STATISTICAL ANALYSIS PLAN (SAP)

Study: N01379

Product: Brivaracetam

An open-label, multicenter, follow-up study to evaluate the long-term safety and efficacy of brivaracetam used as adjunctive treatment in subjects aged 16 years or older with epilepsy

SAP/Amendment Number	Date
Final SAP	27 January 2014
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Class
BMI	body mass index
bpm	Beats per minute
BRV	brivaracetam
BUN	blood urea nitrogen
CHMP	Committee for Medicinal Products for Human Use
CR CL	creatinine clearance
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
ECG	electrocardiogram
EDV	Early Discontinuation Visit
ER	emergency room
EU	European Union
F	Female
FDA	Food and Drug Administration
FEV	Full Evaluation Visit
FV	Final Visit
GGT	Gamma-glutamyl transpeptidase
HADS	Hospital Anxiety and Depression Scale
HDL	High-density lipoprotein
HRQoL	Health-Related Quality of Life
ILAE	International League Against Epilepsy
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
M	Male
MEV	Minimal Evaluation Visit
N/A	Not applicable
PBO	placebo
PCST	potentially clinically significant treatment-emergent
PGS	primary generalized seizures
POS	partial onset seizure
PT	preferred term
QOLIE-31-P	Patient Weighted Quality of Life in Epilepsy Questionnaire
RBC	Red Blood Cell
SAE	serious adverse event

SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	Upper Limit of Normal
V	Visit
VAS	visual analog scale
WBC	White Blood Cell
WHO-DRL	World Health Organization Drug Reference List
YEV	Yearly Evaluation Visit

1 INTRODUCTION

This statistical analysis plan (SAP) defines the scope of statistical analyses and provides a detailed description of statistical methodology for the statistical analyses to support the final clinical study report for N01379.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

To evaluate the long-term safety and tolerability of brivaracetam (BRV) at individualized doses with a maximum of 200mg/day in subjects suffering from epilepsy

2.1.2 Secondary objective

To evaluate the maintenance of efficacy over time of BRV (for subjects with partial onset seizures [POS] and subjects with primary generalized seizures [PGS])

2.1.3 Exploratory objectives

Exploratory objectives for subjects with POS/PGS:

- To explore the effects of BRV on subjects' Health-Related Quality of Life (HRQoL)
- To explore direct medical resource use
- To explore any change in socio-professional status
- To assess the role of gene variants of synaptic vesicle protein 2 (SV2) in affecting response to BRV (as part of a DNA analysis at the program level)

2.2 Study variables

2.2.1 Safety variables

2.2.1.1 Primary safety variables

- Occurrence of a treatment-emergent adverse event (TEAE)
- Withdrawal due to adverse event (AE)
- Occurrence of a serious adverse event (SAE)

2.2.1.2 Other safety variables

- Laboratory tests (blood chemistry, hematology, urinalysis, and endocrinology)
- Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate) and body weight
- Electrocardiogram (ECG)
- Physical and neurological examinations

- Change in Hospital Anxiety and Depression Scale (HADS) scores from the Baseline of the previous study to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years

2.2.2 Efficacy variables

2.2.2.1 Secondary efficacy variables

For subjects with focal-onset epilepsy:

- POS (type I) frequency per 28 days during the Evaluation Period
- Percent reduction in POS (type I) frequency per 28 days from Baseline of the previous study to the Evaluation Period
- Responder rate for POS (type I) frequency over the Evaluation Period. A responder is defined as a subject with a ≥50% reduction in seizure frequency from the Baseline Period of the previous study

No secondary efficacy variables are defined for subjects with generalized epilepsy

2.2.2.2 Other efficacy variables

For subjects with focal-onset epilepsy:

- Percentage of subjects continuously seizure-free for all seizure types (I+II+III) for at least 6 months and at least 12 months during the Evaluation Period

For subjects with generalized epilepsy:

- Generalized (type II) seizure days per 28 days during the Evaluation Period
- Percent reduction in generalized (type II) seizure days per 28 days from Baseline of the previous study to the Evaluation Period
- Responder rate for generalized (type II) seizure days over the Evaluation Period. A responder is defined as a subject with a ≥50% reduction in seizure days from the Baseline Period of the previous study.
- Percentage of subjects continuously seizure-free for all seizure types (I+II+III) for at least 6 months and at least 12 months during the Evaluation Period

The following will be evaluated separately for subjects with focal-onset epilepsy and subjects with generalized epilepsy:

- Change in Patient Weighted Quality of Life in Epilepsy Questionnaire (QOLIE-31-P) scores from Baseline of the previous study to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years

2.2.2.3 Pharmacoeconomic variables

Due to the inconsistencies in data captured and collection forms across LTFU studies, the following variables will be provided in subject data listings only, but will not be evaluated or descriptive summarized:

- Direct costs (healthcare provider consultations not foreseen by the protocol, concurrent medical procedures, concomitant medications, hospitalizations, and emergency room [ER] visits) during the first 2 years of the Evaluation Period
- Socio-professional data for each assessment for the first 2 years and for the last assessment during the first 2 years of the Evaluation Period

2.3 Study Design and Conduct

This is an open-label, long-term follow-up, multicenter, noncomparative, single-arm study of BRV. The primary objective is to evaluate the long-term safety and tolerability of BRV at individualized doses up to a maximum of 200mg/day in subjects with epilepsy. The secondary objective is to evaluate the maintenance of efficacy of BRV. Exploratory objectives are to assess the effects of BRV on subjects' HRQoL, obtain information on the direct costs, explore changes in socio-professional status, and assess the role of gene variants of SV2. DNA analysis will only be done for those subjects coming from N01358.

Study N01379 enrolled subjects 16 years of age and older who had completed N01358 or N01258. Study N01358 enrolled subjects with refractory partial onset seizures (POS) whether or not secondarily generalized and N01258 enrolled subjects with localization-related or generalized epilepsy (designated as "PGS subjects").

Subjects from N01258 were started at an oral dose of BRV 200mg/day (2 equally divided doses administered twice daily) and should be maintained at this dose for at least 2 weeks unless the subject is unable to tolerate treatment. Subjects from N01358 were started on oral BRV at a dose of 150mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks unless the subject was unable to tolerate treatment.

Subjects who enroll in the study entered an Evaluation Period during which treatment with BRV was initiated. The dose of BRV can be adjusted based on the individual subject's seizure control and tolerability. Dose increases can be made in increments of 50mg/day on a weekly basis up to a maximum of 200mg/day; dose decreases can be made in steps of 50mg/day on a weekly basis. Subjects who discontinue treatment with BRV enter a Down-Titration Period during which the dose of BRV is decreased in steps of 50mg/day on a weekly basis with a last down-titration step at 20mg/day for 1 week. Subjects who have completed the Down-Titration Period or subjects who discontinue during the Evaluation Period without entering the Down-Titration Period enter a Post-Treatment Period for a minimum of 2 weeks and a maximum of 4 weeks.

The maximum allowable daily dose for this study is 200mg/day based on the protocol. It is recommended that the daily dose be administered in 2 equal intakes.

Dose adjustment to concomitant AEDs may be made at any time during the study and subjects may start new AEDs. Concomitant AEDs may also be discontinued.

The visit schedule for this study is the same without regard to the subject's previous study. Study visits at Months 2, 6, 12, 18, 24, and so forth are either Full Evaluation Visits (FEVs)

or Yearly Evaluation Visits (YEVs) at which a greater number of assessments are performed. Study visits at Months 1, 3, 9, 15, 21, and so forth are Minimal Evaluation Visits (MEVs). In addition, a phone call is scheduled at the end of the Down-Titration Period and a Drug-Free Final Visit (FV) is scheduled at the end of the Post-Treatment Period. The study schedule, as just described, is shown in Table 2–1.

Table 2–1: Study Schedule

1st Year Follow-up		
Month	**Visit**	**Type of Visit**
M0	V1	Entry Visit (EV)
M1	V2	MEV
M2	V3	FEV
M3	V4	MEV
M4		
M5		
M6	V5	FEV
M7		
M8		
M9	V6	MEV
M10		
M11		
2nd and subsequent years follow-up		
M12	V7	YEV
M15	V8	MEV1
M18	V9	FEV
M21	V10	MEV2
...	...	...

FEV=Full Evaluation Visit; MEV=Minimal Evaluation Visit; M=month, V=Visit, YEV=Yearly Evaluation Visit

All subjects should have a Visit 1 at the start of N01379. Visit 1 will correspond to the last visit from the previous study and should be the visit at which study drug is dispensed for N01379.

This study will run throughout the duration of the clinical development period of brivaracetam, and will continue until a marketing authorization is granted by any Health Authority in an indication for the adjunctive treatment in adults with refractory POS, whether or not secondarily generalized, until the Sponsor decides to close the study, until a managed access program, named patient program, compassionate use program, or similar type of access program is established as allowed per country-specific requirement in addition to legal and regulatory guidelines, or until brivaracetam development is stopped by the Sponsor.

2.4 Determination of Sample Size

No sample size calculation was done. Sample size was dependent upon recruitment into and completion of preceding studies.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be carried out using SAS® Version 9.1 or higher.

Descriptive statistics, such as the mean, standard deviation (SD), median, 25th percentile, 75th percentile, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, will be provided. Denominators for percentages will generally be based on the set of subjects with at least 1 assessment at the time point or at least 1 assessment during the time interval being summarized.

All summaries will be descriptive; no statistical hypothesis testing is planned.

Unless otherwise noted, summaries will present BRV overall, which will include all subjects exposed to BRV during the study.

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

3.2 Analysis time points

3.2.1 First and last dose of BRV

Unless otherwise noted, all references to the first dose of BRV in this SAP refer to the first dose of BRV during N01379 (ie, not the first dose of BRV from the previous study in which subjects participated in prior to N01379). Unless otherwise noted, all references to the last known dose of BRV in this SAP refer to the last dose of BRV taken across any study periods (ie, not necessarily the last dose of BRV during the Evaluation Period).

3.2.2 Relative day

Relative day will be calculated with Day 1 representing the day of first dose of BRV, the previous day is Day -1 and each day prior to that is Day -2, Day -3, etc. Subsequent relative days to Day 1 will be Day 2, Day 3, etc. For days after the last dose of BRV, relative day will be calculated as the current date minus the date of last dose of BRV and including a '+' to denote post treatment days (eg, the day after the last dose of BRV will be Day +1). Relative day will not be calculated for partial or missing dates.

3.2.3 Study Entry Visit

The study Entry Visit (EV) corresponds to assessments performed at the time of entry into N01379. Subjects will not have any interruption in study drug dosing during the transition to N01379. Selected assessments from the following visits from the previous study will be summarized at EV:

Study	Visit (Time Point)
N01258	Visit 7 (at Week 2)
N01358	Visit 7 (at Week 20)

The following assessments are to be performed for all subjects at the above time points: laboratory parameters, vital signs, and ECGs; the results for these assessments will be summarized at EV. For study N01258, the following selected assessments will be used for summary at EV for laboratory parameters, vital signs, and ECGs

Assessment	Visit (Time Point)
Laboratory	Laboratory assessment done on AM at Visit 7
Vital signs	60 minutes after IV dose on AM at Visit 7
ECGs	12 hours after IV dose on AM at Visit 7

Body weight is not recorded at Visit 1 for N01379. The body weight recorded at the above study visits for the previous studies will be summarized for EV.

3.2.4 Study periods

The Baseline Period for N01379 corresponds to the Baseline Period of the previous studies, and is defined for seizure outcomes and direct cost parameters. The Baseline Period is defined as study days on or after the date of Visit 1 and prior to the date of Visit 2 for N01258 and study days on or after the date of Visit 1 and prior to the date of Visit 3 for N01358.

The study is divided into 3 periods: Evaluation Period, Down-Titration Period, and Post-Treatment Period. A subject is classified as "discontinued" if the subject has a termination case report form (CRF) or has an early discontinuation visit (EDV). A subject is classified as "completed" if this subject completes the full extent of the study as defined in the protocol at database lock.

A "discontinued" subject can be potentially slotted into the 3 periods of the study. The following algorithms will be used to slot the subject appropriately into the Evaluation Period, Down-Titration Period, and Post-Treatment Period.

- For Evaluation Period, the start date is the date of first dose of BRV, and the following algorithm is used to determine the end date:
    - If the subject enters the Down-Titration Period, then the date of EDV is the end date;
    - If the subject does not enter the Down-Titration Period but meets 1 of the following criteria, the Evaluation Period ends on date of last dose of BRV:
        - Without an EDV but having a termination CRF,
        - With an EDV and having a termination CRF,
        - With an EDV and the date of EDV prior to the database lock date and having no termination CRF.

- A subject is considered entering Down-Titration Period only if the subject has an EDV and at least 1 dose of study drug after the date of EDV, the start date of Down-Titration Period is set as 1 day after the date of EDV, and the Down-Titration Period ends on date of last dose of BRV. A subject without an EDV but having a termination CRF or with an EDV but without any dosing of study drug after the EDV will not have the Down-Titration Period, and no artificial Down-Titration Period will be created for analysis.
- A subject is considered entering the Post-Treatment Period if the subject has at least 1 contact (scheduled visit, unscheduled visit, or telephone contact) after the date of last dose of BRV. The Post-Treatment Period starts 1 day after date of last dose of BRV irrespective of entering the Down-Titration Period, and there is no end date.

A "completed" subject can potentially have Evaluation Period, Down-Titration Period, and Post-Treatment Period. At the time of study termination by the Sponsor, subjects will discontinue the study drug following the down titration process or will be converted without titration to commercial BRV where available; alternatively, subjects may be initiated without down-titration in a managed access program, named patient program, compassionate use program, or similar type of access program as allowed per country specific requirements in addition to legal and regulatory guidelines.

3.2.5 Monthly time intervals

A month is defined as 30 days and time intervals based on monthly durations are defined as a multiple of 30 days (eg, 12 months is defined as 360 days). The following definitions of 3-month and 6-month intervals are based on 30-day months where the date of first dose of BRV is Day 1:

Interval	Duration Definition
Months 1-3	Days 1-90
Months 4-6	Days 91-180
Months 7-9	Days 181-270
Months 10-12	Days 271-360
Months 1-6	Days 1-180
Months 7-12	Days 181-360
Months 13-18	Days 361-540
Months 19-24	Days 541-720

Subsequent 3- and 6-month intervals are defined in a similar manner.

Six-month intervals are defined for the evaluation of direct and indirect cost parameters. Statistical summaries for direct and indirect cost parameters will only present results through the first 2 years of treatment. Three-month intervals will be used for analysis of efficacy outcomes and AEs.

For the analysis of efficacy outcomes, a subject is included in the analysis for a 3-month interval if the end date is on or after the *last day* of the 3-month interval and the subject diary was completed for at least 1 day during the 3-month interval.

For the analysis of AEs, a subject is included in the analysis for a 3-month interval if the end date is on or after the *first day* of the 3-month interval.

3.2.6 Last Value on BRV Treatment

Last Value for QOLIE-31-P, HADS, and socio-professional data is the last assessment strictly after the date of first dose of BRV and up to and including the YEV at the end of the second year and any EDVs for subjects who did not complete through the YEV at the end of the second year.

Last Value for clinical laboratory parameters, vital signs, and ECGs is the last available result obtained after the first dose of BRV and prior to or on the date of last dose of BRV. All scheduled and unscheduled assessments within this time period will be considered. Last Value will be determined separately for each laboratory parameter for hematology, chemistry, urinalysis, and endocrinology assessments.

3.2.7 Exposure duration and exposure duration cohorts

At the final analysis, the overall duration of exposure (or On Treatment Period) will be calculated as the date of last dose of BRV minus the date of first dose of BRV plus 1 day.

Each subject will be classified into one or more of the following exposure duration cohorts based on the duration of BRV exposure as calculated above:

All subjects	≥1 day
≥3 months	≥90 days
≥6 months	≥180 days
≥12 months	≥360 days

This categorization will continue in 6-month increments past 12 months up to a time point that will be determined based on cumulative exposure at the time of the database lock.

3.2.8 Study visit cohorts

Study visit cohorts are defined for summaries of QOLIE-31-P and HADS. Six-month, 12-month, 18-month, and 24-month cohorts are defined. Subjects will be classified into a study visit cohort if they attend the scheduled visit at the time point defined by the cohort. For example, subjects will be included in the 18-month study visit cohort if they attend the scheduled visit at 18 months (ie, FEV at Month 18). Subjects may be classified in more than 1 cohort. Generally, subjects included in a cohort for a later visit will be included in all earlier study visit cohorts (eg, 6-month and 12-month study visit cohorts for subjects in the 18-month study visit cohort), although this may not be the case in the event of a missed visit or if an unscheduled visit is conducted in lieu of a scheduled visit.

3.3 Definition of Baseline Values

Baseline for all study outcomes will be based on baseline from the previous studies. For assessments performed at scheduled and unscheduled visits, Baseline will generally be the last result obtained or prior to the randomization visit of the previous study. Baseline will be defined separately for each hematology, blood chemistry, urinalysis, and endocrinology parameter.

Baseline for the evaluation of seizure frequency and seizure days will be calculated from the core study seizure diary based on the rules defined in Section 3.8.1.

3.4 Protocol deviations

The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined separately in the Specification of Protocol Deviations document. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all subjects.

3.5 Analysis populations

3.5.1 Safety Population

The Safety Population will consist of all subjects who took at least 1 dose of study drug.

Summaries of demographics and baseline characteristics, medical history, AEDs, non-AEDs, HADS, study drug exposure, and safety outcomes will be provided for the Safety Population.

3.5.2 Efficacy populations

Efficacy Populations will consist of all subjects who took at least 1 dose of study drug and have at least 1 seizure diary day during the Evaluation Period. Separate Efficacy Populations are defined for subjects with focal epilepsy from N01358 and N01258 and subjects with generalized epilepsy from N01258.

A subject will be excluded from the Efficacy Analysis Set for POS or PGS if either they did not receive at least 1 dose of BRV, or the clinical database indicates that the daily seizure diary was not completed for any days on or after the first dose of BRV and on or prior to the end date of the Evaluation Period (see Section 8). Subjects were assigned to a POS population or a PGS population in the previous study, based on diagnosis or medical history.

Seizure outcomes will be summarized for either the Efficacy Population for POS of the Efficacy Population for PGS. Summaries of epilepsy history and QOLIE-31-P will be provided for the Efficacy Populations for both POS and PGS.

3.6 Treatment Assignment and Treatment Groups

This is an uncontrolled study in which all subjects receive BRV in doses that are optimally adjusted for each subject. Generally, statistical summaries will present all subjects combined as a single treatment arm unless otherwise indicated.

3.7 Coding dictionaries

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Reference List (WHO-DRL). Prior and concomitant medical procedures will not be coded.

3.8 Definitions of study-specific derived variables

3.8.1 Calculation of seizure frequency/days

3.8.1.1 Initial seizure data processing

Each seizure code in the clinical database will be reported as 1 of the following codes based on the 1981 International League Against Epilepsy (ILAE) classification: I, IA, IA1, IA2, IA3, IA4, IB, IB1, IB2, IC, II, IIA, IIB, IIC, IID, IIE, IIF, or III. Seizures identified as type III seizures will be reviewed prior to database lock to ensure that such seizures were not misclassified.

With regard to cluster seizures, investigator sites are to report the number of cluster episodes rather than reporting the estimated number of individual seizures. Therefore, no imputation will be applied for the seizure counts corresponding to reports of cluster seizures.

3.8.1.2 Calculation of adjusted seizure frequency

The following derivations apply only to subjects with Partial Onset Seizures.

Baseline POS frequency for seizure types I, IA, IB, IC, and for all seizure types (I+II+III) will be obtained from the Baseline Period of the previous double-blind study.

The total number of seizures for seizure types I, IA, IB, and IC and the total number of seizures for all seizure types (I+II+III) will be calculated overall, by 3-month time intervals, and over the cohort interval for each exposure duration cohort.

All seizure diary during evaluation period will be considered for these calculations.

Twenty-eight day adjusted seizure frequency for seizure types I, IA, IB, and IC, and for all seizure types (I+II+III) will be calculated overall, within each 3-month time interval, and over each exposure duration cohort interval by dividing the total number of seizures for each seizure type by the number of days for which the diary was completed overall, within each 3-month interval, and within each exposure duration cohort interval, and multiplying the resulting value by 28.

3.8.1.3 Calculation of adjusted seizure days

The following derivations apply only to subjects with Primary Generalized Seizures, based on the 1981 ILAE classification, Primary Generalized Seizures include the generalized seizure types and unclassified seizure types.

Baseline seizure days for seizure types II, IIA through IIF, and for all seizure types (I+II+III) will be obtained from the Baseline Period of the previous study.

The total number of seizure days for seizure types II, IIA through IIF, and the total number of seizure days for all seizure types (I+II+III) will be calculated overall, by 3 month time intervals, and over the cohort interval for each exposure duration cohort. The same seizure diary data defined in the Section 3.8.1.2 for POS frequency will be considered.

Twenty-eight day adjusted seizure days for seizure types II, IIA through IIF, and for all seizure types (I+II+III) will be calculated overall, within each 3-month time interval, and over each exposure duration cohort interval by dividing the total number of seizure days for each seizure type by the number of days for which the diary was completed overall (ie, over the periods defined in the Section 3.8.1.2), within each 3-month interval, and within each exposure duration cohort interval, and multiplying the resulting value by 28.

3.8.2 QOLIE-31-P

The QOLIE-31-P is an adaptation of the original QOLIE-31 (Cramer et al, 1998). The QOLIE-31-P includes 30 items grouped into 7 multi-item subscales (seizure worry [5 items], overall quality of life [2 items], emotional well-being [5 items], energy/fatigue [4 items], cognitive functioning [6 items], medication effects [3 items], and social function [5 items]) and a health status item. The QOLIE-31-P total score, subscale scores, and health status item score are calculated according to the scoring algorithm described below, with scores ranging from 0 to 100 and higher scores indicating better functioning. In addition to these 31 items, the QOLIE-31-P includes 7 items assessing the degree of "distress" associated with the topic of each subscale (ie, distress items) and 1 item asking about the relative importance of each subscale topic (ie, prioritization item).

Subscale Scores

As a first step to calculating the subscale scores, the individual responses for the 30 subscale items are rescaled to a 0 to 100 scale with higher scores reflecting better functioning; the rescaled values for each item are defined in Section 13.1. Each subscale score is then calculated by summing the rescaled responses for that subscale and dividing by the number of items without a missing response. A subscale score will be calculated only if at least 50% of the items within the subscale are present.

Total Score

Total score is calculated as a weighted sum of the subscale scores based on the weighting in Section 13.1. Total score will be missing if at least 1 subscale score is missing. Total score will range from 0 to 100 with a higher score reflecting better functioning.

Health Status Item

Responses for the health status item is a multiple of 10 ranging from 0 to 100 with a higher score corresponding to a better health status. The health status item response is analyzed without rescaling.

Distress Items

Each subscale includes 1 distress item. The response for each distress item is an integer ranging from 1 to 5. The response for each distress item will be converted to a 0 to 100 scale (ie, 0, 25, 50, 75, and 100) with a higher score corresponding to greater distress.

Prioritization Item

The response for each subscale for the prioritization item is an integer ranging from 1 to 7. The prioritization ranking is analyzed without rescaling.

3.8.3 HADS

The HADS assessment consists of 14 items that are each scored on a 4-point scale ranging from 0 to 3, with a higher score corresponding to worse anxiety or depression. The depression and anxiety scores will be calculated by summing the scores for the items corresponding to each subscale, as described in the Hospital Anxiety and Depression Scale Manual (Snaith and Zigmond, 1994): the depression score is calculated as the sum of all even-numbered items; the anxiety score is calculated as the sum of all odd-numbered items. Scores for each subscale range from 0 to 21, with higher scores corresponding to a greater level of anxiety or depression.

Missing items will be replaced by the mean of non missing items from the same subscale when calculating the above, provided at least 50% of the items (ie, at least 4 of 7 items) within the subscale are present. A subscale score will not be calculated if more than 50% of the items are missing within a subscale. This rule applies separately to the subscale scores for anxiety and depression; for example, it may be possible to calculate the depression score in cases where the anxiety score is not calculated due to non response.

3.9 Subject site transfers

Subjects may have transferred from one site to another through the course of participation in the study. Subjects that transferred from one site to another site, for whatever reason, have generally retained their subject number. However, in some cases, the subject number changed. When this is true, the most recently assigned subject number will be used for analyses and subject data listings. A record of any change in subject numbers will be presented in the Section 13.2.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

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

4.2 Handling of dropouts or missing data

Seizure frequency (subjects with POS) and seizure days (subjects with PGS) will be calculated over non missing diary days during each study period or time interval as described in Section 3.2.4 and Section 3.2.5; diary days for which seizure data were not obtained will not be considered in the calculation of seizure frequency or seizure days. Because the evaluation of efficacy is not the primary objective of this study, and because this is an uncontrolled study in a variable setting, which allows individualized optimization of dosing

of BRV and concomitant AEDs, no summaries assessing the impact of missing seizure diary days are planned.

For subjects who prematurely discontinue during the Evaluation Period, the calculation of POS frequency and PGS seizure days will be based on available seizure diary while the subject was receiving BRV. The presence of such dropouts may influence the evaluation of the long-term outcomes for subjects who either do not discontinue or do not discontinue early in the study. Therefore, as described below, selected summaries will be produced by exposure duration cohorts to allow an assessment of long-term outcomes without the potentially confounding influence of earlier discontinuations.

4.3 Interim analyses and data monitoring

Interim summaries were produced to support regulatory submissions for marketing authorization while this study is ongoing. There are no statistical concerns with such interim assessments for this study design.

4.4 Multicenter studies

Efficacy and safety outcomes will not be assessed for individual investigator sites due to the low expected number for enrollment within each investigator site.

4.5 Multiple comparisons/multiplicity

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

4.6 Use of an "Efficacy Subset" of subjects

All subjects who receive at least 1 dose of study drug and have at least 1 diary record during the Evaluation Period will be included in efficacy summaries. No additional efficacy subsets are defined for this study.

4.7 Active-control studies intended to show equivalence

This section is not applicable for this study.

4.8 Examination of subgroups

Selected summaries will be provided for the following subgroups as specified within each of the following sections:

- Two mappings of countries to regions are defined, 1 based on the classification requested by Food and Drug Administration (FDA), and 1 based on the regional classification for the CHMP (Committee for Medicinal Products for Human Use).

Countries will be mapped to geographic regions as follows for the FDA:

Geographic Region (FDA)	Country
North America	Canada, United States, Puerto Rico
Latin America	Brazil, Mexico
Western Europe	Austria, Belgium, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Réunion, Spain, Sweden, United Kingdom, Switzerland
Eastern Europe	Bulgaria, Czech Republic, Estonia, Latvia, Hungary, Lithuania, Poland, Romania, Russia, Serbia and Montenegro, Turkey, Ukraine
Asia/Pacific/Other	Australia, Hong Kong, India, Israel, Japan, Singapore, South Africa, Republic of Korea, Taiwan, Tunisia

Countries will be mapped to geographic regions as follows for the CHMP:

Geographic Region (CHMP)	Country
North America	Canada, United States, Puerto Rico
Latin America	Brazil, Mexico
Europe (European Union [EU] member states) *	Austria, Belgium, Bulgaria, Czech Republic, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Réunion, Romania, Spain, Sweden, United Kingdom
Europe (non-EU member states)	Russia, Serbia and Montenegro, Switzerland, Turkey, Ukraine
Asia/Pacific/Other	Australia, Hong Kong, India, Israel, Japan, Singapore, South Africa, Republic of Korea, Taiwan, Tunisia

* EU member states plus Norway.

- Seizure type (Partial Onset Seizures, Primary Generalized Seizures)
- Randomized treatment in the previous study (placebo [PBO], BRV) (TEAEs only)

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

Due to differences in data format across studies, in order to facilitate summary of subject disposition, the reasons for discontinuation for individual studies will be collapsed as follows for summaries:

LTFU Category	CRF Reason
ADVERSE EVENT	ADVERSE EVENT
LACK OF EFFICACY	LACK OF EFFICACY
	LOSS OF EFFICACY
LOST TO FOLLOW-UP	LOST TO FOLLOW-UP
SUBJECT CHOICE	CONSENT WITHDRAWN
	WITHDRAWAL OF CONSENT FOR PERSONAL REASONS NOT RELATED TO AES
	WITHDRAWAL OF CONSENT FOR PERSONAL REASONS NOT RELATED TO AES OR LACK OF EFFICACY
OTHER	PROTOCOL VIOLATION
	OTHER REASON
	OTHER
MISSING	If subject discontinued the study and the termination CRF is not available

Only 1 primary reason for discontinuation should have been reported. In the event that more than 1 reason is specified in the clinical database, both reasons will be summarized and a footnote will be added to the summary table to indicate that at least 1 subject is counted for multiple reasons for discontinuation.

An overall summary of disposition will be provided for all enrolled subjects (ie, all subjects who signed informed consent). The following will be summarized:

- The number of subjects in the Safety Analysis Set
- The number of subjects excluded from the Safety Analysis Set
- The number of subjects completed the study
- The number of subjects discontinued from the study, including the reason for discontinuation. If subject discontinued the study and the termination CRF is not available, the reason for discontinuation will be reported as “MISSING”.

Additionally, an overall summary of disposition will present the following for subjects in the Safety Analysis Set:

- The number of subjects completed the study
- The overall number of subjects discontinued and the number of subjects discontinued by primary reason for discontinuation. If subject discontinued the study and the termination CRF is not available, the reason for discontinuation will be reported as “MISSING”.

Overall subject disposition will also be summarized by geographic region and seizure type for the Safety Analysis Set.

The number of subjects within each geographic region and the number of subjects within each seizure type will be summarized for the Safety Analysis Set.

Kaplan-Meier estimates of the percentage of subjects completing 3, 6, 12, 24, 36, 48, and 60 months of treatment with BRV will be provided. This analysis will be based on the duration of exposure to BRV as defined in Section 3.2.7. Subjects who have permanently discontinued will be analyzed as events on the last day of treatment with study drug; subjects who complete the study will be censored on the last day of treatment with study drug.

The date of first subject in (date of earliest Visit 1), date of last subject out (date of last scheduled or unscheduled visit), number of enrolled subjects, and the number of subjects in each analysis set or seizure type will be summarized overall and by investigator site. Subjects who transferred sites will be summarized according to their original site.

5.2 Protocol Deviations

The number and percentage of subjects with at least 1 important protocol deviation will be summarized overall and by category of protocol deviation for the Safety Analysis Set.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

Demographics summaries will be based on demographic data from follow-up studies for subjects who enrolled in a follow-up study that collected demographic data. Otherwise, demographics summaries will be based on demographic data collected in the previous double-blind study.

Age, age category (<17, 17 to <65, and ≥65 years), gender, racial group and overall racial group (see below), body weight (kg), height (cm), body mass index (BMI) (kg/m^2), and BMI category (<18.5, 18.5 to <25, 25 to <30, 30 to <40, ≥40) will be summarized for the Safety Analysis Set. Demographic data will be summarized overall and by subgroup for seizure type and geographic region.

Racial group was not collected in a consistent manner across studies. For this reason, racial group will be collapsed as follows for statistical summaries:

Category	CRF Racial Group
American Indian/Alaskan Native	American Indian/Alaskan Native
Asian	Asian, Asian/Pacific Islander, Indian/Pakistani
Black	Black, African-American
Native Hawaiian or Other Pacific Islander	Native Hawaiian or Other Pacific Islander
White	White, Caucasian, Hispanic
Other/Mixed	Other, Other/Mixed, Mixed Race

moreover, the overall racial group will be collapsed as follows for statistical summaries:

Category	Racial Group from Previous Study
White	White, Caucasian, Hispanic

Black	Black, African-American
Asian	Asian, Native Hawaiian or Other Pacific Islander, Asian/Pacific Islander, Indian/Pakistani
Other	American Indian/Alaskan Native, Other, Other/Mixed

All subjects should be classified into one of the above categories.

Racial group, ethnicity (Hispanic or Latino, Not Hispanic or Latino), and racial subgroup (Indian/Pakistani, Japanese, Other) were not collected in a consistent manner across all studies; these variables will be provided in subject data listings if available in the clinical data from the previous study but will not be summarized.

6.2 Medical and procedure history

6.2.1 Medical history diseases

The summary of medical history will be based on the medical history at the time of entry into the previous study.

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

6.2.2 Procedure history and concomitant procedures

Medical procedures are not coded and will only be provided in subject data listings.

6.3 History of epilepsy

All of the following are summarized using data collected at the time of entry into the previous studies or from the Baseline Period of the previous studies.

6.3.1 Etiology of epilepsy

The number and percentage of subjects with each type of etiology as specified on the CRF (genetic, congenital, etc) from the previous studies will be summarized for the Efficacy Analysis Sets for POS and PGS. A subject will be counted as having a particular etiology if that etiology was either confirmed or suspected based on the investigator's assessment. Etiology of epilepsy is not collected for subjects from previous study N01258.

6.3.2 Epileptic seizure profile

The number and percentage of subjects experiencing each seizure type at any time prior to study entry will be summarized for the Efficacy Analysis Sets for POS and PGS. The following seizure types will be summarized: I, IA, IA1 through IA4, IB, IB1, IB2, IC, II, IIA through IIF, III. A subject with a history of a more specific seizure type will be counted in all higher levels of seizure types (eg, a subject with a history of IB1 seizures will be counted for seizure types I, IB, and IB1).

6.3.3 Classification of epileptic syndrome

The number and percentage of subjects with each epileptic syndrome will be summarized for the Efficacy Analysis Sets for POS and PGS. This summary will include the number and percentage of subjects within the following categories: localization-related epilepsy; idiopathic, symptomatic, and cryptogenic localization-related epilepsy; generalized epilepsy; and idiopathic, symptomatic, and cryptogenic generalized epilepsy.

6.3.4 Focus localization

The number and percentage of subjects with each category of focus localization (unknown, frontal, temporal, parietal, occipital) will be summarized for the Efficacy Analysis Set for POS. Subjects may be counted in more than 1 category of focus localization. A category for no available data will be included in the summary to account for subjects from N01258 since focus localization was not obtained for subjects from N01258. Percentages will still be out of the full POS Efficacy Analysis Set, including subjects from N01258.

6.3.5 History of epileptic seizures

History of epileptic seizures, including the number and percentage of subjects with a history of status epilepticus and quantitative summaries of epilepsy duration, age at onset of first seizure, and percent of life with epilepsy, will be summarized for the Efficacy Populations for POS and PGS.

6.3.6 Seizure types experienced during baseline of the prior study

The number and percentage of subjects experiencing each seizure type during the Baseline Period will be summarized for the Efficacy Analysis Sets for POS and PGS based on the Baseline seizure diary data from the previous studies. The following seizure types will be summarized: I, IA, IB, IC, II, and IIA through IIF, and III as well.

Subjects will be counted for all higher levels of seizure type categories corresponding to the seizure types or seizure sub-types reported on the CRF.

6.4 Medications

Medications recorded on the Concomitant Medications CRF and the Concomitant Medications (AEDs only) CRF will be classified as either AEDs or non-AEDs based on the preferred drug name search criteria, which are documented outside of the SAP.

- The medication is not an AED if it does not meet the search criteria based on preferred drug name, regardless of which CRF is used for reporting the medication. However, further review will be performed for medications that are recorded on the Concomitant Medications (AEDs only) CRF but are not included in the AEDs search criteria;
- For non-benzodiazepine medications, if the medication meets the search criteria for an AED based on preferred drug name, then the medication will be classified as an AED regardless of indication and regardless of which CRF the medication is recorded on;

- For benzodiazepines (identified using the search criteria), if the benzodiazepine is recorded on the Concomitant Medications (AEDs only) CRF, then the benzodiazepine will be classified as an AED;
- For benzodiazepines (identified using the search criteria), if the benzodiazepine is recorded on the Concomitant Medications CRFs, then the benzodiazepine will not be classified as an AED.

After medications are classified as AEDs or non-AEDs, the standard date imputation algorithms for start and stop date of the medication and first dose and last dose of BRV in the study will be applied. If an AED was taken at any time during dosing with BRV, then the AED is classified as a concomitant AED.

6.4.1 Non-AEDs taken at study entry

The number and percentage of subjects taking non-AED medications at study entry for the previous double-blind study will be summarized by WHO-DRL primary therapeutic group (Anatomic Therapeutic Class [ATC] level 1), therapeutic subgroup (ATC level 2), and preferred drug name for the Safety Analysis Set.

6.4.2 Number of previous AEDs

The number and percentage of subjects taking an AED prior to entry into the previous study will be summarized by WHO-DRL preferred drug name for the POS and PGS Efficacy Analysis Sets based on the following categorization: 0-1 AEDs, 2-4 AEDs, and ≥5 AEDs.

6.4.3 History of previous AED use

The number and percentage of subjects who had taken at least 1 AED prior to entry into the previous study will be summarized overall and by WHO-DRL preferred drug name for the POS and PGS Efficacy Analysis Sets.

6.4.4 AEDs taken at study entry

The number and percentage of subjects taking AEDs at study entry for the previous double-blind study will be summarized by WHO-DRL preferred drug name for the POS and PGS Efficacy Analysis Sets.

6.4.5 Concomitant AEDs

A concomitant AED is an AED which was taken during administration of BRV in N01379 study, regardless of the start and stop date of the AED. The number and percentage of subjects taking concomitant AEDs will be summarized by WHO-DRL preferred drug name for the POS and PGS Efficacy Analysis Sets.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Study drug compliance will not be assessed due to the complexities associated with the calculation and interpretation of study drug compliance for this study. Study drug dosing will be provided in subject data listings.

8 EFFICACY ANALYSES

In general, all study outcomes based on seizure frequency will be summarized for the Efficacy Analysis Set for POS and all study outcomes based on seizure days will be summarized for the Efficacy Analysis Set for PGS.

The derivations of 28-day adjusted seizure frequency and 28-day adjusted seizure days are described in detail in Section 3.8.1.2 and Section 3.8.1.3, respectively.

All summaries of efficacy data are descriptive; no statistical testing will be performed.

Because study N01258 was a safety study, subjects were not required to meet seizure frequency requirements during the Baseline Period, and the Baseline Period was short (ie, 7 days). Therefore, subjects from N01258, whether subjects with POS or PGS, will be excluded from efficacy summaries in the variables of percent reduction in POS frequency and responder rates, but subjects from N01258 will be included in the efficacy summary in the variable of the percent of subjects continuously seizure free as this variable is independent from baseline.

8.1 Statistical analyses of secondary efficacy variables

The following variables are summarized for the Efficacy Population for POS.

8.1.1 Partial onset seizure frequency

Twenty-eight day adjusted POS frequency will be summarized with quantitative descriptive statistics for all subjects for the Baseline Period, the On Treatment Period, and by 3-month time intervals over the On Treatment Period. The summary over the On Treatment Period will include all subjects in the POS Efficacy Analysis Set. Similar summaries will be provided for the full cohort interval and by 3-month time intervals for each exposure duration cohort.

8.1.2 Percent reduction in POS frequency

Percent reduction in POS frequency from Baseline to the On Treatment Period will be calculated as follows, where On Treatment Period Frequency is the 28-day adjusted POS frequency during On Treatment Period and Baseline Period Frequency is the 28-day adjusted POS frequency during the Baseline Period of the previous study.

$$\%\,\text{Reduction} = 100 \times \frac{\text{Baseline Period Frequency} - \text{On Treatment Period Frequency}}{\text{Baseline Period Frequency}}$$

A similar calculation applies to each 3-month time interval over the On Treatment Period and for the cohort interval for each exposure duration cohort.

Percent reduction from Baseline for POS frequency will be summarized with quantitative descriptive statistics for the On Treatment Period, and by 3-month time intervals over the On Treatment Period. The summary over the On Treatment Period will include all subjects in the POS Efficacy Analysis Set. Similar summaries will be provided for the full cohort interval

and by 3-month time intervals for each exposure duration cohort. Percent reduction from Baseline for POS frequency will be summarized in the same manner by geographic region.

8.1.3 Responder outcome for POS frequency

Responders over the On Treatment Period are defined as subjects with a 50% or greater reduction in 28-day adjusted POS frequency from Baseline to the On Treatment Period. A similar calculation applies to each 3-month time interval over the On Treatment Period and for the cohort interval for each exposure duration cohort.

The number and percentage of responders for POS frequency will be summarized for the On Treatment Period, and by 3-month time intervals over the On Treatment Period. The summary over the On Treatment Period will include all subjects in the POS Efficacy Analysis Set. Similar summaries will be provided over the full cohort interval and by 3-month time intervals for each exposure duration cohort. Responder rates for POS frequency will be summarized in the same manner by geographic region.

8.2 Analysis of other efficacy variables

8.2.1 Subjects with partial onset seizures

All of the following variables are summarized for the Efficacy Population for POS.

8.2.1.1 Specified Month seizure freedom

The numbers and percentages of subjects who are seizure free for all seizure types for any continuous 6-month interval, 12-month interval, 18-month interval, and so forth will be summarized overall for the period of time that subjects are being treated with BRV and by Exposure Duration Cohort. The overall summary will present the number and percentage of subjects who reported no seizures for the specified duration of seizure freedom and the seizure diary was completed for at least 90% of days within the seizure-free interval. Subjects whose duration of BRV treatment was less than the specified duration of seizure freedom will be considered failures for seizure-freedom. Summaries by exposure duration cohort will present the number and percentage of subjects who reported no seizures for the specified duration of seizure freedom at any time during the cohort interval (eg, through the end of Month 6 for the 6-month cohort) and the seizure diary was completed for at least 90% of days within the seizure-free interval. Percentages are relative to the number of subjects within each Exposure Duration Cohort.

A subject is seizure free for a 6-month interval if the subject did not report any seizures in the 6-month interval and the seizure diary was completed for at least 90% of days within the seizure-free interval. The percentage of days for which seizure diary was completed within a given 6-month interval will be calculated as follows based on a 30-day month:

$$\%\ \text{of days diary was done} = 100 \times \left[\frac{180 - \text{number of days diary was not done in the interval}}{180}\right]$$

A similar calculation applies for 12-month seizure freedom based on 360 days, 18-month seizure freedom based on 540 days, and so forth.

8.2.2 Subjects with Primary Generalized Seizures

The following variables are summarized for the Efficacy Population for PGS.

8.2.2.1 All type seizure days

Twenty-eight day adjusted all other type seizure days will be summarized with quantitative descriptive statistics in the same manner as 28-day adjusted POS frequency.

8.2.2.2 Percent reduction in all type seizure days

Percent reduction in all other type seizure days from Baseline will be calculated in the same manner as percent reduction in POS frequency as described in Section 8.1.2. This variable will be summarized in the same manner as percent reduction in POS frequency.

8.2.2.3 Responder outcome for all type seizure days

Responder outcome for all other type seizure days will be derived in a manner similar to the responder outcome for POS frequency as described in Section 8.1.3. This variable will be summarized in the same manner as 50% responder outcome for POS frequency.

8.2.2.4 Specified month seizure freedom

Specified month seizure freedom for subjects in the PGS Efficacy Analysis Set will be derived in a manner similar to specified month seizure freedom for the POS Efficacy Analysis Set as described in Section 8.2.1.1. This variable will be summarized in the same manner as specified month seizure freedom for subjects in the POS Efficacy Analysis Set.

8.2.3 QOLIE-31-P

The scoring algorithm for QOLIE-31-P is described in Section 13.1. QOLIE-31-P will be summarized for the POS and PGS Efficacy Analysis Sets. QOLIE-31-P is assessed at the following time points for subjects with POS and subjects with PGS: Month 2, Month 6, Month 12, Month 18, and Month 24. QOLIE-31-P is also assessed at EDVs for subjects who discontinue prior to the YEV at the end of the second year.

Observed values for QOLIE-31-P total score and subscale scores for Seizure Worry, Daily Activities/Social Function, Energy/Fatigue, Emotional Well-Being, Cognitive Function, Medication Effects, Overall Quality of Life, and Health Status will be summarized for Months 2, 6, 12, 18, and 24 and Last Value for the Efficacy Analysis Sets for POS and PGS. For each time point, summary statistics will be presented for the baseline scores for subjects with a change from baseline at the time point in addition to summaries of the observed values and changes from baseline at each time point. Only subjects with a non-missing change from baseline will be summarized at each time point.

The above scores will be also summarized for the 6-Month, 12-Month, 18-Month, and 24-Month Study Visit Cohorts, including summaries of the baseline scores for all subjects within each study visit cohort and summaries of observed values and changes from baseline for each time point for each study visit cohort.

Similar summaries will be provided for QOLIE-31-P distress items Seizure Worry, Daily Activities/Social Function, Energy/Fatigue, Emotional Well-Being, Cognitive Function, Medication Effects, Overall Quality of Life. Only subjects with a non-missing change from baseline will be summarized at that time point.

The rankings of prioritization items (Seizure Worry, Daily Activities/Social Function, Energy/Fatigue, Emotional Well-Being, Cognitive Function, Medication Effects, and Overall Quality of Life) will be summarized at the same time points as above and for all subjects and by study visit cohort as defined above. Changes from baseline will not be summarized, and only the numbers of subjects and sample means will be presented

8.2.4 Direct cost parameters

Direct costs data are collected based on concurrent medical procedures, healthcare provider consultations not foreseen by protocol, hospital stays, and ER visits

Direct cost parameters will not be summarized but will be provided in subject data listings.

8.2.5 Indirect cost parameters

The number of school or working days lost will not be summarized but will be provided in subject data listings.

8.2.6 Socio-professional data

Socio-professional data are collected at the following time points: Month 12 and Month 24. Socio-professional data are also collected at EDVs for subjects who discontinue prior to the YEV at the end of the second year. These additional assessments will not be summarized but will be provided in subject data listings.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

Plasma samples to analyze BRV or concomitant AED plasma concentrations are not collected. As such, this section is not applicable.

10 IMMUNOLOGICAL PROCEDURES

This section is not applicable for this study.

11 SAFETY ANALYSES

Safety is assessed with AEs, laboratory tests (blood chemistry, hematology, urinalysis, endocrinology, and pregnancy test), vital signs, body weight, ECGs, physical examination, and neurological examination. Summary tables will be provided for AEs; blood chemistry, hematology, urinalysis, and endocrinology; vital signs; body weight; and ECGs. No summary tables will be provided for pregnancy testing, physical examination, and neurological examination.

All safety summaries will be based on the Safety Population.

11.1 Extent of exposure

A daily dose will be calculated for each study day from the day of first dose of BRV to the day of last dose of BRV for the purposes of calculating modal dose. Daily dose will be calculated as the sum of the AM and PM dose for each day.

Modal daily doses will be calculated across all study days on or after the day of first dose of BRV and up to and including the day of last dose of BRV. Modal daily dose is the most frequently taken daily dose during this period. In the event of a tie, the modal dose will be set to the lower of the tied doses. Modal daily dose will be categorized as follows:

Category	Definition
5 mg/day	<20mg/day
20mg/day	≥20mg/day to <50mg/day
50mg/day	≥50mg/day to <100mg/day
100mg/day	≥100mg/day to <150mg/day
150mg/day	≥150mg/day to <200mg/day
200mg/day	≥200mg/day

Subject years of exposure will be calculated by summing the exposure duration in days for all subjects being summarized, and dividing the resulting value by 365.25.

Subject years of exposure will be presented overall and by modal dose for the Safety Analysis Set. The subject years of exposure presented by modal dose will be the total subject years of exposure of subjects with that modal dose.

The number and percentage of subjects exposed to BRV will be summarized overall and by modal dose category. The number and percentage of subjects in each Exposure Duration Cohort (≥3 months, ≥6 months, ≥12 months, and so forth) will be summarized.

The number and percentage of subjects within each modal dose category will be summarized for each Exposure Duration Cohorts; percentages will be relative to the total number of subjects in each Exposure Duration Cohort.

In addition to the overall summaries of the above, the above will also be summarized by subgroup for region (North America, Europe [EU member states], Europe [non-EU member states], Asia/Pacific/Other), and seizure type (Partial Onset Seizures, Primary Generalized Seizures).

11.2 Adverse events

11.2.1 Definition of treatment-emergent AE

AEs will be classified as either pre-study or treatment-emergent. Pre-study AEs are defined as AEs which had onset prior to the date of the first dose of BRV. TEAEs are defined as AEs that had onset on or after the day of first BRV dose. AEs with an incomplete onset date will be classified as TEAEs if the month and year of onset (when only the month and year are specified) is the same as the month and year of the first BRV dose or the year of onset (when only year is specified) is the same as the year of first BRV dose.

11.2.2 General summaries of TEAEs

Pre-treatment AEs will be provided in a subject data listing; no summaries of pre treatment AEs are planned.

An overall summary of AEs will provide the overall number of TEAEs and the numbers and percentages of subjects with at least 1 TEAE, with a TEAE that led to permanent discontinuation of study drug, with a drug-related TEAE, with a severe TEAE, with a treatment-emergent SAE, and with a drug-related treatment-emergent SAE. The number and percentage of subjects who died will also be summarized. This summary will be provided for all subjects in the Safety Analysis Set and also by subgroup for geographic region and seizure type.

The following summaries of TEAEs will be provided by MedDRA SOC and PT. All summaries are for the combined Evaluation, Down-Titration, and Post-Treatment Periods unless otherwise indicated.

Overall Incidence Summaries

- Incidence of TEAEs
- Incidence of TEAEs by 3-month time interval
- Incidence of TEAEs by study period (Evaluation, Down-Titration, Post-Treatment)
- Incidence of TEAEs for TEAEs occurring in at least 5% of subjects
- Incidence of TEAEs by 3-month time intervals for TEAEs occurring in at least 5% of subjects overall
- Incidence of non-serious TEAEs occurring in at least 5% of subjects

The incidence of TEAEs occurring in at least 5% of subjects will be summarized overall as noted above and also by subgroup for geographic region, seizure type, and randomized treatment from the previous double-blind study.

A subject is included in a 3-month interval if the subject was receiving BRV at any time during that interval based on their duration of exposure to BRV (eg, a subject with exposure for 91 days is included in the time interval for Months 1-3 and Months 4-6). Summaries of AEs by 3-month intervals will include all subjects who are classified into each time interval as defined above. TEAEs which had onset prior to or on the date of the last dose of BRV) are included in summaries by 3-month time intervals.

Maximum Intensity and Causality

- Incidence of TEAEs by maximum intensity
- Incidence of drug-related TEAEs

Serious Adverse Events

- Incidence of treatment-emergent SAEs

Discontinuations due to TEAE

- Incidence of TEAEs leading to permanent discontinuation of study drug

TEAEs of interest

AEs of interest will be identified based on MedDRA search criteria, which are documented outside of the SAP. The following summaries will be provided for AEs of interest:

- Incidence of TEAEs of interest
- Incidence of TEAEs of interest by 3-month time interval

For the summary by maximum intensity, each subject will be counted at most once per SOC or PT according to the maximum intensity of all AEs within that SOC or PT. Severe intensity will be assumed for AEs for which intensity is not specified.

Drug-related AEs are AEs for which the relationship to study drug is specified as Related or AEs for which relationship is not specified.

11.3 Clinical laboratory evaluations

Clinical laboratory parameters (blood chemistry, hematology, urinalysis, and endocrinology) are assessed at all FEVs, YEVs, EDVs, and at FV and may also be assessed at Unscheduled Visits.

11.3.1 Hematology and blood chemistry parameters

Observed values for each planned hematology and blood chemistry parameter will be summarized for Baseline, Study Entry, and each scheduled visit during the Evaluation Period for which laboratory parameters were assessed, Last Value, EDV, and FV. Change from Baseline will be summarized for all post-Baseline time points including EV. Only laboratory parameters planned per protocol will be summarized; results for laboratory parameters not planned per the protocol will only be provided in subject data listings.

The number and percentage of subjects with an on-treatment potentially clinically significant treatment-emergent (PCST) value, PCST low value, and PCST high value will be summarized. This summary will consider all assessments after the first dose of BRV and prior to or on the date of the last dose of BRV. Percentages will be relative to the number of subjects with an on-treatment assessment.

Additionally, the number and percentage of subjects with a PCST value, PCST low value, and PCST high value will be summarized for Baseline, Study Entry, each visit during the Evaluation Period for which laboratory parameters were scheduled to be assessed, EDV, Last Value, and FV. Percentages for each parameter and time point will be relative to the number of subjects with a value at that time point.

PCST criteria (Sections 13.3 and 13.3.2) are based on FDA Division of Neuropharmacologic Drug Products guidelines with some UCB-defined additions.

Creatinine clearance, when available from the central laboratory, will be provided in subject data listings only and will not be summarized.

11.3.2 Macroscopic urinalysis

Quantitative urinalysis parameters will be summarized in the same manner as hematology and blood chemistry parameters. Response categories are negative, 1+, 2+, and 3+ for the qualitative urinalysis parameters occult blood, leukocytes, glucose, protein, and ketones and negative and positive for nitrates. Outcome values for these parameters are mapped to the levels Negative, 1+, 2+, and 3+ as follows for purposes of summary tables and the determination of PCST:

Category	Definition
Negative	"Negative", "NEGATIVE", or other outcomes that clearly reflect a negative finding
1+	"1+", "+" , "Trace", "TRACE", or other outcomes that clearly reflect trace amount
2+	"2+" or "++"
3+	"3+", "+++", or other outcomes that clearly reflect the data above 3+ (eg, "4+", "5+" etc) or more than 4 plus signs (eg, "++++", "+++++"etc)

For qualitative urinalysis parameters (occult blood, leukocytes, glucose, protein, ketones, and nitrates), the number and percentage of subjects with each response category will be summarized for Baseline, Study Entry, each scheduled visit during the Evaluation Period for which urinalysis parameters were scheduled to be assessed, Last Value, EDV, and FV. Percentages for each parameter will be relative to the number of subjects with a result at each time point.

For occult blood, leukocytes, glucose, protein, ketones, and nitrates, the number and percentage of subjects with an on-treatment PCST value, PCST low value, and PCST high value will be summarized. This summary will consider all assessments after the first dose of BRV and prior to or on the date of the last dose of BRV. Percentages will be relative to the number of subjects with an on-treatment assessment.

Additionally, for occult blood, leukocytes, glucose, protein, ketones, and nitrates, the number and percentage of subjects with a PCST value, PCST low value, and PCST high value will be summarized for Baseline, Study Entry, each visit during the Evaluation Period for which laboratory parameters were scheduled to be assessed, EDV, Last Value, and FV. Percentages for each parameter and time point will be relative to the number of subjects with a value at that time point.

11.3.3 Endocrinology parameters

Endocrinology parameters will be summarized in the same manner as hematology and blood chemistry parameters.

Observed values for each planned endocrinology parameter will be summarized for Baseline, EV, each scheduled visit during the Evaluation Period for which the parameter was assessed,

Last Value, EDV, and FV. Change from Baseline will be summarized for all post-Baseline time points including EV.

The number and percentage of subjects with an on-treatment potentially clinically significant treatment-emergent (PCST) value, PCST low value, and PCST high value will be summarized for each planned endocrinology parameter. All scheduled and unscheduled endocrinology assessments after the day of first dose of BRV and prior to or on the day of last dose of BRV across all study periods will be considered. Percentages for each parameter will be relative to the number of subjects with at least 1 result within this time period.

Additionally, the number and percentage of subjects with PCST value, PCST low value, and PCST high value will be summarized for endocrinology parameters for EV, each visit during the Evaluation Period for which endocrinology parameters were scheduled to be assessed, EDV, and Last Value. Percentages for each parameter and time point will be relative to the number of subjects with a result at that time point.

11.3.4 Microscopic urinalysis

In microscopic urinalysis, a small sample of urine is centrifuged to remove the liquid. The sediment is then examined under a microscope. The number and percentage of subjects with a microscopic urinalysis finding will be summarized. All scheduled and unscheduled assessments after the day of first dose of BRV will be considered. Percentages will be relative to the number of subjects with at least 1 on-treatment microscopic assessment.

Additionally, the number and percentage of subjects with a microscopic finding will be summarized for Baseline, Study Entry, and each visit during the Evaluation Period for which urinalysis parameters were scheduled to be assessed, Last Value, EDV, and FV. Percentages for each parameter and time point will be relative to the number of subjects who had a microscopic assessment at that time point.

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

11.4.1 Vital signs

Vital signs are assessed at all FEVs, MEVs, YEVs, EDVs, and at FV, and may also be assessed at Unscheduled Visits. Body weight is assessed at all FEVs, YEVs, EDVs, and at FV, and may also be assessed at Unscheduled Visits.

Observed values for SBP, DBP, pulse rate, and body weight will be summarized for Baseline, Study Entry, each visit during the Evaluation Period for which vital signs or body weight were assessed, EDV, Last Value, and FV. Changes from Baseline for SBP, DBP, pulse rate, and body weight will be summarized for all post-Baseline time points.

The number and percentage of subjects with an on-treatment PCST value, PCST low value, and PCST high value will be summarized for SBP, DBP, pulse rate, and body weight. This summary will consider all assessments after the first dose of BRV and prior to or on the date of the last dose of BRV. Percentages will be relative to the number of subjects with an on-treatment assessment.

Additionally, the number and percentage of subjects with a PCST value, PCST low value, and PCST high value will be summarized for the above parameters for Study Entry, each visit during the Evaluation Period for which vital signs or body weight were scheduled to be assessed, Last Value, EDV, and FV. Percentages will be relative to the number of subjects with a value at each time point.

PCST criteria (Section 13.3.3) are based on FDA Division of Neuropharmacologic Drug Products guidelines with some UCB-defined additions.

11.4.2 Electrocardiograms

ECGs are assessed at all YEVs, EDVs, and at FV, and may also be assessed at Unscheduled Visits.

The number and percentage of subjects with no abnormality, an abnormal but not clinically significant finding, and a clinically significant finding will be summarized overall. This summary will consider all assessments after the first dose of BRV and prior to or on the date of the last dose of BRV. Percentages will be relative to the number of subjects with an on-treatment assessment.

Additionally, the number and percentage of subjects with no abnormality, an abnormal but not clinically significant finding, and a clinically significant finding will be summarized for Baseline, Study Entry, each visit during the Evaluation Period for which an ECG is scheduled to be performed, Last Value, EDV, and FV. Percentages will be relative to the number of subjects with an ECG assessment at each time point. Subjects are counted at most once at each time point based on the worst observed outcome across all abnormalities reported at that time point.

A subject number listing will be provided that identifies subjects with a clinically significant finding after the first dose of BRV for each type of ECG abnormality.

11.4.3 Physical examination

Physical examination findings were not recorded on the CRF; no summaries of physical examination findings are planned.

11.4.4 Neurological examination

A listing of visits where the neurological examination was not done will be; no summaries of neurological examination findings are planned.

11.4.5 HADS

The scoring algorithm for HADS is described in Section 3.8.3.

HADS is assessed at the following time points: Month 2, Month 6, Month 12, Month 18, and Month 24. HADS is also assessed at EDVs for subjects who discontinue prior to the YEV at the end of the second year.

Observed values for HADS depression and anxiety scores will be summarized for Baseline and Last Value for the Safety Analysis Set. Additionally, observed values will be

summarized for Baseline and by visit for each study visit cohort. Change from Baseline will be summarized at each visit during the Evaluation Period.

For summaries of observed values at each time point, only subjects with a change from Baseline value at that time point will be summarized. Additionally, the mean and SD for each Baseline score will be provided at each post-Baseline time point for subjects included in the summary of change from Baseline.

11.4.6 Columbia-Suicide Severity Rating Scale

With global amendment 2 to the protocol, the Columbia-Suicide Severity Rating Scale (C-SSRS) was added as an assessment at all study visits. Specific rules are provided to the study sites with regard to the identification of AEs or SAEs based on the outcome of this assessment. Because clinical events of interest will be recorded as AEs or SAEs, no study variable is defined for this assessment and no analyses are planned for the C-SSRS within the context of this study. However, subject data listings of the data for the C-SSRS will be provided. Additional listings will be provided for the subset of subjects with suicidal ideation and the subset of subject with actual suicide attempts.

Suicide ideation includes a "yes" answer to any 1 of the 5 suicidal ideation questions:

- [redacted]

Suicide attempt includes response of a "yes" answer to any 1 of the 3 suicide attempt questions:

- [redacted]

12 REFERENCES

Cramer JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann B. Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. Epilepsia 1998, 39(1): 81-88.

Snaith RP, Zigmond AS. The hospital anxiety and depression scale manual. London; nferNelson Publishing Company Ltd. 1994.

13 APPENDICES

13.1 QOLIE-31-P total and subscale score calculations

The following outlines the calculation of the subscale scores for the QOLIE-31-P. The rescaled responses are provided for each item. The subscale scores are calculated by summing the rescaled responses for that subscale and dividing by the number of items with a non-missing response. Note that the divisors shown assume that all items for each subscale have a response; the divisor will differ if there are missing responses. A subscale score will be calculated only if at least 50% of the items within the subscale are present.

	Response							Final Score
Scale/Item Numbers	**1**	**2**	**3**	**4**	**5**	**6**	**Subtotal**	**0-100 point scale**
Seizure Worry								
30.	0	20	40	60	80	100	_____	
31.	0	33.3	66.7	100	—	—	_____	
32.	0	50	100		—	—	_____	
33.	0	33.3	66.7	100	—	—	_____	
34.	100	75	50	25	0		_____	
						TOTAL :	_____	÷ 5 = _____
Overall Quality of Life								
1.	Multiply each response by 10						_____	
36.	100	75	50	25	0	—	_____	
						TOTAL :	_____	÷ 2 = _____
Emotional Well-Being								
7.	0	20	40	60	80	100	_____	
8.	0	20	40	60	80	100	_____	
9.	100	80	60	40	20	0	_____	
10.	0	20	40	60	80	100	_____	
11.	100	80	60	40	20	0	_____	
						TOTAL :	_____	÷ 5 = _____
Energy/Fatigue								
2.	100	80	60	40	20	0	_____	
3.	100	80	60	40	20	0	_____	
4.	0	20	40	60	80	100	_____	
5.	0	20	40	60	80	100	_____	
						TOTAL :	_____	÷ 4 = _____
Cognitive Functioning								
19.	0	20	40	60	80	100	_____	
20.	0	33.3	66.7	100	—	—	_____	
21.	0	20	40	60	80	100	_____	
22.	0	20	40	60	80	100	_____	

23.	0	20	40	60	80	100	_____	
24.	100	75	50	25	0	—	_____	
						TOTAL :	_____	÷ 6 = _____
Medication Effects								
28.	0	33.3	66.7	100	—	—	_____	
26.	100	75	50	25	0	—	_____	
27.	100	75	50	25	0	—	_____	
						TOTAL :	_____	÷ 3 = _____
Daily Activities/Social Functioning								
13.	0	20	40	60	80	100	_____	
14.	0	25	50	75	100	—	_____	
15.	0	25	50	75	100	—	_____	
16.	100	75	50	25	0	—	_____	
17.	100	75	50	25	0	—	_____	
						TOTAL :	_____	÷ 5 = _____

Total score is calculated as a weighted sum of the subscale scores based on the weighting shown below. Total score will be missing if at least 1 subscale score is missing. Total score will range from 0 to 100 with a higher score reflecting better functioning.

QOLIE-31-P Scale		Final Scale Score		Weight		Subtotal
Seizure worry	(a)	_____	×	0.08	=	_____
Overall quality of life	(b)	_____	×	0.14	=	_____
Emotional well-being	(c)	_____	×	0.15	=	_____
Energy/fatigue	(d)	_____	×	0.12	=	_____
Cognitive functioning	(e)	_____	×	0.27	=	_____
Medication effects	(f)	_____	×	0.03	=	_____
Daily activities/Social functioning	(g)	_____	×	0.21	=	_____
TOTAL SCORE: Sum subtotals (a) through (g)						_____

13.2 Subject site transfers

CRF#	Initial Site Subject #	Transfer Site Subject #
[redacted]		

13.3 PCST Criteria

13.3.1 Hematology parameters

Parameter	UCB Conventional Units	SI Units	CF
Hematocrit	For 1 m to < 6 m: ≤ 25% For 6 m to < 2 y: ≤ 27% For 2 y to < 4 y: ≤ 29% For 4 y to < 12 y: ≤ 32% (Female[F]); ≤ 35% (Male [M]) For ≥ 12 y: ≤ 32% (F); ≤ 37% (M)	For 1 m to < 6 m: ≤ 0.25 For 6 m to < 2 y: ≤ 0.27 For 2 y to < 4 y: ≤ 0.29 For 4 y to < 12 y: ≤ 0.32 (F); ≤ 0.35 (M) For ≥ 12 y: ≤ 0.32 (F); ≤ 0.37 (M)	0.01
Hemoglobin	For < 6 m: ≤ 9.7 g/dL For 6 m to < 12 y: ≤ 10.0 g/dL For ≥ 12 y: ≤ 9.5 g/dL (F); ≤ 11.5 g/dL (M)	For < 6 m: ≤ 97 g/L For 6 m to < 12 y: ≤ 100 g/L For ≥ 12 y: ≤ 95 g/L (F); ≤ 115 g/L (M)	10
Platelets	≤ 75 x 10^9/L or ≥ 700 x 10^9/L	≤ 75 x 10^9/L or ≥ 700 x 10^9/L	Not applicable (N/A)
White Blood Cell (WBC)	For < 17 y: ≤ 3.0 x 10^9/L or ≥ 20 x 10^9/L; For ≥ 17 y: ≤ 2.8 x 10^9/L or ≥ 16 x 10^9/L;	For < 17 y: ≤ 3.0 x 10^9/L or ≥ 20 x 10^9/L; For ≥ 17 y: ≤ 2.8 x 10^9/L or ≥ 16 x 10^9/L;	N/A
Red Blood Cell (RBC)	For < 17 y: ≤ 2.5 x 10^6/mm^3 For ≥ 17 y: ≤ 2.0 x 10^6/mm^3 (F); ≤ 2.5 x 10^6/mm^3 (M)	For < 17 y: ≤ 2.5 x 10^{12}/L For ≥ 17 y: ≤ 2.0 x 10^{12}/L (F); ≤ 2.5 x 10^{12}/L (M)	1
Eosinophils	≥ 10% or ≥ 0.7 x 10^9/L	≥ 0.10 or ≥ 0.7 x 10^9/L	0.01 or N/A
Neutrophils	≤ 15% or ≤ 1.0 x 10^9/L	≤ 0.15 or ≤ 1.0 x 10^9/L	0.01 or N/A
Basophils	≥ 5% or ≥ 0.4 x 10^9/L	≥ 0.05 or ≥ 0.4 x 10^9/L	0.01 or N/A
Monocytes	≥ 20% or ≥ 1.5 x 10^9/L	≥ 0.20 or ≥ 1.5 x 10^9/L	0.01 or N/A
Lymphocytes	For 1 m to < 6 m: ≤ 22% or ≥ 80% ≤ 2.1 x 10^9/L or ≥ 8.5 x 10^9/L For 6 m to < 2 y: ≤ 15% or ≥ 80% ≤ 1.5 x 10^9/L or ≥7.5 x 10^9/L For 2 y to < 12 y: ≤ 12% or ≥ 80% ≤ 1.0 x 10^9/L or ≥ 7.5 x 10^9/L For 12 y to < 17 y: ≤ 10% or ≥ 80% ≤ 0.5 x 10^9/L or ≥ 5.5 x 10^9/L For ≥ 17 y: ≤ 10% or ≥ 80% ≤ 0.5 x 10^9/L or ≥ 4.5 x 10^9/L	For 1 m to < 6 m: ≤ 0.22 or ≥ 0.80 ≤ 2.1 x 10^9/L or ≥ 8.5 x 10^9/L For 6 m to < 2 y: ≤ 0.15 or ≥ 0.80 ≤ 1.5 x 10^9/L or ≥7.5 x 10^9/L For 2 y to < 12 y: ≤ 0.12 or ≥ 0.80 ≤ 1.0 x 10^9/L or ≥ 7.5 x 10^9/L For 12 y to < 17 y: ≤ 0.10 or ≥ 0.80 ≤ 0.5 x 10^9/L or ≥ 5.5 x 10^9/L For ≥ 17 y: ≤ 0.10 or ≥ 0.80 ≤ 0.5 x 10^9/L or ≥ 4.5 x 10^9/L	0.01 N/A 0.01 N/A 0.01 N/A 0.01 N/A 0.01 N/A

13.3.2 Hematology parameters

Parameter	UCB Conventional Units	SI Units	CF
AST (SGOT)	≥ 3 times of ULN	≥ 3 times of ULN	N/A
ALT (SGPT)	≥ 3 times of ULN	≥ 3 times of ULN	N/A
ALP	For < 17 y: ≥ 2 times of ULN, if normal range adjusted to the age range; For ≥ 17 y: ≥ 3 times of ULN	For < 17 y: ≥ 2 times of ULN, if normal range adjusted to the age range; For ≥ 17 y: ≥ 3 times of ULN	N/A
GGT	≥ 3 times of ULN, if baseline value ≤ 3 times of ULN	≥ 3 times of ULN, if baseline value ≤ 3 times of ULN	N/A
BUN	≥ 30 mg/dL	≥ 10.71 mmol/L	0.357
Urea	≥ 60 mg/dL	≥ 10.02 mmol/L	0.167
Creatinine	For < 17 y: ≥ 1.5 mg/dL; For ≥ 17 y: ≥ 2.0 mg/dL	For < 17 y: ≥ 132.6 umol/L; For ≥ 17 y: ≥ 176.8 umol/L	88.4
Creatinine clearance (calc)	For < 12 y: < 70 ml/min (Schwartz)[a] For ≥ 12 y: < 70 ml/min (Cockroft)[b]	For < 12 y: < 70 ml/min (Schwartz)[a] For ≥ 12 y: < 70 ml/min (Cockroft)[b]	N/A
Total bilirubin	≥ 2.0 mg/dL	≥ 34.2 umol/L	17.1
Glucose	≤ 50 mg/dL or ≥ 180 mg/dL	≤ 2.775 mmol/L or ≥ 9.99 mmol/L	0.0555
Total Protein	For ≥ 1 m to < 6 m: ≤ 3.6 g/dL or ≥ 7.8 g/dL For ≥ 6 m to < 17 y: ≤ 4.7 g/dL or ≥ 9.5 g/dL For ≥ 17 y: ≤ 4.5 g/dL or ≥ 9.0 g/dL	For ≥ 1 m to < 6 m: ≤ 36 g/L or ≥ 78 g/L For ≥ 6 m to < 17 y: ≤ 47 g/L or ≥ 95 g/L For ≥ 17 y: ≤ 45 g/L or ≥ 90 g/L	10
Albumin	For < 17 y: ≤ 2.4 g/dL or ≥ 6.5 g/dL For ≥ 17 y: ≤ 2.5 g/dL or ≥ 6.5 g/dL	For < 17 y: ≤ 24 g/L or ≥ 65 g/L For ≥ 17 y: ≤ 25 g/L or ≥ 65 g/L	10
Globulin	For < 17 y: ≤ 1.2 g/dL or ≥ 5.0 g/dL For ≥ 17 y: ≤ 1.5 g/dL or ≥ 5.0 g/dL	For < 17 y: ≤ 12 g/L or ≥ 50 g/L For ≥ 17 y: ≤ 15 g/L or ≥ 50 g/L	10
Sodium	For < 17 y: ≤ 120 mEq/L or ≥ 155 mEq/L For ≥ 17 y: ≤ 115 mEq/L or ≥ 155 mEq/L	For < 17 y: ≤ 120 mmol/L or ≥ 155 mmol/L For ≥ 17 y: ≤ 115 mmol/L or ≥ 155 mmol/L	1
Potassium	For < 17 y: ≤ 3.0 mEq/L or ≥ 6.5 mEq/L For ≥ 17 y: ≤ 3.0 mEq/L or ≥ 5.8 mEq/L	For < 17 y: ≤ 3.0 mmol/L or ≥ 6.5 mmol/L For ≥ 17 y: ≤ 3.0 mmol/L or ≥ 5.8 mmol/L	1
Calcium	For < 17 y: ≤ 7 mg/dL or ≥ 11.5 mg/dL For ≥ 17 y: ≤ 7 mg/dL or ≥ 15.5 mg/dL	For < 17 y: ≤ 1.75 mmol/L or ≥ 2.875 mmol/L For ≥ 17 y: ≤ 1.75 mmol/L or ≥ 3.875 mmol/L	0.25

Uric Acid	For < 12 y: ≥ 8 mg/dL For ≥ 12 y: ≥ 8 mg/dL (F); ≥ 9.5 mg/dL (M)	For < 12 y: ≥ 475.84 umol/L For ≥ 12 y: ≥ 475.84 umol/L (F); ≥ 565.06 umol/L (M)	59.48
Cholesterol	≥ 300 mg/dL	≥ 7.77 mmol/L	0.0259
HDL	≤ 25 mg/dL	≤ 0.65 mmol/L	0.0259
LDL	≥ 200 mg/dL	≥ 5.18 mmol/L	0.0259
Triglycerides	≥ 300 mg/dL	≥ 3.42 mmol/L	0.0114

[a] Schwartz equation (patients <12): Cr Cl ml/min = [Height (cm) * 0.55] / serum creatinine
[b] Cockroft equation (patients ≥12): Male: Cr Cl ml/min = [(140-age) x body weight (kg)] / (72 x serum creatinine),
Female: Cr Cl ml/min = [(140-age) x body weight (kg)] / (72 x serum creatinine)] x 0.85

ALT=alanine aminotransferase; ALP=Alkaline phosphatase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CR CL=creatinine clearance; GGT=Gamma-glutamyl transpeptidase; HDL=High-density lipoprotein; LDL=low-density lipoprotein; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; ULN=Upper Limit of Normal.

13.3.3 Urinalysis

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

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

13.3.4 Vital signs and body weight

Pulse rate	For 1 m to < 12 m: ≤ 110 bpm and a decrease of ≥ 20 bpm from baseline or ≥ 180 bpm and an increase of ≥ 20 bpm from baseline For 12 m to < 3 y: ≤ 90 bpm and a decrease of ≥ 20 bpm from baseline or ≥ 150 bpm and an increase of ≥ 20 bpm from baseline For 3 y to < 12 y: ≤ 65 bpm and a decrease of ≥ 20 bpm from baseline or ≥ 130 bpm and an increase of ≥ 20 bpm from baseline For 12 y to < 17 y: ≤ 60 bpm and a decrease of ≥ 20 bpm from baseline or ≥ 120 bpm and an increase of ≥ 20 bpm from baseline For ≥ 17 y: ≤ 50 bpm and a decrease of ≥ 30 bpm from baseline or ≥ 120 bpm and an increase of ≥ 30 bpm from baseline

bpm=Beats per minute.

Systolic blood pressure	For 1 m to < 12 m: < 60 mmHg and a decrease of > 20 mmHg from baseline or > 110 mmHg and an increase of > 30 mmHg from baseline For 12 m to < 6 y: < 70 mmHg and a decrease of > 20 mmHg from baseline or > 120 mmHg and an increase of > 30 mmHg from baseline For 6 y to < 13 y: < 70 mmHg and a decrease of > 20 mmHg from baseline or > 130 mmHg and an increase of > 30 mmHg from baseline For 13 y and < 17 y: < 90 mmHg and a decrease of > 20 mmHg from baseline or > 140 mmHg and an increase of > 30 mmHg from baseline For ≥ 17 y: < 90 mmHg and a decrease of > 30 mmHg from baseline or > 180 mmHg and an increase of > 40 mmHg from baseline
Diastolic blood pressure	For 1 m to < 12 m: < 40 mmHg and a decrease of > 15 mmHg from baseline or > 60 mmHg and an increase of > 20 mmHg from baseline For 12 m to < 6 y: < 45 mmHg and a decrease of > 15 mmHg from baseline or > 80 mmHg and an increase of > 20 mmHg from baseline For 6 y to < 13 y: < 50 mmHg and a decrease of > 15 mmHg from baseline or > 85 mmHg and an increase of > 20 mmHg from baseline For 13 y to < 17 y: < 55 mmHg and a decrease of > 20 mmHg from baseline or > 90 mmHg and an increase of > 30 mmHg from baseline For ≥ 17 y: < 50 mmHg and a decrease of > 20 mmHg from baseline or > 105 mmHg and an increase of > 30 mmHg from baseline
Weight	For < 17 y: < 3% or > 97% of the normal body weight growth curve ranges for the age at date of weight assessment [(a)] and gender; For ≥ 17 y: change of ≥ 7% of baseline weight

[(a)] Once the subject reaches 17 years of age use the body curve criteria of a 17 year old regardless of their age in the study.

14 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN

Rational for the amendment

The primary purpose for the amendment is (1) remove rules and definitions based on data cutoffs for interim analyses; (2) remove the summary analysis for direct cost parameter and indirect cost parameters, and as well as Socio-professional data.

Change #1 (global)

Removed all rules and definitions based on data cutoffs for interim analyses throughout SAP.

Change #2

Section 8.2.4 Direct cost parameters, Section 8.2.5 Indirect cost parameters, Section 8.2.6 Socio-professional data

Removed all direct/indirect cost parameters and socio-professional data summary analysis.

Change #3

Removed signature page. Using e-signature approval process through Source Submission.

Approval Signatures

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Document Approvals	
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