 Clinical laboratory evaluations

Laboratory parameters will be grouped according to the laboratory function panel.

Category	Panel	Parameter
Hematology	Red Blood Cell (RBC)	• RBC count • Hemoglobin • Hematocrit • RBC Indices (MCV, MCH, %Reticulocytes)
	Platelet	• Platelet count
	White Blood Cell (WBC)	• WBC count
	WBC Differential	• Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Clinical Chemistry	Electrolytes	• Potassium • Sodium
	Minerals	• Calcium
	Metabolic	• Glucose
	Kidney function	• Blood Urea Nitrogen (BUN) • Creatinine

	Proteins	• Total Protein
	Liver Function	• Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT) • Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT) • Alkaline phosphatase • Total and direct bilirubin
Urinalysis	Routine urinalysis	• Specific gravity • pH • glucose • protein • blood, ketones • bilirubin • urobilinogen • nitrite • leukocyte • esterase by dipstick • Microscopic examination (if blood or protein is abnormal)

All clinical laboratory parameters will be listed by treatment sequence, participant, variable and period/visit, changes from Baseline (as defined in Section 5.1.1.1.5) for continuous values, flags for measurements outside the reference ranges, and relative day (calculated as described in Section 5.1.1.1.1) for the RS. The listing will include the treatment (tablet or dry syrup) received at the time of measurement if applicable (the treatment received in the corresponding Dosing Period will be assigned).
For the flags for results that are out of reference range, values that are below the lower limit of the reference range will be flagged as 'L' (low) and values that are above the upper limit of the reference range will be flagged as 'H' (high).
Any laboratory variable that are given as '<xx' or '>xx' in the database will be imputed with the absolute value of the number without the sign (e.g., <2.2 will be imputed as 2.2) for the calculation of descriptive statistics and changes from Baseline.

10.3.1.1 Laboratory values over time

For clinical laboratory parameters (hematology and clinical chemistry), observed results and changes from Baseline will be summarized using descriptive statistics by treatment (tablet or dry syrup) at scheduled time point, as applicable.

10.3.1.2 Individual Subject Changes of Laboratory Values

Shift tables from Baseline to post-Baseline scheduled time point will be presented by treatment (tablet or dry syrup). These summaries will present a cross-tabulation of Baseline values against post-Baseline values categorized as below reference range, within reference range and above reference range. Each cell will include the corresponding number and percentage of participants. These summaries will only be presented for selected variables in Section 10.3.1.

10.3.1.3 Potential drug-induced liver injury

A separate listing will present participants who meet one or more of the following potential drug induced liver injury (PDILI) criteria at any visit:

- ALT and/ or AST ≥3x Upper limit of normal (ULN) and Total bilirubin <2x ULN who do not exhibit temporally associated symptoms of hepatitis or hypersensitivity
- ALT or AST increase ≥3x ULN and Total bilirubin ≥2x ULN
- ALT or AST ≥3x ULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity

Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness. Hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).
The listing will display only visits for which at least one of the above criteria was fulfilled for a given participant and will display all results obtained at that visit for the specified parameters for the SS.

A summary of participants who met the criteria for PDILI will be presented by treatment (tablet or dry syrup) and in total.

By-participant listings of suspected hepatic events will be presented for the SS.

By-participant listings of family DILI-relevant medical history for PDILI will be presented for the RS.

By-participant listings of information related to potential hepatic event will be presented by treatment sequence, and time point and treatment (tablet or dry syrup) for the SS.

10.3.2 Vital Signs

The following vital signs measurements will be obtained: Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), pulse rate, respiratory rate, and body temperature.

10.3.2.1 Vital Sign Values Over Time

Vital signs variables and changes from Baseline will be summarized using descriptive statistics by treatment (tablet or dry syrup) at each scheduled time point.

10.3.2.2 Individual Subject Changes of Vital Sign Values

By-participant listings of all vital sign variables and change from Baseline will be presented by treatment sequence, period, visit, treatment (tablet or dry syrup) and time point for the RS.

10.3.3 Electrocardiograms

The following twelve-lead ECG variables will be obtained: heart rate, PR, QRS, QT intervals, and QTcF.

For the results measured in triplicate, the averaged value at each time point will be used for by-visit summaries.

10.3.3.1 Electrocardiogram Values Over Time

Twelve-lead ECG variables and changes from Baseline will be summarized using descriptive statistics by treatment (tablet or dry syrup) at each scheduled time point.

The following cut-points in QTcF (raw data and change from Baseline) will be summarized categorically by treatment (tablet or dry syrup) (number and percentage of participants) and timepoint.

Raw QTcF data:

- <450msec
- ≥450msec to <480msec
- ≥480msec to <500msec
- ≥500msec

Change from Baseline QTcF:

- <30msec
- ≥30msec to <60msec
- ≥60msec

Electrocardiogram findings will be listed for the RS.

10.3.3.2 Individual Subject Changes of Electrocardiograms Values

By-participant listings of all twelve-lead ECG variables, change from Baseline and findings will be presented by treatment sequence. period, visit, treatment (tablet or dry syrup) and time point for the RS.

10.3.4 Other safety endpoint(s)

By-participant listings of physical examination data will be presented by treatment sequence, and time point and treatment (tablet or dry syrup) for the RS.

By-participant listings of pregnancy test and alcohol breath test data will be presented for the ES.

Impact of COVID-19 will be summarized by impact category and overall. By-participant listings of impact of COVID-19 will be presented for the ES.

10.4 Other Analyses

Not applicable.

10.5 Subgroup analyses

Not applicable.

10.6 Interim Analyses

Not Applicable.

10.7 Data Monitoring Committee (DMC) or Other Review Board

Not applicable.

11 SUPPORTING DOCUMENTATION

11.1 Appendix 1 Non-key analysis specifications

11.1.1 Baseline characteristics and demographics

The BMI value collected in the eCRF will not be used for this summary. The BMI will be recalculated using the following formula and reported to 1 decimal place:

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

11.1.2 Protocol deviations

All protocol deviations will be reviewed on an ongoing basis as part of the data cleaning and evaluation process. After all data have been verified/entered into the database, and prior to database lock, a Data Evaluation Meeting (DEM) will be performed. The purpose of this review meeting will be to examine all protocol deviations, define the PK-PPS, and to verify the quality of the data. If PK parameters are needed to define PK-PPS, it will be performed based on the ADPP (Pharmacokinetic Parameters Analysis Data). The data evaluation will also help in guiding decisions on how to manage data issues on a case-by-case basis (e.g., missing values, dropouts, and protocol deviations).

Important Protocol Deviations (IPDs) that are considered to impact the study participant's data validity for analysis of the primary study objective will be identified and classified by the deviation types listed in the PD specification document.

Accepted deviations from theoretical time points will be described in the appropriate documents and included in the electronic Trial Master File. After the data review, resolution of all issues, and documentation of all decisions, the database will be locked.

11.1.3 Medical history

Medical history will be collected at the Screening Visit.

11.1.4 Prior/concomitant/follow-up medications

If a participant takes a medication before the study medication administration, this medication will be categorized as 'prior medication'. This includes medications that started prior to study medication administration and continued after.
Medication not stopped before the date of study medication administration will be classified as 'concomitant medication'. Medication will also be labeled as 'concomitant medication' when the start date is between the date (including the date) of study medication administration and the date of the participant's last study visit.
From the definitions above, any medication that started prior to dosing and continued after dosing will be classified as both prior and concomitant.
Any medications with missing dates and/or times will be handled as described in Section 6.3 in order to classify them as prior or concomitant.

11.1.5 Data derivation rules

Not applicable.

11.1.6 AEs of Special Interest

The AEs of special interest for BRV are as follows (by PT): autoimmune nephritis, nephritis, nephritis allergic, tubulointerstitial nephritis, and uveitis syndrome.

11.1.7 Potentially Clinically Significant Criteria for Safety Endpoints

Not applicable.

11.1.8 Compliance

Study participant compliance to treatment will be ensured by the administration of IMP under the Investigator's (or designated site personnel's) supervision. Drug accountability must be recorded on the Drug Accountability Form.

11.2 Appendix 2: Changes to Protocol-Planned Analyses

Not Applicable.

11.3 Appendix 3: Standard Reporting Procedures

11.3.1 PK concentrations

When reporting individual data in listings the following rules will apply:

- Missing data will be reported as NV (no value).

- Concentrations below the limit of quantification will be reported as BLQ (below the limit of quantification).
- Concentrations will be listed to the same number of significant figures supplied by the bioanalytical laboratory.

When reporting individual data in figures the following rules will apply:

- BLQ values prior to C_{max} will be set to 0 for purposes of plotting the figure (to capture lag-time).
- Actual sampling times will be used.

When summarizing the data in tables the following rules will apply:

- To calculate descriptive statistics, BLQ values will be set to half the LLOQ value and missing values will be excluded.
- When the total number of BLQ and missing values exceeds one third of the total then only minimum and maximum will be reported for this time point. Other descriptive statistics will be reported as missing ("-"). The minimum will be reported as "BLQ".
- When the summary statistic includes one or more replaced BLQ values then a footnote will be included to say, "contains one or more BLQ value replaced by half the LLOQ value".
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these will be presented as the minimum and maximum with other descriptive statistics reported as missing ("-").
- If no participants have data, only n=0 will be presented. The other descriptive statistics will be left blank.
- Descriptive statistics for plasma concentration data will be reported to the same level of precision as the individual data for the minimum and maximum, and to 1 additional decimal place or 1 additional significant figure– depending on the reporting format of the original data with a maximum of 3 significant digits, i.e., 35.12 will be 35.1, 0.0004649 will be 0.000465 - for the mean (arithmetic and geometric), median, SD and the 95% CI for the geometric mean.
- Geometric CV will be reported as a percentage to 1 decimal place

When summarizing the data in figures the following rules will apply:

- The data plotted in the figure will match the data presented in the summary table, with the exception of missing values prior to C_{max} which should be set to 0 in the figure (to capture lag-time).
- Nominal sampling times will be used.

Both linear and semi-logarithmic scales will be presented.

11.3.2 PK parameters

When reporting individual data in listings the following rules will apply:

- Individual PK parameters will be reported to 3 significant figures.
- If a parameter cannot be calculated, it will be reported as NE (not estimable i.e., if input data is missing which prevents calculation) or NC (not calculable i.e., if the data were available but the calculation was considered unreliable).

When summarizing the data in tables the following rules will apply:

- The derived PK parameters will be considered as source data and this data without rounding will be used for calculation of summary statistics of PK parameters.
- Descriptive statistics will be reported to 4 significant figures for the mean (arithmetic and geometric), median and standard deviation (SD) and to 3 significant figures to the others including the 95% CI for the geometric mean.
- Geometric CV will be reported as a percentage to 1 decimal place.
- 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 (i.e., not estimable).
- 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 ("-")

11.4 Appendix 4: PK parameter calculations

Pharmacokinetic parameters will be calculated by non-compartmental analysis methods from the concentration-time data following these guidelines:

- Actual time will be used in the calculation of all derived pharmacokinetic parameters.
- There will be no imputation of missing data.
- BLQ values at the beginning of a subject profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero. Embedded BLQ values (i.e., occurring between two measurable data points) and BLQ values occurring post-C_{max} will be considered missing.

Pharmacokinetic parameters will be estimated according to the guidelines presented in Table 11-1.

Table 11-1: Pharmacokinetic Parameter and Estimation

Parameter	Guideline for Derivation
C_{max} and t_{max}	Obtained directly from the observed concentration-time data
C_{last}	Last observed (quantifiable) concentration, obtained directly from the observed concentration versus time curve

Parameter	Guideline for Derivation
$AUC_{(0\text{-}t)}$	The AUC from zero time (pre-dose) to the time of last quantifiable concentration ($AUC_{(0\text{-}t)}$ will be calculated by a combination of linear and logarithmic trapezoidal methods. Unless specifically requested and justified the linear up/log down trapezoidal method will be employed. The $AUC_{(0\text{-}t)}$ is the sum of areas up to the time of the last quantifiable sample: $$AUC_{(0\text{-}t)} = \int_0^t \mathbf{C(t)dt}$$
AUC	The area from zero time extrapolated to infinite time will be calculated as follows: $$AUC = AUC_{(0\text{-}t)} + \frac{C_{last}}{\lambda_z}$$ where C_{last} is the last observed quantifiable concentration.
AUC_{extr}	The percentage of AUC obtained by extrapolation will be calculated as follows: $$AUC_{extr} = \frac{AUC - AUC(0-t)}{AUC} \times 100$$ Unless otherwise determined by PK Scientist's best knowledge and judgment, if the AUC_{extr} is greater than 20%, AUC_{extr} and all dependent parameters (i.e., AUC, MRT, V_Z/F and CL/F) will be flagged in listings and excluded from summary tables and statistical analysis of PK parameters. The reason for flagging/exclusion will be footnoted in parameter listings.
λ_z and $t_{½}$	1. The apparent terminal phase rate-constant (λ_z) will be estimated by linear regression of concentration versus time data presented in a log-linear scale. Best fit option should be used in WinNonlin; however, each determination must then be checked manually. 2. Data are primarily monotonically decreasing in magnitude and are representative of the actual decline in the log concentration-time curve. 3. Only those data points that are judged to describe the terminal log-linear decline will be used in the regression. 4. A minimum number of three data points in the terminal phase will be used in calculating λ_z with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope). Unless otherwise determined by PK Scientist's best knowledge and judgment, if the adjusted correlation coefficient (R^2 adjusted) is <0.8, λ_z will be flagged in listings, and excluded from the summary tables and statistical analysis of PK parameters together with all the λ_z dependent parameters (i.e., AUC_{extr}, $t_{½}$, AUC, MRT, CL/F and V_z/F). The reason for flagging/exclusion will be footnoted in parameter listings 5. Unless otherwise determined by PK Scientist's best knowledge and judgment, the interval used to determine λ_z should be equal or greater than

Parameter	Guideline for Derivation
	2-fold the estimated $t_{½}$. If the interval is less than 2-fold $t_{1/2}$, λ_z, together with all the derived parameters (i.e., AUC_{extr}, $t_{½}$, AUC, MRT, CL/F and V_z/F), will be flagged in listings and either: (i) excluded from summary tables and statistical analysis of PK parameters, or (ii) included and a rationale for inclusion will be presented in the analysis documentation. The reason for flagging/exclusion will be footnoted in parameter listings. 6. The $t_{½}$ will be calculated as follows: $t_{½} = \frac{Ln2}{\lambda_z} \approx \frac{0.693}{\lambda_z}$
CL/F	Apparent clearance of parent drug will be calculated from: $CL/F = \frac{Dose}{AUC}$
V_Z/F	Apparent Volume of distribution $V_Z/F = (CL/F)/ \lambda_z$
AUMC	The area under the first moment curve from zero to infinity: $AUMC = AUMC_{(0-t)} + \frac{C_{last} * t_{last}}{\lambda_z} + \frac{C_{last}}{{\lambda_z}^2}$
MRT	The mean residence time (i.e., of the unchanged drug in the systemic circulation) after single oral dose: $MRT = \frac{AUMC}{AUC}$

12 REFERENCES

Guideline on performing NCA analysis Global Exploratory Development (GED) -2017

Approval Signatures

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