STATISTICAL ANALYSIS PLAN

AMENDMENT 1

Study: EP0231

Product: Brivaracetam

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

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

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Regulatory Agency Identifier Number(s):

Registry	ID
EudraCT Number	Not Applicable
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VERSION HISTORY

SAP Version	Date	Change	Rationale
Final	19 Mar 2024	Not Applicable	Original version
Amendment 0.1	Date of Last Signature	Update the analysis set for PK parameter listing in section 4.6.1.1.2	To make consistence with TLF mock shell
Amendment 1	28 Jun 2024	Update the PK parameters that to be summarized in section 4.6.1.1.2; Remove percent deviation from section 4.6.1.1.1.	To make consistence with TLF mock shell; DEM decision due to meaninglessness of percent deviation.

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 EP0231. 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: 14 Dec 2023
- Electronic Case Report Form (eCRF) v1.0: 21 Dec 2023

1.1 Objectives and endpoints

Table 1–1: Objectives and Endpoints

Objectives	Endpoints
Primary objective	
• To assess bioequivalence between the BRV 50mg tablet and BRV 50mg dry syrup after multiple oral doses in healthy male Japanese participants	Primary PK endpoints from plasma BRV concentrations: • $C_{max,ss}$ • AUC_{tau}
Secondary objective	
• To evaluate the safety and tolerability of multiple oral doses of the BRV 50mg tablet and BRV 50mg dry syrup in healthy male Japanese participants	Secondary safety endpoints: • Incidence of TEAEs • Incidence of treatment-emergent SAEs • Incidence of TEAEs leading to discontinuation
Other objectives	
• To evaluate other PK parameters after multiple oral doses of the BRV 50mg tablet and BRV 50mg dry syrup in healthy male Japanese participants	Other PK endpoints from plasma BRV concentrations: • C_{trough} • CL_{ss}/F • $t_{max,ss}$
• To further evaluate the safety and tolerability after multiple oral doses of the BRV 50mg tablet and BRV 50mg dry syrup in healthy male Japanese participants	Other safety endpoints: • Change from Baseline in clinical laboratory test parameters (ie, hematology, clinical chemistry, and urinalysis) • Change from Baseline in vital signs (SBP, DBP, body temperature, respiratory rate, and heart rate) • 12-lead ECG parameters and findings • Physical examinations

AUC_{tau}=area under the curve during a dosing interval at steady state; BRV=brivaracetam; CL_{ss}/F=apparent total body clearance at steady state; $C_{max,ss}$=maximum plasma concentration at steady state; C_{trough}=measured concentration at the end of a dosing interval at steady state; DBP=diastolic blood pressure; ECG=electrocardiogram; PK=pharmacokinetics; SAE=serious adverse event; SBP=systolic blood pressure; TEAE=treatment-emergent adverse event; $t_{max,ss}$=time of $C_{max,ss}$

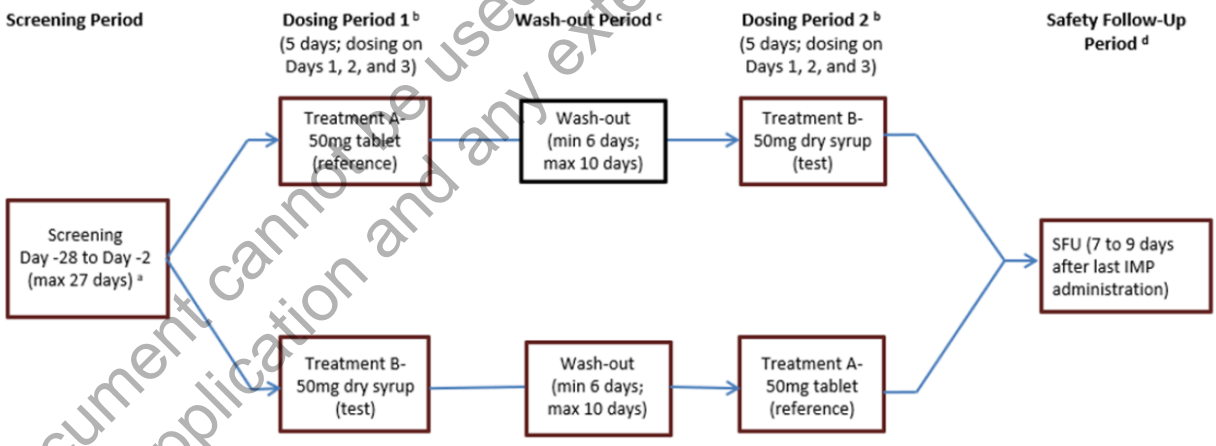
1.2 Study design

EP0231 is a single-center, multiple-dose, open-label, randomized, group sequential design, 2-way cross-over study to assess the bioequivalence of BRV 50mg tablet and BRV 50mg dry syrup in healthy male Japanese participants after oral administration under fasted conditions. In addition, the safety and tolerability of BRV will be evaluated.
Participants will enter a Screening Period (2 to 28 days before administration of investigational medicinal product [IMP]), and eligible participants will start the Dosing Period. The Dosing Period consists of 2 periods (Dosing Period 1 and Dosing Period 2) of 5 days each (Day -1 to Day 4) with a total of 5 administrations of BRV 50mg on Day 1 and Day 2 (morning and evening doses 12 hours apart), and Day 3 (morning dose only).
Participants will receive 1 of the following treatments in each Dosing Period under fasting conditions according to randomly assigned treatment sequences (A-B or B-A):

- Treatment A – multiple doses of BRV 50mg tablets
- Treatment B – multiple doses of BRV 50mg dry syrup (1.25g of granules for oral suspension 4% w/w)

The Dosing Periods will be separated by a Wash-Out Period (minimum of 6 days and preferably no more than 10 days between the final dose in Dosing Period 1 and the first dose in Dosing Period 2 for each participant) and followed by a Safety Follow-Up (SFU) Visit, 7 to 9 days after the last administration of IMP. Participants who prematurely discontinue the IMP/study will be encouraged to return for an SFU Visit, 7 to 9 days after the final IMP administration. Refer to the study schematic in Figure 1-1.

Figure 1-1: Schematic Diagram



BRV=brivaracetam; DMC=Data Monitoring Committee; IMP=investigational medicinal product; max=maximum; min=minimum; SFU=Safety Follow-Up; w/w=weight/weight
a Following a Screening Period (up to 27 days before the start of Dosing Period 1), eligible participants 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. After the first cohort (approximately 60 evaluable participants) has completed both Dosing Periods, an interim analysis will be performed, and an internal DMC will determine whether the primary objective is achieved, futility of the study is confirmed, or whether the study should continue with recruitment of the second cohort (approximately 30 evaluable participants).

[b] Each Dosing Period is 5 days each (Day -1 to Day 4). Brivaracetam 50mg will be administered twice daily (morning and evening doses 12 hours apart) as 50mg tablets (Treatment A [Reference]) or dry syrup (1.25g of BRV granules for oral suspension 4% w/w; Treatment B [Test]). On Day 1 and Day 2, participants will fast for at least 2 hours before and after IMP administration. On Day 3, only the morning dose will be administered, and the participants will fast for 10 hours before and 4 hours after IMP administration. For each Dosing Period, participants will be admitted to the study site on Day -1 (1 day before dosing) and will be discharged on the morning of Day 4, approximately 24 hours after last administration of IMP in each Dosing Period, at the discretion of the Investigator.
[c] The Dosing Periods will be separated by a Wash-Out Period (minimum of 6 days and preferably no more than 10 days between the final dose in Dosing Period 1 and the first dose in Dosing Period 2) for each participant.

[d] An SFU Visit will occur 7 to 9 days after the final IMP administration. Participants who prematurely discontinue the IMP/study will be encouraged to return for an SFU Visit within 7 to 9 days after the final IMP administration.

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

Table 1-2: Schedule of Activities

Procedure	Screening Period	Dosing Period 1 or Dosing Period 2 [a]					SFU [b]
	2 to 28 days before administration of IMP	Check in Day -1	Day 1	Day 2	Day 3	Day 4	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					
Verification of withdrawal criteria [c]		X	X	X	X	X	
Medical/surgical history	X	X					
Physical examination	X	X				X	X
Height and weight	X						
Viral serology (HBsAg, HCV, HIV, and syphilis)	X						
Alcohol and drug (including cotinine) testing	X	X					
COVID-19 precautions [d]	X	X					X
Vital signs [e]	X	X	X	X	X	X	X
Clinical laboratory tests (hematology, clinical chemistry, and urinalysis)	X	X				X	X
Randomization [f]		X					
12-lead ECG [g]	X		X			X	X
IMP administration [h]			X	X	X		
Blood sampling for PK [i]			X	X	X		
Recording of prior and concomitant medication and procedures	X	X	X	X	X	X	X
Recording of AEs	X	X	X	X	X	X	X
Confinement		X	X	X	X	X [j]	

AE=adverse event; BRV=brivaracetam; COVID-19=coronavirus disease 2019; 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; w/w=weight/weight

Table 1-2: Schedule of Activities

Procedure	Screening Period	Dosing Period 1 or Dosing Period 2 [a]					SFU [b]
	2 to 28 days before administration of IMP	Check in Day -1	Day 1	Day 2	Day 3	Day 4	7 to 9 days after the last administration of IMP

[a] Each participant will enter 2 Dosing Periods, separated by a Wash-Out Period. Dosing Period 2 will begin after the Wash-Out Period (minimum of 6 days and preferably no more than 10 days between the final IMP administration in Dosing Period 1 and the first IMP administration in Dosing Period 2).

[b] An SFU Visit will occur 7 to 9 days after the last administration of IMP. Participants who prematurely discontinue the IMP/study will be encouraged to undergo an SFU Visit within 7 to 9 days after the last administration of IMP.

[c] Confirmation that participants do not fulfill the withdrawal or stopping criteria (Section 7 of the protocol) will occur on Day -1, before dosing on Days 1, 2, and 3, and prior to discharge on Day 4.

[d] Coronavirus disease 2019 precautions will be performed in alignment with the study site's local requirements (refer to Section 2.3.1 of the protocol for additional details).

[e] Vital signs (blood pressure [systolic blood pressure and diastolic blood pressure], heart rate, respiratory rate, and body temperature) will be taken at the Screening Visit; for each Dosing Period (on Day -1 check in, Day 1 predose and 12 hours postdose [before the evening dose is administered]), Day 2 [premorning dose] and Day 3 predose, and Day 4 prior to discharge); and at the SFU Visit.

[f] Randomization will occur only for Dosing Period 1; either on Day -1 after all assessments for Day -1 are performed or Day 1 before any assessments for Day 1 are performed. Each participant will be randomly assigned to 1 of 2 treatment sequences (A-B or B-A).

[g] Single 12-lead ECGs will be recorded at Screening, for each Dosing Period (Day 1 predose and Day 4 prior to discharge), and at the SFU Visit.

[h] Investigational medicinal product administration: Brivaracetam 50mg will be administered twice daily (approximately 12 hours apart) as 50mg tablets (Treatment A [Reference]) or dry syrup (1.25g of BRV granules for oral suspension 4% w/w; Treatment B [Test]). On Day 1 and Day 2, participants will fast for at least 2 hours before and after IMP administration. On Day 3, only the morning dose will be administered, and the participants will fast for 10 hours before and 4 hours after IMP administration.

[i] For each Dosing Period, blood samples for PK analysis will be collected on Day 1 (before the morning and evening doses [0 and 12hr]), Day 2 (before the morning and evening doses [24 and 36hr]), and Day 3 (predose [48hr] and 10min, 15min, 20min, 30min, 45min, 60min, 75min, 90min, 2hr, 6hr, 9hr, and 12hr postdose).

[j] Participants will check out of the clinical unit the morning of Day 4, approximately 24 hours after the final dose of IMP administered, at the discretion of the Investigator.

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, corresponding to 50mg of BRV) (Test) and BRV 50mg tablet (Reference) after multiple oral doses according to $C_{max,ss}$ and AUC_{tau}.

Null hypothesis (H_0): the adjusted Test/Reference geometric mean ratio is smaller than 0.80 or larger than 1.25.
Alternative hypothesis (H_1): the adjusted Test/Reference geometric mean ratio is within 0.80 to 1.25.

The confidence intervals (CIs) of the adjusted Test/Reference geometric mean ratio will be calculated corresponding to the Lan-DeMets alpha spending function approximating a Pocock boundary (Lan and DeMets, 1983), while maintaining the overall 2-sided significance level of 0.1.
Based on the hypotheses, bioequivalence between the Test (dry syrup) and Reference (tablet) formulations will be concluded if the CIs for $C_{max,ss}$ and AUC_{tau} are contained in the range of 0.80 to 1.25.

In the case that the CIs for $C_{max,ss}$ and AUC_{tau} are not contained in the range of 0.80 to 1.25, bioequivalence can still be concluded if the following criteria are met: 1) the point estimate of the adjusted GMR (Test/Reference) for $C_{max,ss}$ and AUC_{tau} are contained in the range of 0.90 to 1.11, and 2) in vitro dissolution rates of Test (dry syrup) and Reference (tablet) formulations are available and are deemed similar according to the Japanese bioequivalence guideline (PSEHB/PED Notification No. 0319-1, 2020).

2.1 Multiplicity adjustment

Since the analyses of primary endpoints are planned at the interim analysis and the final analysis, Lan-DeMets alpha spending function approximating a Pocock boundary will be applied in order to control the overall Type I error rate.

3 POPULATIONS FOR ANALYSIS

3.1 Enrolled Set

All participants who have signed the informed consent will be included in the Enrolled Set (ES).

3.2 Randomized Set

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

3.3 Safety Set

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

3.4 Pharmacokinetic Set

The Pharmacokinetic Set (PKS) consists of all study participants who are randomized, receive at least 1 dose of active IMP and have at least 1 quantifiable post-Baseline PK measurement.

All PKS participants who have a sufficient number of bioanalytical assessments to calculate reliable estimates for the primary PK parameters for both BRV formulations will be included in the statistical analysis.
If a participant's predose concentration on Day 1 is greater than 5% of the $C_{max,ss}$ value on Day 3 in a Dosing Period, the participant's data from that Dosing Period will be excluded from the statistical analysis. If a participant's predose concentration on Day 1 is greater than 5% of the $C_{max,ss}$ value on Day 3 for both Dosing Periods, the participant will be excluded from the statistical analysis.
If vomiting occurs at or before 2 times the median $t_{max,ss}$ for the tablet and the dry syrup within a Dosing Period, the participant's data from that period will be excluded from the statistical analysis. If vomiting occurs at or before 2 times the median $t_{max,ss}$ within a Dosing Period, for both Dosing Periods, the participant will be excluded from the statistical analysis.
If (1) a PK sample is missing and the $C_{max,ss}$ is the sample immediately preceding or following the missing sample or (2) 2 or more samples are missing, then the participant's data from that period will be excluded from the statistical analysis.

4 STATISTICAL ANALYSES

4.1 General considerations

Statistical analysis and generation of tables, figures, and data listings will be performed using SAS Version 9.4 or higher.
A complete set of listings containing both all documented data and all calculated data will be generated. Missing data will not be imputed.
For categorical endpoints, the number and percentage of participants in each category will be presented. The denominator for percentages will be based on the number of participants appropriate for the purpose of the analysis. For continuous endpoints, descriptive statistics will include number of participants, mean, standard deviation (SD), median, minimum, and maximum. The descriptive statistics for plasma concentrations and PK parameters will be described in Section 4.6.1.1.1 and Section 4.6.1.1.2.

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%, no decimal will be presented. If the percentage is 0, no percentage will be presented. Typically, the unit (%) 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.

Standard reporting procedures of PK concentrations and parameters in listings, tables, and figures are described in Appendix 12 (Section 6.12).

The analysis outputs prepared as Interim Analyses (IA) for DMC (IA-DMC), All Analyses (All) are indicated as follows:

- IA-DMC will be performed at IA for DMC after Cohort 1 is completed.
- All analyses will be performed either at IA after Cohort 1 is completed or Final Analyses (FA) after Cohort 2 is completed. If bioequivalence (BE) or futility is confirmed by DMC at IA and the study is terminated at IA early after Cohort 1 is completed, the IA (All) will be performed at IA. Otherwise, the FA will be performed after Cohort 2 is completed.

TLF shells will clarify “Interim Analyses (DMC)”, “Interim Analyses (All)” or “Final Analyses”.

4.1.1 Analysis time points

4.1.1.1 Relative day for listings

Relative day will be derived with the date of the first 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 the first IMP administration + 1

i.e., the day of the first 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 the first IMP administration within the same Dosing Period
e.g., the day prior to the first 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 the 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 the last IMP administration in Dosing Period

Relative day will be prefixed with '+' and will be calculated as follows:
Relative day = Current date – Date of the last IMP administration within the same Dosing Period
e.g., the day after the last 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 the 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.

4.1.1.2 Analysis periods

The total duration of the study for an individual study participant is 21 days to 53 days and will include:

- A Screening Period (2 to 28 days before IMP administration)
- Two Dosing Periods (5 days each, with IMP administration on Day 1 and Day 2 (morning and evening doses 12 hours apart), and Day 3 (morning dose only) of each Dosing Period
- A Wash-out Period following Dosing Period 1 (minimum of 6 days and preferably no more than 10 days between the final dose in Dosing Period 1 and the first dose in Dosing Period 2 for each participant)
- An SFU Visit/Withdrawal Visit (7 to 9 days after the last IMP administration)

Table 4-1: 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, 1, 2, 3 and + 1
Wash-out Period	Defined as Relative Day + 2 to + 6 (~ + 10)
Dosing Period 2	Defined as Relative Day -1, 1, 2, 3 and +1
Safety Follow-Up Period	Defined as Relative Day + 2 to + 7 (~ + 9)

4.1.2 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.

Table 4-2: Definition of Baseline

Measurement	Definition of Baseline
Vital Signs	Day 1, Pre-dose value in each period. If this value is unavailable, Day -1 check in value will be imputed in the period. If those values are 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.
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)	Day -1, check in 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. Baseline for Dosing Period 1 can be used for Dosing Period 2 if any other baseline value is unavailable.

4.1.3 Mapping of assessments performed at Early Discontinuation 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.

4.1.4 Treatment assignment and treatment groups

Treatment assignment for the SS and PKS 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 BRV formulation 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.

4.1.5 Multicenter studies

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

4.1.6 Center pooling strategy

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

4.2 Primary endpoint analyses

Statistical analyses will be performed on the PKS.

The bioavailability of BRV dry syrup (1.25g of granules for oral suspension 4% w/w, corresponding to 50mg of BRV) (Test) will be compared with BRV 50mg tablet (Reference).

4.2.1 Definition of endpoints

The primary endpoints are defined as follows:

- Maximum plasma concentration at steady state, $C_{max,ss}$
- Area under the curve during a dosing interval at steady state, AUC_{tau}

4.2.2 Main analytical approach

The primary PK parameters $C_{max,ss}$ and AUC_{tau} will be evaluated according to a linear mixed model, adapted to cross-over experimental designs. The model will include treatment (BRV formulation), period, and sequence as fixed effects. The participant (nested within the sequence)

will be included as a random effect. Since the participant is entered as a random effect in the linear mixed model, the data from the nonaffected Dosing Period (i.e., evaluable data) can still be used for the bioequivalence assessment even if the data from the other Dosing Period are excluded from the analysis. The dependent variables will be logarithmically (ln) transformed prior to statistical testing, following the usual recommendations.

This linear mixed model is represented as:

$log(Yijkl) = \mu + Si(j) + Qj + Fk + Pl + eijkl$, where

- $log(Yijkl)$ 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,
- $Si(j)$ is the random effect of the *i*-th subjects nested to the *j*-th sequence,
- Qj is the fixed effect for the *j*-th sequence,
- Fk is the fixed effect for the *k*-th treatment,
- Pl is the fixed effect for the *l*-th period,
- $eijkl$ is the (residual) random error in observing $log(Yijkl)$.

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.

Adjusted geometric mean ratio (GMR) (Test/Reference) and the corresponding CIs will be calculated corresponding to the Lan-DeMets alpha spending function approximating a Pocock boundary (Lan and DeMets, 1983), while maintaining the overall 2-sided significance level of 0.1. Bioequivalence between the Test (dry syrup) and Reference (tablet) formulations will be concluded if the CIs for $C_{max,ss}$ and AUC_{tau} are included in the range of 0.80 to 1.25. [IA-DMC, All]

SAS code for Lan-DeMets alpha spending function approximating a Pocock boundary

```
PROC SEQDESIGN bscale=pvalue;
Pocock_type: design alpha=0.05 alt=upper stop=reject info=cum(percent_interim,1)
                    nstages=2 method=ERRFUNCPOC ;
RUN;
```

Note: **percent_interim** is the number of participants for PKS at Interim analysis divided by 90.

For example, if an alpha is derived as 0.03817 for interim analysis, 2-sided (1 - 0.03817 times 2) times 100 % confidence interval for GMR will be derived to demonstrate the bioequivalence. Accordingly, 2-sided (1 -0.02704 times 2) times 100 % confidence interval for GMR will be derived to demonstrate the bioequivalence only if cohort 2 is conducted.

In the case that the CIs for $C_{max,ss}$ and AUC_{tau} are not contained in the range of 0.80 to 1.25, bioequivalence can still be concluded if the following criteria are met:

1) The point estimate of the adjusted GMR (Test/Reference) for $C_{max,ss}$ and AUC_{tau} are contained in the range of 0.90 to 1.11.

2) In vitro dissolution rates of Test (dry syrup) and Reference (tablet) formulations are available and are deemed similar according to the Japanese bioequivalence guideline (PSEHB/PED Notification No. 0319-1, 2020).

In parallel, the 1-sided (upper) 95% CI of the adjusted GMR (Test/Reference) for $C_{max,ss}$ will be calculated to confirm if the upper boundary is less than 0.8700 for $C_{max,ss}$. [IA-DMC]

Inter-participant and intra-participant variability for each parameter will also be derived from these analyses as geoCVs. [IA-DMC, All]

Geometric least squares means and the corresponding 90% CI for each treatment (tablet or dry syrup) will be provided as well. [IA-DMC, All]

4.2.3 Supportive and sensitivity analyses

Not applicable.

4.3 Secondary endpoint analyses

All safety analyses will be performed using the SS unless otherwise specified.

4.3.1 Secondary endpoints

4.3.1.1 Definition of endpoint(s)

The secondary endpoints are defined as follows:

- Incidence of TEAE
- Incidence of treatment-emergent SAEs
- Incidence of TEAEs leading to discontinuation

Adverse events with a start date prior to the first dose of IMP will be defined as pretreatment 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.

Missing or partially missing date and/or times will be imputed to determine if an AE is regarded as TEAE using the imputation rule described in Section 4.5.2.

4.3.1.2 Main analytical approach

An overview of the occurrence and incidence of TEAEs will be provided by BRV formulation (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
- TEAEs leading to discontinuation

[All]

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

- Incidence of TEAEs
- Incidence of treatment-emergent SAEs
- Incidence of TEAEs leading to discontinuation

[All]

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.

4.4 Exploratory endpoint analysis

Not applicable.

4.5 Other Safety analyses

All safety analyses will be performed using the SS unless otherwise specified.

4.5.1 Extent of exposure

Exposure will be summarized by Dosing Period, BRV formulation (tablet or dry syrup), and overall. [All]
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 and dose. [All]

4.5.2 Adverse events

An overview of the occurrence and incidence of TEAEs will be provided by BRV formulation (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:

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

[All]

Summaries of the occurrence and incidence of TEAEs will be provided by BRV formulation (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 Drug-related TEAEs
- Incidence of TEAEs leading to death
- Incidence of TEAEs by maximum intensity
- Incidence of TEAEs of special interest
- Incidence of non-serious TEAEs above threshold of 5% of participants

[All]

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

Adverse events with missing 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 BRV formulation (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, dosing period at onset, BRV formulation (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 or

ongoing if applicable), the AE duration, pattern of event, intensity, relationship, action taken and outcome. In addition, the listing will flag TEAEs, SAEs, AEs leading to discontinuation and AEs of special interest. [All]
A glossary of AE terms including reported term, SOC and PT will also be presented. [All]

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 end/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 4-3 for the calculation of duration of each AE. AE duration is computed and reported in day and time format.

Table 4-3: 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/time 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/time is on or after IMP administration in Dosing Period 2.

4.5.3 Additional safety assessments

4.5.3.1 Clinical laboratory evaluations

Laboratory parameters will be grouped according to Appendix 2 of the protocol.
All clinical laboratory parameters will be listed by treatment sequence, participant, variable and period/visit, changes from Baseline (as defined in Section 4.1.2) for continuous values, flags for

measurements outside the reference ranges, and relative day (calculated as described in Section 4.1.1.1) for the RS. The listing will include the BRV formulation (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.

[All]

Additional laboratory tests including serology, alcohol detect test, and urine drug screen will be listed for the ES. [All]

4.5.3.1.1 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 BRV formulation (tablet or dry syrup) at scheduled time point, as applicable. [All]

4.5.3.1.2 Individual participant changes of laboratory values

Shift tables from Baseline to post-Baseline scheduled time point will be presented by BRV formulation (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. [All]

4.5.3.1.3 Potential drug-induced liver injury

A separate listing will present all visits including unscheduled visits for participants who has any incident of ALT and/or AST≥3x Upper limit of normal (ULN), Total bilirubin ≥1.5x ULN or ALP > 1.5 x ULN.

The listing will display visits for which at least one of the above criteria was fulfilled for a given participant and will display all of the following results obtained at that visit for the specified parameters for the SS.

- Potential hepatotoxicity with hepatitis
- Potential hepatotoxicity with hypersensitivity
- ALT and/ or AST ≥3x ULN and Total bilirubin ≥1.5x ULN at any same visit
- ALT and/ or AST ≥3x ULN and Total bilirubin ≥2x ULN at any same visit
- ALT and/ or AST ≥3x ULN, Total bilirubin ≥2x ULN and ALP <2x ULN at any same visit

[All]

A summary of participants who met the following criteria will be presented by BRV formulation (tablet or dry syrup) and in total. [All]

- Potential hepatotoxicity with symptoms potentially associated with hepatitis or hypersensitivity
- Potential hepatotoxicity without symptoms potentially associated with hepatitis or hypersensitivity
- ALT and/ or AST ≥3x ULN and Total bilirubin ≥1.5x ULN at any same visit
- ALT and/ or AST ≥3x ULN and Total bilirubin ≥2x ULN at any same visit
- ALT and/ or AST ≥3x ULN, Total bilirubin ≥2x ULN and ALP <2x ULN at any same visit

A summary of participants who met the following criteria at any visit will be presented by BRV formulation (tablet or dry syrup) and in total. In addition, individual occurrences will be shown. [All]

- AST ≥ 3 x ULN
- AST ≥ 5 x ULN
- AST ≥ 8 x ULN
- AST ≥ 10 x ULN
- AST ≥ 20 x ULN

- ALT ≥ 3 x ULN
- ALT ≥ 5 x ULN
- ALT ≥ 8 x ULN
- ALT ≥ 10 x ULN
- ALT ≥ 20 x ULN

- AST or ALT ≥ 3 x ULN
- AST or ALT ≥ 5 x ULN
- AST or ALT ≥ 8 x ULN
- AST or ALT ≥ 10 x ULN
- AST or ALT ≥ 20 x ULN

- Total bilirubin ≥ 1.5 x ULN
- Total bilirubin ≥ 2 x ULN

- ALP ≥ 1.5 x ULN

- New ratio value (ALT or AST, whichever produced the highest x ULN/ ALP x ULN value) of 5 or greater

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

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

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

Time course for liver function tests (AST, ALT, ALP and Total bilirubin) will be displayed superimposed in a single plot by participant for participants meeting a criterion, ALT and/ or AST ≥3x ULN, Total bilirubin ≥2x ULN and ALP <2x ULN at any same visit from the SS. [All]

4.5.3.2 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.

4.5.3.2.1 Vital sign values over time

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

4.5.3.2.2 Individual participant 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, BRV formulation (tablet or dry syrup) and time point for the RS. [All]

4.5.3.3 Electrocardiograms

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

4.5.3.3.1 Electrocardiogram values over time

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

The following cut-points in QTcF (raw data and change from Baseline) will be summarized categorically by BRV formulation (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

[All]

Electrocardiogram findings will be listed for the RS. [All]

4.5.3.3.2 Individual participant changes of electrocardiograms values

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

4.5.3.4 Other safety endpoint(s)

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

By-participant listings of impact of COVID-19 will be presented for the ES. [All]

4.6 Other analyses

4.6.1 Other endpoints and/or parameters

The other PK endpoints are defined as follows:

- Measured concentration at the end of a dosing interval at steady state, C_{trough}
- Apparent total body clearance at steady state, CL_{ss}/F
- Time of maximum plasma concentration at steady state, $t_{max,ss}$
- Time of the last measurable concentration, t_{last}
- Area under the curve from time zero (pre-dose) to the last quantifiable concentration, AUC_{last}
- Apparent terminal elimination half-life, $t_{1/2}$
- Terminal elimination rate constant, λ_z
- Percentage of AUC_{tau} obtained by extrapolation beyond t_{last}, $\%AUC_{ex}$

4.6.1.1 Pharmacokinetics

All pharmacokinetic analyses will be performed using the PKS unless otherwise specified.

4.6.1.1.1 Plasma concentration-time profiles

For each Dosing Period, blood samples for PK analysis will be collected on Day 1 (before the morning and evening doses [0 and 12hr]), Day 2 (before the morning and evening doses [24 and 36hr]), and Day 3 (predose [48hr] and 10min, 15min, 20min, 30min, 45min, 60min, 75min, 90min, 2hr, 6hr, 9hr, and 12hr postdose). Allowable deviations from these scheduled PK sampling times are provided in Table 8-1 of the protocol. Individual concentration-time data will be listed for the SS by treatment sequence. [All]

Concentration listings will include nominal PK sampling time, actual sampling times relative to dose administration, deviation from nominal time, and concentrations, day, dosing period and sequence, formulation (tablet or dry syrup).
Plasma concentration data will be listed and summarized with the descriptive statistics by BRV formulation (tablet or dry syrup) and scheduled time for the PKS. [All]

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 lnSD is the standard deviation of the log transformed values.

Graphical displays of geometric mean concentrations with its corresponding 95% CI (linear scale and semi-logarithmic scale) on Day 1 to Day 3 and zoomed geometric mean concentrations between 0 and 6 hr on Day 3 will also be presented by BRV formulation (tablet or dry syrup) and scheduled time on semi-logarithmic and linear scales for the PKS. [IA-DMC, All]
Graphical displays of individual plasma concentrations by actual time will be presented on semi-logarithmic and linear scales.
Plasma concentrations will be displayed superimposed in a single plot for both formulations for the PKS. [All]
Spaghetti plots will be presented on Day 3 up to 12 h post-dose separately for BRV formulation, with profiles for all participants superimposed on the same graph for the PKS. [All]

Refer to Appendix 12 (Section 6.12) for standard reporting procedures of individual values and descriptive statistics for plasma concentration data in listings, tables, and figures.

4.6.1.1.2 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 13, Section 6.13.

$C_{max,ss}$, AUC $_{tau}$, CL_{ss}/F, $t_{max,ss}$ and C_{trough} will be listed by participant and summarized with descriptive statistics by BRV formulation (tablet or dry syrup) for the PKS. [IA-DMC, All]

For individual $C_{max,ss}$ and AUC_{tau}, ratio of Test (dry syrup) versus Reference (tablet) will be listed by participant and summarized with descriptive statistics for the PKS. [All]

The ratios between the C_{trough} after the last dose on Day 3 and the pre-dose concentration before each dose with the exclusion of morning dose on Day 1 (R_{trough}) will be listed by participant and summarized with descriptive statistics for the PKS. [All]
For $t_{max,ss}$, a distribution-free 90% CI using Hodges-Lehmann's method will be calculated for the median differences (location shift) between each Test (dry syrup) and the Reference (tablet). 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. [All]

In addition, all individual PK parameters will be listed by formulation (tablet or dry syrup) for the SS. [All]

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 $t_{max,ss}$, for which only median, minimum, and maximum will be reported.

Ping pong plots for individual data in the PK parameters ($C_{max,ss}$ and AUC_{tau}) will also be displayed for the PKS. [All]

Refer to Appendix 12 (Section 6.12.2) for standard reporting procedures of individual values and descriptive statistics for PK parameters in listings and tables.

4.6.1.2 Pharmacodynamics

Not applicable.

4.6.1.3 Population pharmacokinetics

Not applicable.

4.6.1.4 Immunogenicity

Not applicable.

4.6.1.5 Genomics

Not applicable.

4.6.1.6 Biomarkers

Not applicable.

4.6.1.7 Pregnancy outcomes

Not applicable.

4.6.1.8 Health care utilization related endpoints

Not applicable.

4.6.1.9 Health technology assessment related endpoints

Not applicable.

4.6.2 Subgroup analyses

Not applicable.

4.7 Interim analyses

The study may consist of 2 cohorts. A formal interim analysis is planned at the end of Cohort 1, once approximately 60 evaluable participants have completed the study. If bioequivalence or futility is not established in the interim analysis, the final analysis is planned at the end of Cohort 2, once all participants (approximately 90) have completed the study (See Section 9.8 of the protocol). The interim analysis, based on a group sequential design, will be an unblinded analysis performed by an internal statistical team independent from the study team and will focus on the analysis for primary PK parameters $C_{max,ss}$ and AUC_{tau}. The results will be reviewed by an internal DMC, which is independent from the study team, and the following decisions will be made:

1. Early stopping of the study due to demonstrating bioequivalence at the end of Cohort 1:
   The study will be stopped early, after Cohort 1, if bioequivalence between the Test (dry syrup) and Reference (tablet) formulations is established for $C_{max,ss}$ and AUC_{tau} (Section 9.3.1 of the protocol).
2. Early stopping of the study for futility at the end of Cohort 1:
   The study will be stopped early, after Cohort 1, in the event that bioequivalence is not established and the 1-sided (upper) 95% CI of the adjusted GMR (Test/Reference) is less than 0.8700 for $C_{max,ss}$. This corresponds to the GMR of this study being markedly lower than that of single-dose bioequivalence study (EP0110).
3. Continuing to Cohort 2:
   If bioequivalence or futility is not established, the study will continue to Cohort 2, and the remaining approximately 30 participants will be randomized.

4.8 Changes to protocol-planned analyses

The following evaluation was added in the protocol amendment dated 14 December 2023.

In the case that the CIs for $C_{max,ss}$ and AUC_{tau} are not contained in the range of 0.80 to 1.25, bioequivalence can still be concluded if the following criteria are met:

1) The point estimate of the adjusted GMR (Test/Reference) for $C_{max,ss}$ and AUC_{tau} are contained in the range of 0.90 to 1.11.

2) In vitro dissolution rates of Test (dry syrup) and Reference (tablet) formulations are available and are deemed similar according to the Japanese bioequivalence guideline (PSEHB/PED Notification No. 0319-1, 2020).

4.9 Data Monitoring Committee (DMC) or other review board

As described in Section 9.7 of the protocol, a formal interim analysis is planned at the end of Cohort 1 once approximately 60 evaluable participants have completed the study. The results will be reviewed by an internal DMC, which is independent from the study team. The DMC will make 1 of the following decisions:

1) Early stopping of the study if the study demonstrates bioequivalence at the end of Cohort 1.

2) Early stopping of the study if the study is futile at the end of Cohort 1.

3) Continuing the study to Cohort 2.

Details of the DMC will be provided in the DMC Charters.

5 SAMPLE SIZE DETERMINATION

A total of up to approximately 90 participants are planned to be evaluable for the primary endpoint.
As detailed in Section 9.7 of the protocol, this study may consist of 2 cohorts, with a formal interim analysis once Cohort 1 has completed both Dosing Periods.
The BRV single-dose bioequivalence study (EP0110) between tablet (Reference) and dry syrup (Test) provided estimates of the GMR (Test/Reference) of 0.8700 for C_{max} and 0.9890 for $AUC_{(0-t)}$ and the intraparticipant variability (CV%) of 21.9% for C_{max} and 2.7% for $AUC_{(0-t)}$ (Table 5-1). The BRV multiple-dose PK simulation results based on the EP0110 study data provided estimates of the GMR of 0.9054 for C_{max},ss and 0.9893 for AUC_{tau} and the intraparticipant variability (CV%) of 15.3% for C_{max},ss and 2.7% for AUC_{tau}.

Table 5-1: EP0110 and simulation results of relative bioavailability of BRV tablet formulation vs dry syrup formulation

Parameter	Statistic	EP0110	MD Simulation
C_{max} (µg/mL) [a]	GMR of dry syrup/tablet (Intraparticipant CV%)	0.8700 (21.9)	0.9054 (15.3)
AUC (h*µg/mL) [b]	GMR of dry syrup/tablet (Intraparticipant CV%)	0.9890 (2.7)	0.9893 (2.7)

AUC=area under the curve; $AUC_{(0-t)}$=area under the curve from time 0 to the time of the last quantifiable concentration; AUC_{tau}=area under the curve during a dosage interval at steady state; BRV=brivaracetam; C_{max}=maximum plasma concentration; $C_{max,ss}$=maximum plasma concentration at steady state; CV=coefficient of variation; GMR=geometric mean ratio; MD=multiple-dose
[a] The $C_{max,ss}$ was used for MD simulation results, estimated based upon the EP0110 study data.
[b] The $AUC_{(0-t)}$ was used for EP0110. The AUC_{tau} was used for MD simulation results, based upon the EP0110 study data.

In the event that EP0231 will have results similar to those observed in EP0110 without any improvement by the multiple-dose study design, 116 participants will be needed to provide a power of 90% with a fixed design (no interim analysis). However, because this study is conducted as a multiple-dose study, it is expected that the PK profile variability will be smaller. It is assumed that both the GMR and intraparticipant SD will show improvement (higher GMR and smaller intraparticipant SD) compared with the single-dose study (EP0110), closer to those shown in the multiple-dose PK simulation results. The study assumptions for GMR and intraparticipant CV% (for C_{max}) are based on the approximate middle values of those seen in EP0110 and the multiple-dose PK simulations based on the EP0110 study data, assuming a GMR of 0.89 and intraparticipant SD of 0.183 (corresponding to a CV% of 18.5%).

In the group sequential design for this study, an interim analysis will be performed for bioequivalence or futility after approximately 60 evaluable participants, which is at 90% power for bioequivalence based on the CIs of the adjusted GMR (Test/Reference) with the study assumptions. Should the assumption regarding variability and GMR not hold, with the study consequently not being stopped for demonstrating bioequivalence or futility at the interim analysis, this allows the opportunity to enroll a further approximately 30 participants and assess bioequivalence after approximately 90 evaluable participants. While maintaining the two 1-sided significance level of 0.05, this should be sufficient to state that the true GMR is in the range of 0.80 to 1.25. The two 1-sided significance levels currently used are 0.03817 for the interim analysis and 0.02704 for the final analysis according to the Lan-DeMets alpha spending function approximating a Pocock boundary, assuming 60 evaluable participants in Cohort 1 and 30 evaluable participants in Cohort 2 as the number of participants to be included in the analyses. A total of 90 evaluable participants will provide an overall power of >75% even if the GMR and intraparticipant CV% remain as observed in EP0110.

The probability of study stopping for demonstrating bioequivalence for Cohort 1 (power at Cohort 1), futility at Cohort 1, and proceeding to Cohort 2 are approximately 91%, approximately 1%, and approximately 8%, respectively. If the study continues to Cohort 2, the bioequivalence will be assessed after completing Cohort 2.
In order to ensure a total of up to approximately 90 evaluable participants for the primary endpoints, assuming a rate of dropout and non evaluable participants of approximately 5%, 64 participants for Cohort 1, 32 participants for Cohort 2, and up to 96 participants in total are estimated to be randomized in the study.

6 APPENDIX: SUPPORTING DOCUMENTATION

6.1 Appendix 1: List of Abbreviations

List of Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Curve
AUC_{last}	Area under the Curve from Time Zero (pre-dose) to the Last Quantifiable Concentration
AUC_{tau}	Area under the Curve during a dosage interval at steady state
$\%AUC_{ex}$	Percentage of AUC_{tau} Obtained by Extrapolation from Tlast to Time tau
BE	Bioequivalence
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BRV	Brivaracetam
CI	Confidence Interval
CL_{ss}/F	Apparent Total Body Clearance at Steady State
$C_{max,ss}$	Maximum Plasma Concentration at Steady State
COVID-19	Coronavirus Disease 2019
C_{trough}	Measured Concentration at the End of a Dosing Interval at Steady State
CSR	Clinical Study Report
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure

List of Abbreviations

DEM	Data Evaluation Meeting
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ES	Enrolled Set
FA	Final Analyses
geoCV	Geometric Coefficient of Variation
GMR	Geometric Mean Ratio
IA	Interim Analyses
IMP	Investigational Medicinal Product
IPD	Important Protocol Deviation
λ_z	Terminal Elimination Rate Constant
LLoQ	Lower Limit of Quantification
Max	Maximum
MD	Multiple Dose
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
PDILI	Potential Drug Induced Liver Injury
PED	Pharmaceutical Evaluation Division
PT	Preferred Term
PK	Pharmacokinetic
PKS	Pharmacokinetic Set
PSEHB	Pharmaceutical Safety Environment Health Bureau
QTc	QT Interval Corrected for Heart Rate
QTcF	QTc Using Fridericia's Correction
REML	Restricted Maximum Likelihood
RS	Randomized Set
R_{trough}	Ratio between the C_{trough} after the last dose on Day 3 and the pre-dose concentration before each dose with the exclusion of morning dose on Day 1
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure

List of Abbreviations

SD	Standard Deviation
SFU	Safety Follow-Up
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures and Listings
$t_{½}$	Apparent Terminal Elimination Half-life
t_{last}	Time of the Last Measurable Concentration
$t_{max,ss}$	Time of $C_{max,ss}$
tobs	Actual Sampling Time at Planned Timepoint tau
ULN	Upper Limit of Normal
WHO	World Health Organization

6.2 Appendix 2: Coding dictionaries

Medical history and adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®)), using the MedDRA version 18.1. Medications will be coded using the World Health Organization Drug (WHO-Drug) Sep 2017. Medical procedures will not be coded.

6.3 Appendix 3: Participant disposition

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

[All]

Disposition of participants will be summarized using the ES. [All]
The number and percentage of participants in each analysis set by BRV formulation (tablet or dry syrup) will be calculated based on the RS. [IA-DMC, All]

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. [IA-DMC, All]
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 the first and the last 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.

[All]

By-participant listings of visit dates will be presented by treatment sequence using the RS. [All]
By-participant listings of participant who did not meet study eligibility criteria will be presented overall using the ES. [All]
By-participant listings of participant inclusion in each analysis set will be presented overall using the ES. [All]
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. [All]

6.4 Appendix 4: Baseline characteristics and demographics

Demographic variables including year of birth, age, gender (Male), 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 BRV formulation (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

[All]

Lifestyle data will be summarized by BRV formulation for the SS. [All]
By-participant listings of lifestyle data will be provided by treatment sequence for the RS. [All]

6.5 Appendix 5: Protocol deviations

Important protocol deviations (IPDs) will be summarized by treatment sequence, and overall using the RS as well as participants from the PKS. 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

[IA-DMC, All]

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

6.6 Appendix 6: Medical /surgical history / concomitant medical procedures

By-participant listings of medical history, surgical /procedure history will be provided by treatment sequence for the RS. Medical history will include MedDRA SOC and PT, reported condition, start date and stop date (or status ongoing, as applicable). [All]
A glossary of medical histories including reported term, SOC and PT will also be presented for the RS. [All]
By-participant listings of concomitant medical procedures will be provided by treatment sequence for RS. [All]
Hepatic event supplemental medical history will be listed for the RS. [All]

6.7 Appendix 7: Prior / concomitant 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.

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 4.1.1.1), duration (unit: day, calculated as stop date – start date + 1) and BRV formulation assigned to. [All]
A glossary of medication terms including reported term, preferred term, and ATC levels 1 and 3 will also be presented. [All]
Prior and concomitant medications will be summarized separately for the SS by treatment sequence 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 sequence. [All]

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.

6.8 Appendix 8: Data derivation rules

Not applicable.

6.9 Appendix 9: AEs of Special Interest

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

6.10 Appendix 10: Potentially Clinically Significant Criteria for safety endpoints

Not applicable.

6.11 Appendix 11: Compliance

Any dosing deviations will be assessed in the Data Evaluation Meeting (DEM) for possible impact on the PKS. 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.

6.12 Appendix 12: Standard Reporting Procedures

6.12.1 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) only for the linear plot.
- 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.

6.12.2 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 ("-")

6.13 Appendix 13: 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 6-1.

Table 6-1: Pharmacokinetic Parameter and Estimation

Parameter	Guideline for Derivation
$C_{max,ss}$, C_{trough}, t_{last} and $t_{max,ss}$	Obtained directly from the observed concentration-time data
AUC_{last}	The AUC from zero time (predose) to the time of last quantifiable concentration 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_{last} is the sum of areas up to the time of the last quantifiable sample: $AUC_{last}=\int_0^t C_{last} * dt$
AUC_{tau}	The AUC over the dosing interval will be determined for multiple dose studies using the linear up/log down trapezoidal rule. In case tobs is < tau and tobs is the last non-BLQ/non-missing sample, AUC_{tau} will be calculated by extrapolation to time tau using lambda z. If the elimination phase cannot be characterized, AUC_{tau} will be set to missing. AUC_{tau} values will be flagged based on the PK Scientist's judgement, based on the reliability of extrapolation. Note: tobs is the actual sampling time at planned timepoint tau.
$\%AUC_{ex}$	The percentage of AUC_{tau} obtained by extrapolation will be calculated as follows:

Parameter	Guideline for Derivation
	$\%AUC_{ex} = \frac{AUCtau - AUClast}{AUCtau} \times 100$ $\%AUC_{ex}$ should not exceed 10% for an individual profile. If the $\%AUC_{ex}$ is more than 10%, the individual result should be flagged as all parameters depending on AUC_{tau} (i.e. $AUC_{tau,}$ and CLss/F) should be flagged and footnoted in parameter listing. If $\%AUC_{ex}$ is greater than 10% in more than 20% of the participants, the validity of the study may need to be discussed.
λz 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. 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). The adjusted correlation coefficient (R^2 adjusted) in general should be greater than 0.90. Any value < 0.90 but ≥0.8 will be flagged but may be used at the PK Scientist's best knowledge and judgment. All the derived parameters (i.e. λz, $t_{½}$, AUC_{tau}, CLss/F) will be flagged accordingly. 5. The interval used to determine λz should be equal or greater than 1.5-fold the estimated $t_{½}$ or otherwise flagged and used for descriptive summaries at the PK Scientist's best knowledge and judgment. All the derived parameters (i.e. $t_{½}$, AUC_{tau}, CLss/F) will be flagged from statistical analysis accordingly. 6. The $t_{½}$ will be calculated as follows: $t_{½} = \frac{Ln2}{\lambda_z} \approx \frac{0.693}{\lambda_z}$ Data points may be dropped from the linear regression if the PK Scientist considers the reported values to be anomalous. Any data points so designated should remain in the listings and be identified in the study report with a rationale for exclusion.
CLss/F	Apparent clearance of parent drug will be calculated from: $CLss/F = Dose/AUC_{tau}$
R_{trough}	Ratio between the C_{trough} after the last dose on Day 3 and the pre-dose concentration before each dose with the exclusion of morning dose on Day 1

7 REFERENCES

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