STATISTICAL ANALYSIS PLAN

Study: N01266

Product: Brivaracetam

Open-Label, Single-Arm, Multicenter, Long-Term Study to Evaluate Safety and Efficacy of Brivaracetam Used as Adjunctive Treatment in Pediatric Subjects with Epilepsy

SAP/Amendment Number	Date
Final SAP	24 Dec 2013
Final SAP - Amendment 1	15 Oct 2019
Final SAP - Amendment 2	21 Oct 2020
Final SAP - Amendment 3	22 Jun 2021
Final SAP - Amendment 4	22 Sep 2021

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ADF	average daily frequency
AE	adverse event
AED	antiepileptic drugs
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate aminotransferase
Bayley-III®	Bayley Scales of Infant and Toddler Development ®, Third Edition
BRIEF®	Behavior Rating Inventory of Executive Function®
BRIEF®-P	Behavior Rating Inventory of Executive Function®-Preschool Version
BRV	Brivaracetam
CBCL	Child Behavior Checklist
CS	Clinical Significance
DBL	database lock
DBP	diastolic blood pressure
DE	directly enrolled
DEM	data evaluation meeting
DRC	daily record card
DTV	Down-Titration Visit
ECG	electrocardiogram
eCRF	electronic case report form
EDV	Early Discontinuation Visit
EEG	electroencephalogram
ER	emergency room
EV	Entry Visit
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV	Full Evaluation Visit
FV	Final Visit
GEC	Global executive composite
GGT	gamma glutamyl transferase
HRQoL	health-related quality of life
ICH	International Conference on Harmonization

ILAE	International League Against Epilepsy
LTFU	long-term follow-up
MedDRA©	Medical Dictionary for Regulatory Activities©
MEV	Minimal Evaluation Visit
PCST	possibly clinically significant treatment-emergent
PedsQL	Pediatric Quality of Life Inventory
PGS	primary generalized seizure
PGS*	primary generalized seizure excluding typical absence seizures
POS	partial-onset seizure
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
ScrV	Screening Visit
SD	standard deviation
SS	Safety Set
SV	Safety Visit
UV	Unscheduled Visit
VNS	vagal nerve stimulation
TEAE	treatment-emergent adverse event
TV	Titration Visit
UNC	uncategorized
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 N01266. An additional subset of the analyses described in this SAP will be produced to support regulatory submissions for marketing authorization based on interim data.

The SAP is based on the following study documents:

- Final protocol, 10 Mar 2011
- Protocol Amendment 1, 26 Aug 2011
- Protocol Amendment 2, 09 Dec 2011
- Protocol Amendment 3, 26 Sep 2012
- Protocol Amendment 4, 10 Dec 2013
- Protocol Amendment 5, 14 Dec 2016
- Protocol Amendment 6, 06 Mar 2018
- Protocol Amendment 7, 18 Apr 2018
- Protocol Amendment 8, 25 Jun 2020

The structure and content of this SAP provides sufficient details to meet the requirements identified by the International Conference on Harmonization (ICH) and the Food and Drug Administration (FDA) (ICH Guidance on Statistical Principles for Clinical Trials [E9]).

2 PROTOCOL SUMMARY

This is a Phase 3, open-label, single-arm, multicenter, long-term study to evaluate the safety and efficacy of brivaracetam (BRV) in children with epilepsy. This study is designed for pediatric subjects ≥1 month to <17 years of age who have completed other pediatric BRV studies (herein referred to as "long-term follow-up" [LTFU] subjects) and for at least 100 subjects ≥4 years to <17 years of age with partial-onset seizure (POS) who had not previously enrolled in a pediatric BRV study (herein referred to as "directly enrolled (DE) subjects"), with a planned total enrollment of approximately 600 subjects.

The primary objective is to document the long-term safety and tolerability of BRV. The secondary objective is to assess the efficacy of BRV during long-term exposure. The other objectives are to explore direct cost parameters and to assess the effect of BRV 1) on behavior and cognition using the age-appropriate Achenbach Child Behavior Checklist (CBCL/1½-5 or CBCL/6-18) for LTFU subjects ≥18 months of age at Baseline of their initial BRV study (herein referred to as their "core study") and for all DE subjects, 2) on cognition using the Behavior Rating Inventory of Executive Function® (BRIEF®)/BRIEF®-Preschool Version (BRIEF®-P), and 3) on quality of life using the Pediatric Quality of Life Inventory™ (PedsQL™) for LTFU subjects ≥2 years of age at the Baseline of the core study and for all DE subjects. The Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®) will be used to assess LTFU subjects enrolled in English-speaking countries and in countries where a validated

translation is available and <18 months of age at Baseline of the core study; the Bayley-III will not be used to assess DE subjects since all are to be ≥4 years of age.

The LTFU subjects will enter directly into the Evaluation Period at the Entry Visit (EV) and will continue BRV treatment at the individualized dose they were receiving at the completion of their core study. Directly enrolled subjects will enter N01266 at the Screening Visit (ScrV) and then participate in up to 3 weeks of an Up-Titration Period. If a DE subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than 1mg/kg/day) for 7±2 days during the Up-Titration Period, the subject will attend the EV and enter the Evaluation Period on that dose.

BRV (tablet and oral solution) should be administered twice daily (bid) in 2 equally divided doses. All LTFU subjects must be able to tolerate the minimum dose specified in the core study to be eligible for entry into the Evaluation Period of N01266. All DE subjects must be able to tolerate at least 1mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266.

The maximum allowable BRV dose is 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day. Subjects will receive oral solution or tablets, as appropriate. With the exception of dose adjustments for BRV during the Up-Titration Period, which should be made in accordance with the protocol-specified guidelines, dose adjustments of BRV and any concomitant antiepileptic drugs (AEDs) are allowed at any time based on clinical judgment.

Subjects will receive BRV treatment in this study for at least 3 years, until approval of BRV has been obtained for pediatric subjects in their age range, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines, until subjects transition to another BRV study, or until the investigational product development in the related age range of the pediatric population is stopped by the Sponsor, whichever comes first.

For LTFU subjects, the EV is the first study visit. For DE subjects, the EV occurs after subjects have completed the ScrV and at least 1 Titration Visit (TV), and have maintained acceptable tolerability and seizure control on the same daily dose of BRV (no lower than the minimum specified dose) for 7±2 days of the Up-Titration Period. For subjects who continue in this study until it ends, the Evaluation Period will extend from the EV until the final evaluation visit (Final Visit, FV). For subjects who prematurely discontinue the study, the Evaluation Period will last from the EV until the Early Discontinuation Visit (EDV), followed by a maximum 4-week Down-Titration Period, a 2-week Safety (Drug-Free) Period, and a final Safety Visit (SV). Subjects already enrolled in N01266 may participate in EP0065 (an intravenous [iv] BRV study for pediatric subjects), if eligible, and then resume participation in N01266.

During the Evaluation Period, Minimal Evaluation Visits (MEVs) and Full Evaluation Visits (FEVs) will be performed alternatively every month during the first 3 months and every 3 months thereafter, with a Yearly Evaluation Visit (YEV) every 12 months.

Safety variables include adverse events (AEs), safety laboratory assessments (hematology, biochemistry including hepatic monitoring of alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin, and gamma-glutamyl transferase [GGT], and endocrinology for all subjects and urinalysis for subjects for whom sample collection is feasible), plasma concentrations of BRV and phenytoin (if applicable),

electrocardiograms (ECGs), vital signs, physical and neurological examinations, psychiatric and mental status, body weight, height, and head circumference.

All efficacy variables will be considered exploratory in nature. Seizure counts will be based on the daily record card (DRC) information or electroencephalograms (EEGs) and the disease characteristics of each subject.

Other variables include direct cost parameters (such as concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays) and the change in Achenbach CBCL (CBCL/1½-5 or CBCL/6-18), BRIEF-P/BRIEF, and PedsQL scores, and the change in Bayley-III scales for subjects enrolled in English-speaking countries and countries where a validated translation is available.

Up to 600 subjects may possibly enroll in this study. The number and location of sites will depend on those participating in core studies from which LTFU subjects will be enrolled, and those participating in direct enrollment. Sites of direct enrollment will include, but not be limited to, sites participating in core studies.

2.1 Study objectives

2.1.1 Primary objective

The primary objective is to document the long-term safety and tolerability of BRV.

2.1.2 Secondary objective

The secondary objective is to assess the efficacy of BRV during long-term exposure.

2.1.3 Other objectives

Other objectives include:

- To explore direct cost parameters
- To assess the effect of BRV on behavior using the Achenbach CBCL in subjects ≥18 months of age
- To explore the effect of BRV on cognition using the BRIEF-P/BRIEF in subjects ≥ 2 years of age
- To assess the effect of BRV on cognition using the Bayley-III in subjects <18 months of age (applicable only to LTFU subjects enrolled in English-speaking countries and countries, where a validated translation is available)
- To explore the effect of BRV on health-related quality of life (HRQoL) using the Pediatric Quality of Life Inventory (PedsQL) in subjects ≥ 2 years of age

2.2 Study variables

2.2.1 Primary variables

The primary variables include the following:

- Treatment-emergent AEs
- Treatment-emergent serious adverse events (SAEs)

2.2.2 Secondary variables

For subjects ≥2 years of age (based on DRC data):

- Absolute change in 28-days adjusted POS frequency from Baseline to the end of the Evaluation Period (subjects with POS only)
- Percent change in 28-days adjusted POS frequency from Baseline to the end of the Evaluation Period (subjects with POS only)
- 50% responder rate for total seizures (all types)

For subjects <2 years of age (based on EEG data [recorded at least 24 hours]) or subjects with typical absence seizures (based on EEG data):

- Absolute change in average daily frequency (ADF) of POS (subjects with POS only)
- Percent change in ADF of POS (subjects with POS only)
- 50% responder rate for total seizures (all types)

2.2.3 Other variables

For subjects ≥2 years of age (based on DRC data):

- Responder rate (the percentage of subjects who have a ≥50% reduction in seizure frequency per 28 days from Baseline for POS)
- Absolute change in seizure frequency (total seizures) per 28 days from Baseline to the end of the Evaluation Period
- Percent change in seizure frequency (total seizures) per 28 days from Baseline to the end of the Evaluation Period
- Seizure freedom over the Evaluation Period
- Proportion of seizure-free days over the Evaluation Period

For subjects <2 years of age or subjects with typical absence seizures based on DRC seizure counts:

- Seizure freedom rate over the Evaluation Period (all types) by visit and by time intervals (6 months, 12 months, etc.)
- Proportion of seizure-free days over the Evaluation Period (all types) and by time intervals (6 months, 12 months, etc.)
- Absolute worsening in ADF of total seizures (all types)
- Percent worsening in ADF of total seizure (all types)
- A descriptive summary of seizure frequency by visit based on the DRC data will be also provided for these subjects

In addition, for subjects <2 years of age (based on EEG data [recorded at least 24 hours]) or subjects with typical absence seizures (based on EEG data):

- Responder rate for total POS defined as the percentage of subjects with a ≥50% reduction in ADF of POS recorded on EEG
- Absolute change in ADF of total seizures (all types)
- Percent change in ADF of total seizures (all types)
- Seizure freedom (rate and proportion)
- Absolute worsening of other types of seizures
- Percent worsening of other types of seizures

For subjects with typical absence seizures:

- Number and type of non-absence seizures

For all subjects:

The other variables include the following:

- Physical examinations (including Tanner staging, if applicable depending on subject's development status)
- Neurological examinations
- Psychiatric and mental status
- Laboratory tests (hematology, biochemistry including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT, and endocrinology [follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, triiodothyronine, and tetraiodothyronine] for all subjects and urinalysis for subjects for whom sample collection is feasible)
- ECG
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight
- Height and head circumference
- Plasma concentrations of BRV and phenytoin (if applicable)
- Direct cost parameters: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays
- Change from Baseline as well as categorical shift from Baseline in the Achenbach CBCL score: the Achenbach CBCL/1½-5 for children from 1½ to 5 years old and the Achenbach CBCL/6-18 for children 6 years and older (age at initiation of study drug in N01266 or core study])
- Change from Baseline as well as categorical shift from Baseline in the BRIEF-P/BRIEF score for subjects ≥ 2 years of age (age at initiation of study drug in N01266 or core study)
- Change from core study Baseline in the Bayley-III scales for children <18 months of age at Baseline of the core study (applicable only to LTFU subjects enrolled in English-speaking countries and countries where a validated translation is available)

- Change from Baseline in PedsQL for subjects ≥ 2 years of age (age at initiation of study drug in N01266 or core study)

2.3 Study design and conduct

This is a Phase 3, open-label, single-arm, multicenter, long-term study to evaluate the safety and efficacy of BRV in children with epilepsy. This study is designed for pediatric subjects ≥ 1 month to < 17 years of age who have completed other pediatric BRV studies (LTFU subjects) and for at least 100 subjects ≥ 4 years to < 17 years of age with POS who had not previously enrolled in a pediatric BRV study (DE subjects) with a planned total enrollment of approximately 600 subjects.

2.3.1 Study design for DE subjects

The screening period comprises the screening visit (ScrV).

Directly enrolled subjects will begin receiving BRV in the Up-Titration Period at Titration Visit 1 (TV1) after all inclusion and exclusion criteria are met. The BRV dose will be titrated to optimize tolerability and seizure control. Subjects may enter the Evaluation Period after they have remained on the same daily dose (no lower than the minimum specified dose) for 7±2 days that, in the opinion of the Investigator, has demonstrated acceptable tolerability and seizure control. Up to 3 TVs may be needed before entry into the Evaluation Period.

Evaluation Period starts with the Entry Visit (EV) followed by Minimal Evaluation Visits (MEV), Full Evaluation Visits (FEV), Yearly Evaluation Visits (YEV), possibly Unscheduled Visits (UV) and Early Discontinuation Visits (EDV), if applicable. For more detailed information of visits scheduled, see Table 2–1

Table 2–1: Visit sequence

DE subjects		
	Visit	**Type of visit**
	ScrV	Screening
W1	TV1[a]	TV
W2	TV2[a]	TV
W3	TV3[a]	TV
All subjects		
First year follow-up		
M0	V1	EV[b]
M1	V2	MEV
M2	V3	FEV
M3	V4	MEV[c]
M4	-	-
M5	-	-

M6	V5	FEV
M7	-	-
M8	-	-
M9	V6	MEV[c]
M10	-	-
M11	-	-
Second and subsequent years follow-up[d]		
M12	V7	YEV
M15	V8	MEV
M18	V9	FEV
M21	V10	MEV
and every 3 months thereafter	V11, V12, etc.	YEV, MEV, etc.

BRV=brivaracetam; EV=Entry Visit; FEV=Full Evaluation Visit; LTFU=long-term follow-up; M=Month; MEV=Minimal Evaluation Visit; ScrV=Screening Visit; TV=Titration Visit; V=Visit; W=Week; YEV=Yearly Evaluation Visit

Note: Visits at W1, W2, W3, and M0 will occur 7±2 days after the previous visit; visits and M1, M2, and M3 will occur 30±7 days after the previous visit; visits at M6, M9, M12, M15, M18, M21 and every 3 months thereafter will occur 90±15 days after the previous visit.

"-" denotes that no visit is scheduled in that month.

[a] All DE subjects must participate in at least TV1, but may participate in fewer than 3 TVs as described in Section 7.2.1 of the protocol.

[b] For LTFU subjects, the EV is the final evaluation visit of the core study. For DE subjects, the EV represents the point of entry into the Evaluation Period.

[c] Hepatic monitoring tests only will be performed as described in Section 9.5.1 of the protocol.

[d] Subsequent years will follow the same visit schedule.

In case of early discontinuation, after the EDV, or for subjects who complete the study but do not continue BRV treatment, the Down-Titration Period starts with scheduled Down-Titration Visits (DTV). Dose will be down titrated by a maximum of half the dose every week for a maximum of 4 weeks until a dose of 1mg/kg/day is reached.

After 2 weeks free of study drug, the Safety Period, subjects will complete the Safety Visit (SV).

The study is defined to be completed if the study status on the study termination form is marked as completed. This indicates that all planned visits have taken place. Planned visits are dependent on whether a subject discontinues the study or not, and on whether a subject goes into another study or takes marketed drug after FV.

At each visit, the subject/parent(s)/legal representative(s) will receive a DRC, which has to be filled in daily by parent(s)/legal representative(s) or subject, if applicable, and returned at the next visit. No DRC will be dispensed at the SV or the FV.

The date and the number of epileptic seizures will be recorded on the DRC, as well as the type of seizure (according to individual description of seizures), occurrence of clusters, intake of concomitant AEDs, undesirable events with start and end dates, health care provider consultations not foreseen per protocol, and changes in concomitant medication, if applicable.

The written information will be discussed with the subject/parent(s)/legal representative(s) at each visit in order to ensure completeness and accuracy. As a result of the discussion, the Investigator will assess the seizures according to the International League Against Epilepsy (ILAE) codes and record the seizure types and frequency on the electronic case report form (eCRF); he/she will also confirm the presence of AEs (if applicable). Concomitant medication changes, health care provider consultations not foreseen per protocol, and AEs will be reported by the Investigator on the specific pages of the eCRF.

2.3.2 Study design for LTFU subjects

At the EV, the progress of DE subjects will become aligned with LTFU subjects. The LTFU subjects enter the study in Evaluation Period. The design afterwards is same as with DE, so please refer to Section 2.3.1 for more details.

2.3.3 Study duration per subject

Subject participation will extend from study entry for at least 3 years until approval of BRV has been obtained for pediatric subjects in their age range, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines, until subjects transition to another BRV study, or until the investigational product development in the related age range of the pediatric population is stopped by the Sponsor, whichever comes first.

Study entry is defined as the EV for LTFU subjects and the ScrV for DE subjects.

The end of the study is defined as the date of the last visit of the last subject in the study.

2.3.4 Planned number of subjects and sites

N01266 is planned for a total enrollment of approximately 600 subjects, including at least 100 eligible DE subjects ≥4 years to <17 years of age with POS.

2.4 Determination of sample size

No formal sample size calculation was performed for this study. Originally, up to 500 subjects might have possibly enrolled in this study. The original number was based upon the assumption that 90% of the subjects having completed a core study will rollover into the present study.

Planned enrollment now includes approximately 600 subjects, including at least 100 DE subjects, with no change in the assumption regarding core study completion.

3 DATA ANALYSIS CONSIDERATIONS

The statistical analysis details are addressed in following sections. Directly enrolled subjects, subjects from N01349, EP0065 and other core studies, if applicable, will be analyzed separately as well as pooled as an overall study population, no statistical comparison will be performed.

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, subject data listings and statistical output will be performed using SAS® Version 9.4 or higher. All tables and listings will use Courier New font size 9.

Descriptive statistics will be displayed to provide an overview of the study results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis. Unless otherwise noted, all percentages will be displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%. For continuous parameters, descriptive statistics will include number of subjects (n), mean, standard deviation (SD), median, minimum and maximum.

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

- "n" will be an integer,
- Mean, SD, median will use 1 additional decimal place compared to the original data,
- Minimum and maximum will have the same number of decimal places as the original value.

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

A complete set of listings containing all documented data and all calculated data (eg, change from Baseline) will be generated. Data collected during the Up-Titration Period for DE subjects will be summarized separately.

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 First and final dose of study drug

Unless otherwise noted, all references to the first dose of study drug in this SAP refer to the first dose of study drug during N01266 (i.e., not the first dose of study drug from the core study in which subjects participated prior to N01266 for LTFU subjects). Unless otherwise noted, all references to the final dose of study drug in this SAP refer to the final dose of study drug taken across all study periods (ie, the final dose of study drug across the Up-Titration, Evaluation, and Down-Titration Periods).

3.2.1.2 Relative day

Relative day will be calculated as follows:

- for days prior to the first dose of study drug: the current date minus the date of first dose of study drug
- for days on or after the day of first dose of study drug and prior to or on the day of last dose of study: the current date minus the date of first dose of study drug plus 1
- for days after the day of last dose of study drug: the current date minus the date of last dose of study drug with a leading "+"

Relative day will not be calculated for partial or missing dates.

For monthly time intervals, relative days referring to EV will be calculated as follows (EV relative days):

- for days prior to the first dose of study drug in Evaluation Period: the current date minus the date of EV

- for days on or after the day of first dose of study drug in Evaluation Period and prior to or on the day of last dose of study in Evaluation Period: the current date minus the date of EV plus 1
- for days after the day of last dose of study drug in Evaluation Period: the current date minus the date of last dose of study drug within Evaluation Period with a leading "+"

3.2.2 Summaries at Study Entry

Study Entry denotes when all assessments are collected prior to any BRV allocation in N01266. For DE subjects, assessments at ScrV will be presented. For LTFU patients selected measurements are collected at the final visit and screening of the respective core study. Subjects going through N01266-EP0065-N01266 route will have screening data from the original screening to N01266. For more details, see corresponding Data Integration Plan.

3.2.3 Study periods

Table 3–1 shows which study periods are applicable to DE and LTFU subjects:

Table 3–1: Study periods

	Period	Screening Period	Up-Titration Period			Evaluation Period									Down-Titration Period	Safety Period
	Visit	ScrV	TV1	TV2	TV2	EV	MEV	FEV	MEV	FEV	MEV	YEV	...	FV/EDV	DTV	SV
						V1	V2	V3	V4	V5	V6	V7	...			
Subjects	DE	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)	(x)
	LTFU					x	x	x	x	x	x	x	x	x	(x)	(x)
	Early Discontinuations													x	x	x

(x) – only applicable if the subject does not switch to another BRV study or is taking marketed drug after FV

The study is divided into 5 periods: Screening Period, Up-Titration Period, Evaluation Period, Down-Titration Period, and the Safety Period.

There is a Screening Period for all DE subjects. For DE subjects, this comprises assessments performed prior to the first dose of BRV in N01266. So start date of Screening Period is date of written informed consent and end date is the day before first dose of BRV (TV1-1). Although, patients in LTFU studies will not attend a screening visit, the screening information comprises information collected at various assessments during the core study and consequently will have been collected at different times depending on the domain. Domain specific information is detailed in Section 3.3.

The Up-Titration Period is only applicable to DE subjects, and the start date is the date of the first dose of BRV. The following algorithm is used to determine the end date:

- If the subject enters the Evaluation Period, the date 1 day prior to the EV is the end date
- If the subject does not enter Evaluation Period, the Up-Titration Period ends on the date of the final dose of BRV

For the Evaluation Period, the start date is the date of the first dose of BRV on or after the EV date, and the following algorithm is used to determine the end date:

- If the subject continues the study until it ends, the Evaluation Period ends on the date of FV
- If the subject prematurely discontinues the study, the date of EDV is the end date

A discontinued subject or a subject who completes the study but does not continue BRV treatment will be considered entering the Down-Titration Period only if the subject has a record of at least 1 dose of BRV after the date of EDV. The start date of the Down-Titration Period is set as 1 day after the date of EDV, and the Down-Titration Period ends on the date of the final dose of BRV (DTV).

A discontinued subject without any dosing of BRV after the EDV will not have participated in the Down-Titration Period, and no artificial Down-Titration Period will be created for the purpose of analysis.

A discontinued subject is considered to have entered the Safety Period if the subject has at least 1 contact (scheduled visit, unscheduled visit (UV), or telephone contact) after the date of the final dose (DTV). The Safety Period starts 1 day after the date of the final dose of BRV irrespective of entering the Down-Titration Period, and end date is the date of last contact with the subject.

3.2.3.1 Assignment of safety variables to study periods

In general, safety variables (e.g. AEs) will be allocated to the treatment group based on the dose most recently received. Safety outcomes which can be classified into more than 1 study period as per Section 3.2.3, based on partial dates of onset, will be classified into a study period based on the following prioritization: Up-Titration, Evaluation, Down-Titration, Safety, (for example, an AE that can be classified in both the Evaluation and Safety Period based on a partial date of onset due to a missing day entry, will be classified into the Evaluation Period).

3.2.4 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 definitions of 3- and 6-month

intervals are based on the durations in Table 3–2, which use 30-day months where EV relative days as defined in Section 3.2.1.2 will be used:

Table 3–2: Definition of monthly interval durations during the first year

Interval	EV relative days
Months 1 to 3	1 to 90
Months 4 to 6	91 to 180
Months 7 to 9	181 to 270
Months 10 to 12	271 to 360
Months 1 to 6	1 to 180
Months 7 to 12	181 to 360

Subsequent 3 and 6-month intervals, and 12-month intervals are defined in a similar manner.

Three-month intervals will be calculated for summaries and analyses of efficacy and safety outcomes scheduled to be assessed at each MEV, FEV, YEV and FV. A subject is included in the analysis for a 3-month interval if the end of their evaluation period is on or after the final day of the 3-month interval and the seizure diary was completed for at least 1 day during the 3-month interval.

Six-month intervals will be calculated for summaries and analyses of efficacy and safety outcomes scheduled to be assessed at each FEV, YEV and FV, but not each MEV. Similar to the approach for inclusion in 3-month summaries detailed above, a subject is included in the analysis for 6-month intervals if the end of their evaluation period is on or after the final day of the 6-month interval and the seizure diary was completed for at least 1 day during the 6-month interval.

Six and 12-month intervals will be calculated for analyses of seizure freedom. For further information on subject inclusion into these calculations, see Section 3.10.3.1.

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

3.2.5 Study visit labeling

Visits will be labeled in table summaries (according to the schedule outlined in Table 2–1) as follows:

- “Screening Visit”
- “Up-Titration Visit X”
- “Entry Visit”
- “Month X” for scheduled visits during the Evaluation Period
- “Final Visit”
- “Early Discontinuation Visit”
- “Down-Titration Visit”

- "Safety Visit"
- "Last Value" (see below in Section 3.2.6 for further information)

Listings will also include "Unscheduled Visit" as applicable.

3.2.6 Last Value on BRV treatment

The Last Value on BRV treatment for all assessments is the final available result obtained after the first dose of BRV and prior to or on the date of the final dose of BRV within evaluation period. All scheduled and UV assessments within evaluation period will be considered. Last Value will be determined separately for each vital sign, ECG and laboratory parameter.

3.2.7 Exposure duration and exposure duration cohorts

The overall duration of exposure for each subject will be calculated as the date of the final dose of BRV minus the date of the first dose of BRV plus 1 day.

Each subject will be classified into 1 or more of the following exposure duration cohorts based on the duration of BRV exposure as calculated above:

Table 3–3: Exposure duration cohort definitions

Cohort	Definition
All subjects	≥ 1 day
> 3 months	> 90 days
> 6 months	> 180 days
> 9 months	> 270 days
> 12 months	> 360 days

This categorization will continue in 3-month increments past 12 months up to a time point that will be determined based on a review of cumulative exposure on the database performed prior to database lock (DBL).

3.2.8 Modal dose calculation

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:

Table 3–4: Dose group definitions for calculation of modal dose

Dose group label (mg/kg/day)
>=0.0 to <1.0
1.0 to < 2.0
2.0 to < 3.0
3.0 to < 4.0
>=4.0

For each subject, the mode will then be calculated and they will be assigned to one of the groups in Table 3–4 overall, and by 6-month cohort.

3.2.9 Mapping of assessments performed at Early Discontinuation Visit

Efficacy and safety assessments at an EDV that correspond to a scheduled visit will be summarized at the scheduled visit corresponding to the EDV if the assessment was scheduled to occur at that visit. Such assessments will also be considered for Last Value on BRV treatment (see Section 3.2.6).

In particular, clinical laboratory parameters, vital signs, and body weight are assessed at all Evaluation Period visits, and so all assessments of these variables at EDVs corresponding to a scheduled visit will be mapped to the corresponding scheduled visit.

3.3 Definition of Baseline values

Baseline for all study outcomes will be determined using different methods depending on whether the subject is LTFU or DE.

Unless otherwise specified, Baseline values will be determined as follows:

- DE subjects: the last (most recent) available pre-dose measurement of the corresponding outcome will be used as Baseline
- LTFU subjects:
  - if available, Baseline values from the previous BRV core studies will be used as Baseline
  - otherwise the last (most recent) available measurement assessed between day of final on-treatment measurement in core study and the day before first BRV administration in N01266 will be used as Baseline

For laboratory parameters, vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate), body weight, and ECGs, Baseline values will be determined as follows:

- DE subjects: the last (most recent) available pre-dose measurement of the corresponding outcome will be used as Baseline
- LTFU subjects: the last (most recent) available scheduled or UV assessment up to the day of subjects first BRV administration in core study will be used as Baseline (most recent measurement up to first BRV administration in core study, not in N01266 as in the general definition of Baseline values)

Baseline will be determined separately for each individual clinical laboratory parameter for hematology, biochemistry, endocrinology and urinalysis assessments.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on either the primary outcome of safety and tolerability of BRV, or the secondary outcome of efficacy of BRV for an individual subject. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined separately in project Data Cleaning Plan. To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. 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.

Important protocol deviations will be reviewed as part of the ongoing data cleaning meetings prior to DBL to confirm exclusion from analysis sets.

3.5 Analysis sets

Disposition will be summarized for Enrolled Subjects. Safety variables will be summarized using the Safety Set (SS) and efficacy variables will be summarized using the Full Analysis Set (FAS).

3.5.1 Enrolled Subjects

Enrolled subjects will consist of all subjects with epilepsy who gave informed consent, or for whom informed consent was given by parent(s)/legal representative(s).

3.5.2 Safety Set

The SS will consist of all enrolled subjects who took at least 1 dose of study medication in this long-term study.

3.5.3 Full Analysis Set

The FAS will be used for the analysis of seizure data and will consist of all subjects in the SS, who have at least 1 completed post-Baseline DRC or EEG.

3.6 Treatment assignment and treatment groups

The following table displays the planned titration schedule of BRV for DE subjects during the study:

Table 3–5: Recommended BRV dosing schedule for DE subjects in the Up-Titration Period

Week	Dose per dosing occasion (mg/kg)	BRV dose per day (mg/kg/day)
TV1 (1)	~0.5	~1.0
TV2 (2)	~1.0	~2.0
TV3 (3)	~2.0	~4.0

BRV=brivaracetam; TV=Titration Visit; "~"=approximately

Daily doses will not exceed the maximums of 50mg/day, 100mg/day, and 200mg/day for Weeks 1, 2, and 3 of up-titration, respectively.

3.7 Site pooling strategy

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

3.8 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; the reported procedures will be retained in the study database.

3.9 Possible clinically significant treatment-emergent (PCST) values

Possible clinically significant treatment-emergent values are any laboratory values, vital signs, or ECG parameters meeting the criteria defined in Appendix Section 12.1 which occur any time after screening and after the first dose of BRV has been taken. The PCST criteria will only be applied to analytes that were routinely collected as designated in the protocol. A list of analytes that were to be routinely collected is provided Section 9.2.1 of the protocol.

PCST criteria are based on the FDA Division of Neuropharmacological Drug Products guidelines with some UCB-defined additions.

3.10 Definitions of study-specific derived variables

3.10.1 Definition of treatment-emergent AE

AEs will be classified as either pre-treatment or treatment emergent. In the following definitions, first dose of BRV refers to the first dose in N01266 (i.e., not the first dose of BRV from the core study in which subjects participated prior to N01266 for LTFU subjects). Pre-treatment AEs are defined as AEs which had an onset date at least one day prior to the first dose of BRV. Treatment-emergent adverse events (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 or after the month and year of the first BRV dose or the year of onset (when only the year is specified) is the same or after the year of first BRV dose. AEs with a missing onset date will also be classified as TEAEs provided the subject received at least one dose of BRV.

3.10.2 Epilepsy related variables

The duration of epilepsy is defined as

$$\text{Epilepsy duration (years)} = (\text{Date of informed consent} - \text{date of epilepsy diagnosis})/365.25$$

Or if actual dates are unknown, then use relative ages instead:

$$\text{Epilepsy duration (years)} = \text{Age at informed consent} - \text{age at epilepsy diagnosis.}$$

The percent of life with epilepsy is derived as:

$$\text{Percent of life with epilsepy} = \frac{\text{Epilepsy duration}}{\text{Age at informed consent}} * 100$$

3.10.3 Seizures and seizure categories

Each seizure code in the clinical database will be mapped to exclusively 1 of the following seizure types based on the 1981 ILAE classification: IA, IA1, IA2, IA3, IA4, IB, IB1, IB2, IC, IIA, IIB, IIC, IID, IIE, IIF, or III.

With regard to cluster seizures, study 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. In all the efficacy analyses, clusters will be counted as one seizure (i.e. 1 cluster = 1 seizure) and assigned to the corresponding seizure type.

For the evaluation of this study the categorization of subjects to different seizure categories and the analysis by these seizure categories is essential.

Four different seizure categories need to be distinguished and defined:

- POS – Partial-onset Seizure

  Subjects are categorized as POS subjects at ScrV if either Partial-Onset Seizure is entered on the "ILAE Seizure Classification History" eCRF page at ScrV or if it has been reported on "Historical Seizure Count" eCRF page for the last 3 weeks prior to ScrV with non-zero value.

- PGS – Primary Generalized Seizure

  Subjects are categorized as PGS subjects at ScrV if either Typical Absence Seizure, Atypical Absence, Myoclonic, Clonic, Tonic, Tonic-clonic or Atonic Seizure is entered on the "ILAE Seizure Classification History" eCRF page at ScrV or if one of these seizure types has been reported on "Historical Seizure Count" eCRF page for the last 3 weeks prior to ScrV with non-zero value.

- PGS* – Primary Generalized Seizure excluding Typical Absence

  Subjects are categorized as PGS* subjects at ScrV if either Atypical Absence, Myoclonic, Clonic, Tonic, Tonic-clonic or Atonic Seizure is entered on the "ILAE Seizure Classification History" eCRF page at ScrV or if one of these seizure types has been reported on "Historical Seizure Count" eCRF page for the last 3 weeks prior to ScrV with non-zero value.

- Typical Absence Seizure

  Subjects are categorized as Typical Absence subjects at ScrV if either Typical Absence Seizure is entered on the "ILAE Seizure Classification History" eCRF page at ScrV or if it has been reported on "Historical Seizure Count" eCRF page for the last 3 weeks prior to ScrV with non-zero value.

If a subject fulfills the requirements for Typical Absence, he is categorized into Typical Absence. Otherwise if the subject fulfills the requirements for PGS*, then he is categorized into PGS*. If the subject only fulfills the requirements for POS, then he is categorized into POS. PGS category is the union of PGS* and Typical Absence categories.

For assignment of EP0065 LTFU subjects to seizure categories the "Historical Seizure Count" eCRF data will be obtained from appropriate EP0065 analysis dataset, whereas "ILAE Seizure Classification History" eCRF data is recorded within N01266.

Subjects which have been rolled-over from core trial N01263 have already been categorized as PGS or POS subjects within core analysis dataset. This categorization will be taken over for N01266 study. The assignment of N01263 subjects to PGS subcategories Typical Absence Seizure or PGS* will be done based on "ILAE Seizure Classification History" eCRF data from N01263 analysis dataset. Subjects who cannot be categorized into any of the above categories will be uncategorized (UNC).

All planned analyses by seizure category (Disposition, Demographic and Baseline Characteristics, safety and efficacy analyses) will use these defined categories. The UNC

category will be presented in Demographic table as a variable and will not be displayed in the tables by seizure category. The UNC will be presented as a seizure category in listings.

3.10.3.1 Derivation of efficacy variables

Efficacy variables will be assessed using the seizure count information recorded on the DRC and EEG data. Seizure count information will be evaluated over the Evaluation Period by 3-month periods based on the DRC (EV until EDV or FV). For DE subjects, seizure count information collected during the Up-Titration Period will be summarized separately. The EEG data will be reviewed at 6 months and yearly thereafter and presented by visit or by study period overall (no time interval presentations planned for EEG).

For subjects coming from core studies EP0065 and N01349 no EEG based values are available which can be obtained as Baseline for N01266. Consequently, these patients will be excluded from any efficacy analysis based on EEG data, where Baseline values are considered. If EEG is done in N01266 at any visit after Baseline, data should be used to assess any variables which do not require Baseline (e.g. seizure freedom).

Similarly, EP0065 and N01349 studies do not provide Baseline DRC data as compared to other core studies. EP0065 and N01349 subjects will be included/excluded in the planned analyses as per following table:

Table 3–6: Inclusion/Exclusion of EP0065 and N01349 data

Analysis	EP0065/N01349 included?
Absolute/percent change in ADF by EEG/ Absolute/percent change in 28-days adjusted (POS) seizure frequency by DRC	No
Responder Rate by EEG/ DRC	No
Absolute/percent worsening by EEG/ DRC	No
Seizure free days by DRC	Yes
Seizure freedom by EEG/ DRC	Yes
Average Daily Frequency	Yes (but not to be included in change from Baseline)
New incidence of seizure type	Yes

Calculations based on EEG data (LTFU subjects only)

EEG will be only analyzed for LTFU subjects. The Baseline EEG assessment to confirm POS seizures for DE subjects will not be used to derive efficacy variables. EEG assessments for subjects <2 years of age take 24 hours whereas for subjects ≥ 2 years of age with typical absence seizures only 1-hour EEG assessments were performed.

If the EEG interpretation is different based on EEG data from central reader and from site investigator (response captured in eCRF), then the site investigator interpretation is to be used. Please follow this table:

Table 3–7: EEG interpretation

	Site investigator interpretation = "normal"	Site investigator interpretation = "abnormal"
Central reader interpretation = "Normal"; 0 seizure counts	No problem	Use "Abnormal" with missing counts: ADF missing
Central reader interpretation = "Abnormal"; >0 seizure counts	Use "Normal"; 0 counts	No problem

Calculation of average daily frequency (ADF) of seizures

Average daily frequency (ADF) of seizures based on the EEG data (from central reader or eCRF) is calculated differently for 1-hour and 24-hour EEG:

For 1-hour EEG:

$$\text{ADF} = \text{ Number of seizures from EEG data source considered for 1 hour EEG x } 24$$

For 24-hour EEG (with missing information on interpretable hours):

$$\text{ADF} = \text{ Number of seizures from EEG data source considered for 24 hour EEG}$$

For 24-hour EEG (with information on interpretable hours):

$$\text{ADF} = \frac{\text{Number of seizures from EEG data source considered for 24 hour EEG}}{\text{Number of interpretable hours}} \text{ x } 24$$

The ADF will be calculated including all seizure types and additionally for POS seizures and PGS seizures, separately.

For certain endpoints, multiple EEG assessments are to be combined. In this instance, for n assessments, average ADF is given as:

$$\text{Average ADF} = \frac{\sum_{i=1}^{n} \text{ADF}_i}{n}.$$

Calculation of absolute change/worsening in ADF of seizures

Absolute change in ADF is calculated as:

$$\text{Absolute Change in ADF} = \text{ Baseline ADF} - \text{postBaseline ADF}.$$

Both absolute changes will be calculated, with ADF including all seizure types and additionally based on POS seizures only.

Absolute worsening in PGS ADF is calculated as:

$$\text{Absolute Worsening in PGS ADF} = \text{ postBaseline PGS ADF} - \text{Baseline PGS ADF}.$$

Calculation of percent change/worsening in ADF of seizures

Percent change in ADF is calculated as:

$$\text{Percent Change in ADF} = \frac{\text{Absolute Change in ADF}}{\text{Baseline ADF}} \times 100.$$

Both percent changes will be calculated, with ADF including all seizure types and additionally based on POS seizures only.

Percent worsening in PGS ADF is calculated as:

$$\text{Percent Worsening in PGS ADF} = \frac{\text{Absolute Worsening in PGS ADF}}{\text{Baseline PGS ADF}} \times 100.$$

Calculation of response

Response is defined to be equal to 1 for Percent Change in ADF >=50% and 0 for <50%. Both responses will be calculated, with percent change in ADF including all seizure types and additionally based on POS seizures only.

For subjects <2 years of age response is based on the 24-hour EEGs performed over the Evaluation and Down-Titration Period separately.

For subjects ≥ 2 years of age with typical absence seizures categorization, response is based on the 1-hour EEGs performed over the Evaluation and Down-Titration Period separately.

Calculation of Seizure freedom

The categorical variable Seizure freedom is defined to be equal to 1 if none of the EEG assessments within the reported time period (Evaluation Period or Down-Titration Period) have shown occurrence of any seizures and 0 otherwise.

For subjects <2 years of age seizure freedom is based on the 24-hour EEGs performed over the Evaluation and Down-Titration Period separately.

For subjects ≥ 2 years of age with typical absence seizures categorization, seizure freedom is based on the 1-hour EEGs performed over the Evaluation and Down-Titration Period separately.

Calculation of Seizure freedom rate

Seizure freedom rate will be determined as follows:

$$\text{Seizure freedom rate of Time Period} = 100 \times \left[\frac{\text{Number of subjects who were seizure free over reported Time Period}}{\text{Number of subjects who entered reported Time Period with at least one evaluable EEG assessment during the Time Period}} \right]$$

The denominator includes only those subjects applicable, depending on age group and seizure categorization. See calculation of Seizure freedom.

Calculations based on DRC data

DRC data will be analyzed for DE and LTFU subjects.

Calculation of average daily frequency (ADF) of seizures and 28-day adjusted seizure frequency

Average daily frequency (ADF) of seizures based on the DRC data is calculated over the Evaluation Period, by visit and by 3-month time intervals:

$$\text{ADF} = \frac{\sum_{i=1}^{n} \text{seizure count entered at day i}}{n},$$

where n is the number of days with non-missing seizure count entry in the DRC during the reporting time period. The reporting time period includes the start date but excludes the stop date of the time period.

For DE subjects, Baseline ADF will take DRC data from ScrV to TV1 into account only. For LTFU subjects, Baseline diary data is obtained from Baseline of the core study.

The ADF will be calculated including counts for all seizure types and additionally for POS seizures only.

The 28-day adjusted seizure frequency is calculated as:

$$28\text{day adjusted seizures frequency} = \text{ADF} \times 28$$

The Baseline 28-day adjusted seizure frequency will be calculated using the Baseline ADF.

The 28-day adjusted POS seizure frequency will be calculated using the POS ADF respectively.

Calculation of absolute change/worsening in 28-day adjusted seizure frequency

Absolute change in 28-day adjusted seizure frequency is calculated as:

$$\begin{aligned}&\text{Absolute Change in 28 day adjusted seizure frequency}\\&= \text{Baseline 28 day adjusted seizure frequency}\\&- \text{postBaseline 28 day adjusted seizure frequency.}\end{aligned}$$

Absolute change in 28-day adjusted POS frequency is calculated similarly including 28-day adjusted POS frequencies.

Absolute worsening in 28-day adjusted seizure frequency is calculated as:

$$\begin{aligned}&\text{Absolute Worsening in 28 day adjusted seizure frequency}\\&= \text{postBaseline 28 day adjusted seizure frequency}\\&- \text{Baseline 28 day adjusted seizure frequency.}\end{aligned}$$

Calculation of percent change/worsening in 28-day adjusted seizure frequency

Percent change in 28-day adjusted seizure frequency is calculated as:

$$\text{Percent Change} = \frac{\text{Absolute Change in 28 day adjusted seizure frequency}}{\text{Baseline 28 day adjusted seizure frequency}} \times 100$$

Percent change in 28-day adjusted POS frequency is calculated similarly including 28-day adjusted POS frequencies.

Percent worsening in 28-day adjusted seizure frequency is calculated as:

$$\text{Percent Worsening} = \frac{\text{Absolute Worsening in 28 day adjusted seizure frequency}}{\text{Baseline 28 day adjusted seizure frequency}} \times 100$$

Calculation of response

Response is defined to be equal to 1 for Percent Change in 28-day adjusted seizure frequency >=50% and 0 for <50%.

Response will be calculated in both ways: based on 28-day adjusted seizure frequency, including all seizure types, and based on 28-day adjusted POS frequency, including POS seizures only.

The responder rate is based on the DRC data performed over Up-Titration, Evaluation and Down-Titration Period separately.

Calculation of Proportion of seizure free days

The proportion of seizure free days is calculated as:

$$\text{Proportion of Seizure free days} = \frac{\text{Number of Days with no Seizures on DRC Data}}{\text{Number of Days of recorded DRC Data}}$$

All seizure types will be taken into account. The proportion of seizure free days will be calculated over Evaluation Period, by visit and by 3-month time intervals.

Calculation of Seizure freedom

The categorical variable Seizure freedom is defined to be equal to 1 if the following criteria are fulfilled:

Criterion 1: A subject completed the reported Time Period

- Up-Titration Period: for DE subjects only, if at least one eCRF during Up-Titration Period is entered (only Baseline/TV1, Baseline/TV1 and TV2 or Baseline/TV1, TV2 and TV3 could be entered, dependent on subject's individual titration)
- Evaluation Period: if the FV or EDV eCRF page (named FIN) is entered
- Down-Titration Period: if the eCRF DTV page is entered (DTV is the final visit for the Down-Titration Period)

Criterion 2: The seizure diary was completed for at least 90% of days from start date of the appropriate Time Period up to the day prior to the end date of the appropriate Time Period.

Criterion 3: All entered seizure codes have a count of 0 from the day after start date of appropriate Time Period (ie, not including the start date of appropriate Time Period) up to and including the end date of the appropriate Time Period. (If a seizure code is entered, a missing count will lead to a violation of this criteria, too.)

If one of the criteria is not fulfilled, Seizure freedom is defined to be equal to 0.

Seizure freedom will be based on DRC data collected over the Up-Titration, Evaluation and Down-Titration Period separately. All seizure types will be taken into account.

Calculation of Seizure freedom rate

Seizure freedom rate will be determined as follows:

$$\text{Seizure freedom rate of Time Period} = 100 \times \left[\frac{\text{Number of subjects who were seizure free over reported Time Period}}{\text{Number of subjects who entered reported Time Period with at least one DRC entry during the Time Period}}\right]$$

All seizure types will be taken into account.

Calculation of Seizure freedom by visit

The categorical variable Seizure freedom by visit is defined to be equal to 1 if the following criteria are fulfilled:

Criterion 1: The question "Have there been any seizures since the last visit?" has been answered with "No" and all entered seizure codes in the DCR have a count of 0 since prior visit. (If a seizure code is entered, a missing count will lead to a violation of this criteria, too.)

Criterion 2: The seizure diary was completed for at least 90% of days since prior visit. The percentage of days for which diary data were entered since the prior visit will be calculated as follows:

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

If one of the criteria is not fulfilled, Seizure freedom by visit is defined to be equal to 0.

Seizure freedom by visit will be based on DRC data and eCRF data collected over the Up-Titration, Evaluation and Down-Titration Period separately. All seizure types will be taken into account.

Calculation of seizure freedom by time interval

The categorical variable Seizure freedom by time interval is defined to be equal to 1 if the following criteria are fulfilled:

Criterion 1: All entered seizure codes have a count of 0 from the day after start date of appropriate time interval (i.e., not including the start date of appropriate time interval) up to and including the end date of the appropriate time interval. (If a seizure code is entered, a missing count will lead to a violation of this criteria, too.)

Criterion 2: The seizure diary was completed for at least 90% within the time interval. The percentage of days for which diary data 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 3-month seizure freedom based on 90 days and 12-month seizure freedom based on 360 days.

If one of the criteria is not fulfilled, Seizure freedom by time interval is defined to be equal to 0.

Seizure freedom by time interval will be based on DRC data collected over the Up-Titration, Evaluation and Down-Titration Period separately. All seizure types will be taken into account.

Calculation of Incidences for new seizure types

To calculate incidences of new seizure types and subtypes a shift table from Present at Baseline (Yes, No, Missing, Total) to Present during Evaluation Period (Yes, No, Missing, Total) will be prepared. Subjects who do not have results for subtypes at Baseline will be presented with "not assessed" Baseline results and their respective Evaluation Period result. Whenever only subtype information is available the seizure type results will be derived as follows:

- Seizure type I is Present at Baseline = "Yes" if at least one of the subtypes IA, IB, IC is present at Baseline. It is Present at Baseline = "Missing" if data for all subtypes is missing. Otherwise, Present at Baseline = "No".
  (Same rule is to apply to summarize sub-subtypes IA1, IA2, IA3 and IA4 into IA. IA is Present at Baseline = "Yes" if at least one of the subtypes IA1, IA2, IA3 or IA4 is present at

Baseline. IA is Present at Baseline = "Missing" if data for all sub-subtypes is missing. Otherwise, Present at Baseline = "No".)

- Seizure type II is Present at Baseline = "Yes" if at least one of the subtypes IIA, IIB, IIC, IID, IIE, IIF is present at Baseline. It is Present at Baseline = "Missing" if data for all subtypes is missing. Otherwise, Present at Baseline = "No".
- Seizure type III does not have subtypes, so derivations are not applicable.

Incidences are the percentages for seizures which were not present at Baseline but present during Evaluation Period:

$$\text{Incidence of seizure type} = \frac{\text{Count of subjects with seizure (sub)type not present at Baseline but present in Evaluation Period}}{\text{Total number of subjects with seizure (sub)type not present at Baseline}}$$

Incidences will be calculated separately for Down-Titration Period.

3.10.4 Direct cost parameters

Direct cost parameters will be assessed based on concurrent medical procedures, health care provider consultations not foreseen by protocol, hospital stays, and emergency room (ER) visits.

3.10.4.1 Medications (AED and non-AED)

Each medication will be classified as either an AED or a non-AED, and classification will be conducted at Data Evaluation Meetings (DEM). AED outputs will reflect AED evaluation result of concomitant Benzodiazepine from the data review meetings.

According to the time of intake, medications will be classified into five categories:

- Prior Medications: For DE subjects, prior medications include any medications that started prior to the first dose of study drug in N01266. For LTFU subjects, prior medications include any medications that started prior to the first dose in the core study.
- Previous Medications: Previous medications are a subset of prior medications. For DE subjects, previous medications include any medications that started and stopped prior to the first dose of study drug in N01266. For LTFU subjects, previous medications include any medications that started and stopped prior to the first dose in the core study.
- Medications at study entry: For DE subjects, medications at study entry include any medications taken at ScrV. For LTFU subjects, medications at study entry include any medication taken at entry of the core study.
- Concomitant Medications: Concomitant medications include any medications that were taken at least one day in common with study treatment.
- Follow-up Medications: Follow-up medications include any medication that start after final dose of study drug.

Medications can be either previous or concomitant, not both. Medications with an incomplete onset date will be classified as concomitant, and not previous, 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 the year is specified) is the same as the year of first BRV

dose. Medications with a missing onset date will also be classified as concomitant, and not previous provided the subject received at least one dose of BRV.

3.10.4.2 Concurrent medical procedures

Concurrent medical procedures will be attributed to study periods based on the start date of the procedure. Study periods are as defined in Section 3.2.3.

3.10.4.3 Additional healthcare provider visits

Healthcare provider consultations not foreseen by the protocol will be attributed to study periods based on the date of consultation.

3.10.4.4 Hospital stays

Hospital stays will be attributed to study periods based on admission date.

The duration of each hospital stay will be calculated as discharge date minus the admission date (Hospitalization Visit Date on the CRF) plus 1 day for hospital stays with a discharge date.

The durations of hospital stays will be summed within each of the Evaluation, Down-Titration, and Safety study periods. Subjects with no hospital stays within a study period will have a duration of 0 days for that period. Should distinct records for hospital stays overlap, then the days during the overlap will only be counted once.

Hospital stay durations will be categorized as follows: 1 day, 2-5 days, 6-10 days, 11-15 days and >15 days.

3.10.4.5 Emergency room visits

Emergency room (ER) visits will be attributed to study periods based on admission date.

The duration of each ER visit will be calculated as discharge date minus the admission date (ER Visit Date on the CRF) plus 1 day for emergency room visits with a discharge date.

Both ER visits that result in a subsequent hospital stay and ER visits that do not result in a subsequent hospital stay will be counted.

3.10.5 Questionnaire data

For all questionnaire data where different languages or terminology is used between patients, the differences in questionnaires will be reviewed in a blinded manner prior to database lock in order to determine whether responses may be grouped.

3.10.5.1 Achenbach CBCL

The Achenbach CBCL form is a questionnaire intended to evaluate a child's competencies and behavioral/emotional problems. Depending on the subject's age, 1 of 2 versions of the Achenbach CBCL is used. The Achenbach CBCL/1½-5 checklist is intended for use in children aged between 18 months and 5 years and 11 months. For subjects between 6 years and < 17 years, the Achenbach CBCL/6-18 version is used. The Achenbach CBCL is not applied to children below 18 months of age.

The CBCL/1½-5 checklist comprises 100 questions and the CBCL/6-18 checklist comprises 120 questions with the response options of:

- 0=not true (as far as known)

- 1=somewhat or sometimes true
- 2=very true or often true

The CBCL/1½-5 checklist will be grouped according to syndrome scales according to Table 3–8 and the CBCL/6-18 checklist will be grouped according to the empirically based syndrome scales in Table 3–9.

Table 3–8: CBCL/1½-5 checklist

Syndrome scale	Questions
Aggressive behavior	8, 15, 16, 18, 20, 27, 29, 35, 40, 42, 44, 53, 58, 66, 69, 81, 85, 88, 96
Anxious / depressed	10, 33, 37, 43, 47, 68, 87, 90
Attention problems	5, 6, 56, 59, 95
Emotionally reactive	21, 46, 51, 79, 82, 83, 92, 97, 99
Sleep problems	22, 38, 48, 64, 74, 84, 94
Somatic complaints	1, 7, 12, 19, 24, 39, 45, 52, 78, 86, 93
Withdrawn	2, 4, 23, 62, 67, 70, 71, 98

Table 3–9: CBCL/6-18 checklist

Syndrome scale	Questions
Aggressive behavior	3, 16, 19, 20, 21, 22, 23, 37, 57, 68, 86, 87, 88, 89, 94, 95, 97, 104
Anxious / depressed	14, 29, 30, 31, 32, 33, 35, 45, 50, 52, 71, 91, 112
Attention problems	1, 4, 8, 10, 13, 17, 41, 61, 78, 80
Rule-breaking behavior	2, 26, 28, 39, 43, 63, 67, 72, 73, 81, 82, 90, 96, 99, 101, 105, 106
Social problems	11, 12, 25, 27, 34, 36, 38, 48, 62, 64, 79
Somatic complaints	47, 49, 51, 54, 56a, 56b, 56c, 56d, 56e, 56f, 56g
Thought problems	9, 18, 40, 46, 58, 59, 60, 66, 70, 76, 83, 84, 85, 92, 100
Withdrawn / depressed	5, 42, 65, 69, 75, 102, 103, 111

The sum of the raw score of values within each syndrome scale will be calculated for each subject according to the questionnaire used.

Standardized T-scores are determined from each subject's raw syndrome score based on the subject's age and sex. Tables mapping each raw score to the appropriate T-score are provided in the CBCL Professional Manual and will be reproduced programmatically.

Further T-scores will be categorized with regard to clinical significance (CS) to summarize categorical shift from Baseline. The legacy categories for CS are defined as follows:

- If T-score is < 65 then CS category = "Normal"
- If T-score is 65 - < 70 the CS category = "Borderline"

- If T-score is >= 70 then CS category = "Clinically Significant".

T-scores will also be categorized using the dichotomous approach with regard to CS to summarize categorical shift from Baseline. The categories for CS are defined as follows:

- If T-score is < 65 then CS category = "Normal"
- If T-score is 65=< the CS category = "Borderline or Clinical Range"

Achenbach CBCL will be conducted at ScrV, EV (for DE and LTFU subjects respectively), at FEVs, YEVs and FV/EDV. The version of the Achenbach CBCL appropriate to each subject's age should be administered with the following exception: If a subject completed the Achenbach CBCL/1½-5 at the Baseline assessment and turns 6 years of age between that assessment and the initial YEV, the CBCL/1½-5 should be completed through and including the initial YEV, and subsequently the CBCL/6-18 should be completed. Moreover, if a subject was below 18 months of age at Baseline but turns ≥ 18 months between Baseline and initial YEV, Achenbach CBCL/1½-5 will be assessed at visits after initial YEV.

The change from Baseline will be calculated using T-scores and raw scores by subtracting the Baseline result (ScrV or EV) from the post-Baseline visit result:

$$\text{Change from Baseline} = \text{Score at postBaseline visit} - \text{Score at Baseline}$$

at each visit in the Evaluation Period, if Baseline value is available. A decrease from Baseline (change from Baseline < 0) indicates improvement in behavior, while an increase (change from Baseline > 0) indicates worsening.

3.10.5.2 BRIEF scores

The BRIEF form is a questionnaire entered for subjects ≥ 5 years of age to assess subjects' executive functioning. Executive functions broadly encompass a set of cognitive skills that are responsible for the planning, initiation, sequencing, and monitoring of complex goal-directed behavior.

The BRIEF form should be used for subjects ≥ 5 years of age, and within the following exception: for subjects who completed the BRIEF-P at Baseline assessment and turns 5 years of age between that assessment and the initial YEV, the BRIEF-P should be completed through and including initial YEV, and subsequently the BRIEF should be completed.

The questionnaire comprises 86 questions with entry options of N (never; scored as 1 point), S (sometimes; scored as 2 points) and O (often; scored as 3 points). Higher scores reflect poorer functioning. The questions are categorized in 8 components: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials and Monitor. Additionally, three subscales will be used to calculate subscale scores.

Table 3–10 presents which questions belonging to which component and the constitution of subscales.

Table 3–10: BRIEF components and subscales

Scale/Index	Questions
Inhibit	38, 41, 43, 44, 49, 54, 55, 56, 59, 65
Shift	5, 6, 8, 12, 13, 23, 30, 39

Scale/Index	Questions
Emotional Control	1, 7, 20, 25, 26, 45, 50, 62, 64, 70
Initiate	3, 10, 16, 47, 48, 61, 66, 71
Working Memory	2, 9, 17, 19, 24, 27, 32, 33, 37, 57
Plan/Organize	11, 15, 18, 22, 28, 35, 36, 40, 46, 51, 53, 58
Organization of Materials	4, 29, 67, 68, 69, 72
Monitor	14, 21, 31, 34, 42, 52, 60, 63
BRI	All questions from Inhibit, Shift, and Emotional Control
MI	All questions from Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor
GEC Score	Questions 1-72

BRI=Behavioral Regulation Index, MI=Metacognition Index, GEC=Global Executive Composite.

Standardized T-scores are determined from each subject's raw GEC, BRI, MI, and component scores based on the subject's age and sex. Tables that map each raw score to the appropriate T-score are provided in the BRIEF Professional Manual and will be reproduced programmatically.

In addition, T-scores will be categorized with regard to CS to summarize categorical shift from Baseline. The legacy categories for CS are defined as follows:

- If T-score is 0 - < 50 then CS category = "Normal"
- If T-score is 50 - < 65 the CS category = "Borderline"
- If T-score is >= 65 then CS category = "Clinically Significant".

T-scores will also be categorized using the dichotomous approach with regard to CS to summarize categorical shift from Baseline. The categories for CS are defined as follows:

- If T-score is < 65 then CS category = "Normal"
- If T-score is >= 65 then CS category = "Potentially Clinically Significant".

Two validity scales will also be derived: Negativity to assess the extent to which the respondent answers selected BRIEF items in an unusually negative manner and Inconsistency to assess the extent to which the respondent answers similar BRIEF items in an inconsistent manner. The Negativity scale is the number of items in 8, 13, 23, 30, 62, 71, 80, 83 and 85 with a score of 3, and so has a range of 0 to 9. A score of 4 or less is considered acceptable, 5 to 6 elevated and 7 or more highly elevated.

For the Inconsistency scale, there are 10 item pairs of related questions. The Inconsistency scale is the sum of the absolute values of the difference in scores for the items in each item pair, and so ranges from 0 to 20. The item pairs are questions 7 and 25, 11 and 22, 27 and 17, 33 and 32, 38 and 59, 41 and 65, 42 and 63, 44 and 54, 53 and 60, and 55 and 44. A score of 6 or less is acceptable, 7 or 8 questionable and 9 or more inconsistent.

BRIEF will be conducted at ScrV, EV (for DE and LTFU subjects respectively), at FEVs, YEVs and FV/EDV.
Change from Baseline in BRIEF scores (for raw scores and T-scores) will be calculated as:

$$\text{Change from Baseline in BRIEF} = \text{BRIEF score at postBBaseline visit} - \text{BRIEF score at Baseline}$$

at each visit in the Evaluation Period, if Baseline value is available. A change from Baseline < 0 indicates improvement and a change from Baseline > 0 worsening.

3.10.5.3 BRIEF-P scores

The BRIEF-P is a questionnaire entered for subjects ≥ 2 to < 5 years of age to assess subjects' executive functioning. The questionnaire comprises 63 questions with entry options of N (never; scored as 1 point), S (sometimes; scored as 2 points), and O (often; scored as 3 points). Higher scores reflect poorer functioning. The questions are categorized in 5 components: Inhibit, Shift, Emotional Control, Working Memory and Plan/Organize. Additionally, three subscales will be used to calculate subscale scores.

The BRIEF-P form should be used for subjects ≥ 2 to < 5 years of age, with the following exception: for subjects who completed the BRIEF-P at Baseline assessment and turns 5 years of age between that assessment and the initial YEV, the BRIEF-P should be completed through and including initial YEV, and subsequently the BRIEF should be completed. Moreover, if a subject was below 2 years of age at Baseline but turns ≥ 2 years between Baseline and initial YEV, BRIEF-P will be assessed at visits after initial YEV.

Table 3–11 presents which questions belonging to which component and the constitution of subscales.

Table 3–11: BRIEF-P components and subscales

Scale/Index	Questions
Inhibit	3, 8, 13, 18, 23, 28, 33, 38, 43, 48, 52, 54, 56, 58, 60, 62
Shift	5,10, 15, 20, 25, 30, 35, 40, 45, 50
Emotional Control	1, 6, 11, 16, 21, 26, 31, 36, 41, 46
Working Memory	2, 7, 12, 17, 22, 27, 32, 37, 42, 47, 51, 53, 55, 57, 59, 61, 63
Plan/Organize	4, 9, 14, 19, 24, 29, 34, 39, 44, 49
ISCI	All questions from Inhibit and Emotional Control
FI	All questions from Shift and Emotional Control
EMI	All questions from Working Memory and Plan/Organize
GEC Score	1-63

EMI=Emergent Metacognition Index, FI=Flexibility Index, GEC=Global Executive Composite, ISCI=Inhibitory Self Control Index

Standardized T-scores are determined from each subject's raw GEC, ISCI, FI, EMI, and component scores based on the subject's age and sex. Tables that map each raw score to the

appropriate T-score are provided in the BRIEF-P Professional Manual and will be reproduced programmatically.

Similar to analysis for BRIEF, the T-scores for BRIEF-P will be categorized using the legacy and the dichotomous approach to summarize categorical shift from Baseline. The same categorization as described in Section 3.10.5.2 applies.

Two validity scales will also be derived: Negativity to assess the extent to which the respondent answers selected BRIEF-P items in an unusually negative manner and Inconsistency to assess the extent to which the respondent answers similar BRIEF-P items in an inconsistent manner. The Negativity scale is the number of items in 30, 44, 46, 47, 53, 55, 56, 57,59 and 63 with a score of 3, and so has a range of 0 to10. A score of 2 or less is considered acceptable, 3 as elevated and 4 or more highly elevated.

For the Inconsistency scale, there are 10 item pairs of related questions. The Inconsistency scale is the sum of the absolute values of the difference in scores for the items in each item pair, and so ranges from 0 to 20. The item pairs are questions 1 and 11, 3 and 33, 5 and 45, 10 and20, 11 and 26, 16 and 21, 18 and 52, 33 and 38, 43 and 52, and 48 and 54. A score of 7 or less is acceptable and 8 or more inconsistent.

BRIEF-P will be conducted at ScrV, EV (for DE and LTFU subjects respectively), at FEVs, YEVs and FV/EDV.
Change from Baseline in BRIEF-P scores (raw scores and T-scores) will be calculated as:

$$\text{Change from Baseline in BRIEF} - \text{P} = \text{BRIEF} - \text{P score at postBaseline visit} - \text{BRIEF} - \text{P score at Baseline}$$

at each visit in the Evaluation Period, if Baseline value is available for all BRIEF-P scores (the 5 scales, 3 Indices and GEC scores). A change from Baseline < 0 indicates improvement and a change from Baseline > 0 worsening.

3.10.5.4 PedsQL

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions (Varni et al, 1999). The PedsQL Measurement Model consists of developmentally appropriate forms for pediatric subjects ≥2 years to ≤4 years, ≥5 years to ≤7 years, ≥8 years to ≤12 years, and ≥13 years to ≤18 years of age. PedsQL generic core scores will be calculated for each of the following 4 PedsQL scales for subjects ≥ 2 years of age using most recent pre-dose data:

- Physical functioning
- Emotional functioning
- Social functioning
- School functioning

The underlying item score values 0 to 4 (representing responses of: never, almost never, sometimes, often and almost always) will be transformed by the function: (100 – [response x 25]) in order to generate scores of 0, 25, 50, 75 and 100 where a higher value represents a better HRQoL.

Each dimension score is then calculated as the mean of the transformed item scores from items of the considered dimension. In the case of item-level missing data, these will be replaced by the average of non-missing item scores from the considered dimension, if at least 50% of the items from that dimension are non-missing.

Summary scores will also be generated:

- the Psychosocial Health Summary Score will be calculated as the mean of items (transformed scores after replacement of missing data) from the Emotional, Social, and School Functioning dimensions. However, in the case where the Emotional, Social, or the School Functioning scores would be missing, the Psychosocial Health summary score will be set to missing.

- the Physical Health Summary score (same as Physical functioning dimension).

- the Total score will be calculated as the mean of all PedsQL items (transformed scores after replacement of missing data). However, in the case where one of the dimension scores (Physical, Emotional, Social, or School Functioning) would be missing, the Total score will be set to missing.

PedsQL will be conducted at ScrV, EV (for DE and LTFU subjects respectively), at FEVs, YEVs and FV/EDV. The version of the PedsQL appropriate for each subject's age should be completed, with the following exception: If a subject ages up to the next version of the PedsQL between the Baseline assessment and the initial YEV, the version that was used at the Baseline assessment should be completed through and including the initial YEV, and subsequently the version consistent with his/her age at the time of assessment should be completed.
Change from Baseline in PedsQL score will be calculated as:

$$\text{Change from Baseline in PedsQL} = \text{PedsQL score at postBaseline visit} - \text{PedsQL score at Baseline}$$

if Baseline value is available. A change from Baseline > 0 indicates improvement and a change from Baseline < 0 worsening.

3.11 Changes to protocol-defined analyses

There are no changes to analyses specified in the protocol.

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

The method for handling missing and partial dates for medications and AEs is described in Section 3.10.4.1 and Section 3.2.3.1 respectively. Missing AE intensity or relationship will be imputed according to worst case scenario with severe intensity and assumed to be related. For other safety variables, no imputation methods are planned.

Regarding efficacy variables, endpoints using seizure frequency and seizure free days based on DRC data will be calculated over non-missing diary days during each study period or time interval as described in Section 3.10.3.1; days for which seizure diary data were not obtained will not be considered in the calculation of seizure frequency or seizure days. This is applicable to the analysis taking all seizure categories into account as well as to the analysis taking only POS seizures into account. Generally, compliance with the daily seizure diary is expected to be high in a refractory population and, therefore, the impact of missing diary data is expected to be minimal. 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 Up-Titration, Evaluation or Down-Titration Period, the calculation of seizure frequency, seizure free days and seizure freedom will be based on available seizure diary days while the subject was receiving BRV. This effectively imputes the unobserved seizure frequency after discontinuation with the seizure frequency observed prior to discontinuation. 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.

Endpoints using seizure data from EEG will only include available data. No imputation method will be conducted.

4.3 Interim analyses and data monitoring

Due to the single-arm open-label design of this study, no formal interim analysis as such will be performed. However, data may be reported prior to the completion of this study to support ongoing data cleaning, annual reports, regulatory submissions, and publications.

For regulatory submissions based on interim cutoffs, overall summaries will consider all assessments after the first dose of BRV and prior to or on the date of the clinical cutoff for subjects who are ongoing at the time of the clinical cutoff.

4.4 Multicenter studies

Efficacy and safety outcomes will not be assessed for individual investigator sites due to the expected low 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 BRV and have at least 1 post-Baseline DRC or EEG 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:

- Previous pediatric BRV study experience, labelled with "Cohort" (LTFU subjects overall and by core study, DE subjects)
- Age group (≥ 1 month to < 2 years of age (28 days to 23 months), ≥ 2 to < 4 years of age, ≥ 4 to < 12 years of age, ≥ 12 to < 17 years of age)
- Seizure category (POS, PGS*, Typical Absence, PGS) as defined in Section 3.10.3.
- Geographical region (North America, Latin America, Western Europe, Eastern Europe, Asia/Pacific/Other)

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

An overall summary of disposition will be provided for enrolled subjects, in SS and FAS, and in SS by subgroups, separately. The following will be summarized:

- The number of enrolled subjects
- The number of screen failures (DE subjects only)
- The number of subjects in the SS (applicable for enrolled subjects table only)
- The number of subjects excluded from the SS (applicable for enrolled subjects table only)
- The number of subjects in the FAS (applicable for enrolled subjects table only)
- The number of subjects entering the Up-Titration, Evaluation, Down-Titration Period
- The number of subjects completing the Up-Titration and entering the Evaluation
- The number of subjects completing the study
- The number of subjects ongoing in the study (only applicable before final data base lock)
- The overall number of subjects discontinuing and the number of subjects discontinuing by primary reason for discontinuation. If the subject discontinued the study and the termination CRF is not available, the reason for discontinuation will be reported as "UNKNOWN".

Overall subject disposition will also be summarized by cohort (LTFU vs. DE), and geographical region, by seizure category and by core study for the SS.

The number of subjects by cohort and geographical region will be summarized for the SS.

The number of subjects in each analysis set (Enrolled Subjects, SS and FAS) will be presented by investigator and cohort, including the dates of the first subject in (date of earliest EV for the N01266 study) and the last subject out (date of final scheduled or UV). The table will be presented overall and by region.

The number of subjects and Kaplan-Meier estimates of the percentage of subjects completing 3, 6, 12, 24, 36, 48 and 60 months of treatment with BRV in the N01266 study will be provided. This analysis will be based on duration of exposure to BRV as defined in Section 3.2.7. Subjects who have permanently discontinued will be analyzed as events on the final day of treatment with BRV; subjects who complete the study will be censored on the final day of treatment with BRV.

Subjects who transferred sites will be summarized according to their original site.

Subject disposition will be listed for all subjects enrolled and will include the following information: subject status (screen failure, completed or discontinued), date of informed consent, date and time of first and last study medication (including relative day for last dose), date of premature study termination (if applicable) and primary reason for termination (if applicable) and date of last contact. For screen failures the date and reason for screen failure will be listed.

5.2 Protocol deviations

Important protocol deviations are deviations from the protocol, which potentially could have a meaningful impact on either the primary efficacy outcome or key safety outcomes for an individual subject. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the project Data Cleaning Plan. Important protocol deviations will be reviewed as part of the ongoing data cleaning meetings prior to database lock to confirm exclusion from analysis sets.

The number and percentage of subjects with at least 1 important protocol deviation will be summarized in SS overall and by category of protocol deviation. This summary will be presented overall, by age group, by seizure category and by cohort (see Section 4.8).

All important protocol deviations will be provided in a data listing.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic and other Baseline characteristic variables will be presented for the SS and will be summarized by age group as categorized in Section 4.8, and overall.

Unless otherwise mentioned, for DE subjects, demographic and Baseline variables will be obtained at ScrV, whereas for LTFU subjects, all demographic and Baseline variables will be based on data collected at the time of entry into the core study.

6.1 Demographics and Baseline characteristics

Baseline age will be determined at either ScrV (DE subjects) or EV (LTFU subjects). Age will be calculated based on an assumed date of birth of January 1 for subjects who only have a year of birth based on region-specific regulations.

Body Mass Index will be calculated as:

$$\text{BMI} = \frac{\text{weight in kilograms}}{(\text{height in meters})^2}$$

The age will be calculated as:

- years= (intck('month',brthdtc,rficdtc)-(day(rficdtc) < min(day(brthdtc), day(intnx ('month', rficdtc, 1)-1)))) /12

- months = intck('month',birth,somedate) - (day(somedate) < day(birth));

Age (in years), age (in months), gender, overall racial group (White, Black, Asian, Other), racial group (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed), ethnicity (Hispanic or Latino, not Hispanic or Latino), region (North America, Latin America, Western Europe, Eastern Europe, Asia Pacific and others), weight (kg), height (cm), BMI (kg/m^2), BMI category (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), head circumference (cm) and seizure category at ScrV (POS, PGS*, typical absence seizures, PGS, UNC) will be summarized. This summary will be repeated by cohort, by seizure category, by core study and by geographical region.

All demographic and Baseline characteristics will be listed.

6.2 Medical history and concomitant diseases

The number and percentage of subjects with a medical history condition, including both previous and ongoing conditions will be summarized overall and by primary MedDRA system organ class (SOC) and preferred term (PT). In addition, this summary will also be done by seizure category.

All medical history data will be listed.

6.3 History of epilepsy

6.3.1 Epileptic seizure profile

The number and percentage of subjects experiencing each seizure category at any time prior to study entry will be summarized based on the ILAE Seizure Classification History eCRF.

The overall number and percentage of subjects with a history of Type I (POS), Type II (PGS), or Type III (Unclassified) seizures will also be summarized. A subject will be classified as having a history of Type I seizures if the subject has a history of Type IA, IB, or IC seizures. A subject will be classified as having a history of Type II seizures if the subject has a history of Type IIA1, IIA2, IIB, IIC, IID, IIE, or IIF seizures.

6.3.2 Classification of epileptic syndrome

The number and percentage of subjects with each epileptic syndrome will be summarized based on the Classification of Epileptic Syndromes eCRF and will include the number and percentage of subjects within each of the categories (localization-related, generalized, epilepsies and syndromes undetermined whether focal or generalized, and special syndromes) and subcategories of epileptic syndromes. Additionally, this summary will be done separately for each seizure category.

6.3.3 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 diagnosis, and percent of life with epilepsy will be summarized separately for subjects with POS categorization at Baseline and for subjects with PGS categorization at Baseline.

For derivation of epilepsy duration and percent of life with epilepsy, see Section 3.10.2.

6.3.4 Historical seizure count

The Historical Seizure Count eCRF records the number of seizures of each type experienced by the subject during the 3 weeks prior to study entry. These data will be provided in a subject data listing.

6.4 Previous and concomitant medications

A listing of all medications (previous and concomitant) taken during the study will be presented. See Section 3.10.4.1 for the definition of previous, concomitant and follow-up medications.

For the summarization, similar AEDs are grouped and summarized together. For example: Valproate includes valproate sodium, valproate semisodium, valproate bismuth, valproate magnesium, valpromide, ergenyl chrono, valproic acid; Phenytoin includes phenytoin sodium, phenytoin calcium, mephenytoin, zentronal, metetoin, ethotoin, albutoin, hydantal, phelantin, hydantol D, anirrit, dintoinale, fosphenytoin sodium, phenytoin, fosphenytoin, hydantoin derivatives, hydantoin; Phenobarbital includes phenobarbital sodium, methylphenobarbital, metharbital, alepsal, phenobarbital, kaneuron, epanal. Benzodiazepine AEDs that can be grouped by Bromazepam, Alprazolam, Cloxazolam, Diazepam group, Chlordiazepoxide, Clonazepam, Clobazam, Lorazepam, Clotiazepam, Temazepam, and Clorazepate are considered the same AED at the group level. Combination AEDs are not considered for grouping.

6.4.1 Non-AEDs taken at study entry

Identification of medications as a non-AED will be done using the UCB file: AEDs_ATCs_SEP2017_FINAL_benzo_groups_23JUL2019.xls, which reflects AED evaluation result of concomitant Benzodiazepine from the data review meetings. Queries should be raised for any cases where this disagrees from the value entered in the eCRF field 'Core AED'.

The number and percentage of subjects in the SS taking non-AED medications at the time of study entry will be summarized by WHO-DRL anatomical main group, therapeutic group and preferred drug name.

6.4.2 Number of previous AEDs

The number of AEDs taken prior to study entry will be summarized based on the following categorization: 0-1 AEDs, 2-4 AEDs, and ≥ 5 AEDs. Identification of medications as an AED will be done using the UCB file: AEDs_ATCs_SEP2017_FINAL_benzo_groups_23JUL2019.xls, which reflects AED evaluation result of concomitant Benzodiazepine from the data review meetings. This summary will only include AEDs which stopped prior to study entry. In addition, this summary will also be done by seizure category.

6.4.3 History of previous AED use

The number and percentage of subjects who had taken at least 1 AED prior to study entry will be summarized by preferred drug name. Identification of medications as an AED will be done using the UCB file: AEDs_ATCs_SEP2017_FINAL_benzo_groups_23JUL2019.xls, which reflects AED evaluation result of concomitant Benzodiazepine from the data review meetings. This summary will only include AEDs which stopped prior to study entry. Furthermore, the above described summary will be repeated by seizure category.

6.4.4 History of previous AEDs by reason for AED discontinuation

The number and percentage of subjects who had taken at least 1 AED prior to study entry and who had discontinued AED will be summarized overall, by reason for discontinuation of previous AEDs (insufficient efficacy, remission, adverse drug reaction, tachyphylaxis, unknown, other) and by age group in one table. Additionally, this summary will be done by seizure category.
Percentages for each reason for discontinuation will be relative to the number of subjects taking each AED.

6.4.5 VNS use and Number of AEDs taken at study entry

Identification of medications as an AED will be done using the UCB file: AEDs_ATCs_SEP2017_FINAL_benzo_groups_23JUL2019.xls, which reflects AED evaluation result of concomitant Benzodiazepine from the data review meetings. The number and percentage of subjects taking 1, 2, and 3 AEDs at the time of study entry overall and separately by vagal nerve stimulation (VNS) use at study entry (no VNS or VNS not active versus currently active VNS) will be summarized. This analysis will be done by seizure category in addition.

6.4.6 AEDs taken at study entry

The number and percentage of subjects who had taken at least 1 AED at the time of study entry by WHO-DRL preferred drug name will be summarized. In addition, this analysis will be done by seizure category. Vagal nerve stimulation is allowed and will be counted as a concomitant AED.

6.4.7 Concomitant AEDs

The number and percentage of subjects taking concomitant AEDs overall and by WHO-DRL preferred drug name will be summarized by age group. In addition, this analysis will be done by seizure category.

6.4.8 Concomitant Non-AEDs

The number and percentage of subjects taking concomitant Non-AEDs overall and by WHO-DRL anatomical main group, therapeutic group and preferred drug name will be summarized overall by age group. In addition, this analysis will be done by seizure category.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

BRV compliance will not be assessed due to the complexities associated with the calculation and interpretation of BRV compliance for this study.

BRV dosing will be provided in subject listings.

8 SAFETY ANALYSES

All presentation for safety parameters will be based on the SS and will be summarized by age group and seizure category as categorized in Section 4.8, and overall.

8.1 Extent of exposure

The Evaluation Period BRV exposure duration (in months) will be calculated as the date of the final dose of BRV during the Evaluation Period minus the date of the first dose of BRV in the Evaluation Period plus 1 day divided by 30. The overall study BRV exposure duration (in

months) including Up-Titration Period (only DE subjects), Evaluation Period and Down-Titration Period (only discontinued subjects) will be calculated as the date of the final dose of BRV in this study minus the date of the first dose of BRV in this study plus 1 day divided by 30.

Subject years of exposure are calculated as overall study BRV exposure duration (in months) multiplied by 30 divided by 360.

Both, the evaluation Period BRV exposure duration and the overall study BRV exposure duration will be summarized with quantitative descriptive statistics. The number and percentage of subjects with the following categories of Evaluation Period BRV exposure durations will also be presented: ≤ 6 months, > 6 to ≤ 12 months, > 12 to ≤ 18 months, > 18 to ≤ 24 months, > 24 to ≤ 30 months, > 30 to ≤ 36 months, and > 36 months.

The number and percentage of subjects exposed overall and by 6 month exposure durations (<= 6 months of exposure, > 6 months of exposure, > 12 months of exposure, > 18 months of exposure …) will be presented overall and by modal dose category (see Section 3.2.8). Additionally, the table will show mean subject years of exposure overall and by modal dose categories.

All BRV exposure data will be listed.

8.2 AEs

8.2.1 Overview of TEAEs

The overview of TEAEs will provide numbers and percentages of subjects with any TEAE, with any serious TEAE, with any TEAE that led to permanent discontinuation of BRV, with any drug-related TEAE, with any severe TEAE and with any drug-related serious TEAE. The number and percentage of subjects who died will also be summarized. This summary will be provided by age group in the SS. Additionally, it will be presented by core study, geographical region and seizure category as well as by modal dose category.

TEAEs which occurred during Up-Titration Period for DE subjects will be presented separately.

The criteria for classification of an AE as serious AE can be found in the protocol section 9.1.1.2. AEs are drug-related, if this is marked accordingly in the eCRF.

8.2.2 Incidences of TEAEs

Incidence summaries will be presented by SOC and PT. These tables will include the number and percentage of subjects and number of events by SOC and PT. For the number of subjects by PT, if a subject experiences multiple AE within the same PT, then that PT will only be counted once. As with the PT, for the number of subjects by SOC, if a subject experiences multiple AEs within the same SOC, then that SOC will be counted only once. Percentages will be calculated out of the number of subjects at risk in the SS unless otherwise stated.

Incidence tables are sorted alphabetically by SOC and decreasing by frequency in PT in the overall column. In case of ties, PTs are sorted alphabetically.

The following TEAE summaries will be presented:

- Incidence of TEAEs

- Incidence of TEAEs by 3-month time interval (one table presenting TEAEs starting within time intervals and one presenting those ongoing in the time interval)
- Incidence of drug-related TEAEs by 3-month time interval
- Incidence of TEAEs by 1-year time interval
- Incidence of TEAEs by total duration of exposure cohort (as per categories defined in Section 3.2.7)
- Incidence of TEAEs by study period (Up-Titration, Evaluation, Down-Titration, Safety)
- Incidence of TEAEs by maximum intensity
- Incidence of drug-related TEAEs
- Incidence of serious TEAEs
- Incidence of drug-related serious TEAEs
- 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
- Incidence of TEAEs by 3-month time intervals for TEAEs occurring in at least 5% of subjects by geographical region
- Incidence of non-serious TEAEs occurring in at least 5% of subjects
- Incidence of non-serious TEAEs occurring in at least 5% of subjects by geographical region
- Incidence of drug-related TEAEs occurring in at least 5% of subjects
- Incidence of drug-related TEAEs occurring in at least 5% of subjects by geographical region
- Incidence of TEAEs leading to permanent discontinuation of BRV
- Incidence of drug-related TEAEs leading to permanent discontinuation of BRV

Tables presenting incidence of TEAEs occurring in at least 5% of subjects will include only TEAEs occurring on or above the reporting threshold of 5% in any age group or geographical region.

Additionally, following incidence tables will be presented by total duration of exposure categories:

- Incidence of serious TEAEs
- Incidence of TEAEs leading to permanent discontinuation of BRV

A subject number table will be provided that identifies subjects with any TEAE after the first dose of BRV. This table will be presented by intensity, relationship, treatment-emergence overall and by every subcategory of these variables.

The overview of TEAE, the incidence of TEAEs and incidence of serious TEAEs will be presented by age group, by seizure category, by dose group and by core study.

8.2.3 Incidences of TEAEs of interest

Incidence of TEAEs of interest as per Section 9.1.1.3 in study protocol will be presented separately, by age group as well as by age group and 3-month time interval.

AEs of interest will be identified based on MedDRA search criteria, which are documented outside of the SAP. All AEs which are listed in "BRV List of TEAE Topics of Interest Final 24 Aug 2018.xlsx" document (provided from UCB) and are flagged with "P" or "B" in appropriate column are AEs of interest for this study.

8.3 Clinical laboratory evaluations

Clinical laboratory results will be summarized using conventional units. Observed values and change from Baseline values for hematology, biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT) and endocrinology parameters will be summarized for Baseline, each scheduled visit in the Evaluation Period, Last Value on Treatment, and the Safety Visit (if available). These summaries will be repeated separately for data collected during the Up-Titration visits for DE subjects.

Presentation of urinalysis results will consider subjects by age group for whom sample collection is feasible due to the constraints on collection for subjects below 4 years of age in the protocol. Following age groups will be presented: >=4 to <12 years, >=12 years to <17 years and overall.

In microscopic urinalysis, a small sample of urine is centrifuged to remove the liquid. The sediment is then examined under a microscope. In the urinalysis laboratory test group, other than qualitative responses, a listing of microscopic analysis parameters will be provided; no summaries of microscopic analysis findings are planned.

Response categories are negative, 1+, 2+, and 3+ for the quantitative 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:

Table 8–1: Urinalysis categorization

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, EV, each scheduled visit during the Evaluation Period for which urinalysis parameters were scheduled to be assessed, Last Value on Treatment, and the Safety Visit. Percentages for each parameter will be relative to the number of subjects with a microscopic urinalysis assessment at each time point. The summary will be repeated for the Up-Titration period for DE subjects.

The number and percentage of subjects with any post-Baseline PCST value, any PCST low value, and any PCST high value for hematology, biochemistry and urinalysis will be summarized for the Evaluation and Safety Periods separately and for the Evaluation and Safety Period combined by laboratory parameter overall and by age group. PCST criteria for hematology and biochemistry are presented in Appendix Section 12.1 A urinalysis value is considered PCST abnormal if an upward shift of at least 2 degrees from the Baseline occurs under investigational treatment. Percentages will be relative to the number of subjects with an on-treatment assessment.

Observed values and change from Baseline value tables will only present scheduled visits, whereas for PCST tables, values reported at an UV will be summarized under the preceding scheduled visit if the abnormality was not already reported at the preceding scheduled visit. Treatment emergent for this analysis includes any PCST laboratory abnormalities observed during the Evaluation Period.

A subject number table will be provided that identifies subjects with a PCST finding after the first dose of BRV for each type of laboratory abnormality.

All laboratory parameters (planned and unplanned parameters and assessed on scheduled and unscheduled visits) will be provided in subject data listings.

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

8.4.1 Vital signs

Vital signs, including measurements of blood pressure, supine or sitting pulse rate, and body temperature, are assessed after 5 minutes of rest at the ScrV, TV(s), and EV, MEV, FEV, YEV, FV, and at the EDV, Down-Titration Visit (DTV), and the SV in the case of early discontinuation. For LTFU subjects, at the EV, vital sign data will be obtained from the final visit of the core study (if available) and should not be recorded in the eCRF for N01266. If not available, vital signs data will be recorded within N01266 as for DE subjects.

Observed values and change from Baseline value for SBP, DBP, and pulse rate will be summarized for Baseline, EV, each visit during the Evaluation Period for which vital signs or body weight were assessed, EDV, Last Value on Treatment, FV, the Down-Titration Visit (DTV), and the Safety Visit (if available). This summary will be repeated separately for data collected during the Up-Titration visits for DE subjects.

The PCST criteria are based on FDA Division of Neuropharmacological Drug Products guidelines with some UCB-defined additions.

The number and percentage of subjects with any post-Baseline PCST value, any PCST low value, and any 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 final dose of BRV (excluding Up-Titration Assessments for DE Subjects). Percentages will be relative to the number of subjects with a post-Baseline assessment. This summary will be repeated for the Up-Titration Period for DE Subjects.

Additionally, the PCST table will be provided stratified by visit for all visits during Evaluation Period. Percentages will be relative to the number of subjects with a value at the corresponding visit.

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

All vital signs will be provided in subject data listings.

8.4.2 ECGs

A standard 12-lead ECG is performed at the ScrV, TV(s), and EV, YEV, FV, and at the EDV in the case of early discontinuation. An ECG is performed at the SV only if the ECG results at the EDV are abnormal. At the EV, for LTFU subjects, ECG data will be obtained from the final visit of the core study (if available) and should not be recorded in the eCRF for N01266. If not available, ECG data will be recorded within N01266 as for DE subjects. The Investigator will determine whether the results of the ECG are normal or abnormal and assess the clinical significance of any abnormalities.

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 and by age group. This summary will consider all assessments after the first dose of BRV in the Evaluation and prior to or on the date of the final dose of BRV. Percentages will be relative to the number of subjects with a post-Baseline assessment in the Evaluation Period. This summary will be repeated for the Up-Titration Period for DE Subjects.

Additionally, this table will be provided stratified by visit for all visits during Evaluation Period. Percentages will be relative to the number of subjects with an ECG assessment at the corresponding visit. Subjects are counted only once at each time point based on the worst observed outcome across all abnormalities reported at that time point.

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

All ECG data will be provided in subject data listings.

8.4.3 Physical examination

A listing of abnormal physical examination findings will be provided; no summaries of physical examination findings are planned. Tanner scale will be recorded as part of the physical examination where applicable and will also be listed.

8.4.4 Neurological examination

A standard neurological examination is performed at the ScrV and EV (DE subjects only), FEV, YEV, FV, and at the EDV and the SV in the case of early discontinuation. For LTFU subjects, at the EV, neurological examination data will be obtained from the final visit of the core study and should not be recorded in the eCRF for N01266.

A listing of neurological examination findings will be provided; no summaries of neurological examination findings are planned.

8.4.5 Psychiatric and mental status

Psychiatric and mental status is reported by recording the presence or absence of psychiatric symptoms, mental impairment, and behavioral problems at the ScrV and EV (DE subjects only), FEV, YEV, FV, and at the EDV and the SV in the case of early discontinuation. For LTFU subjects, at the EV, psychiatric and mental status data is obtained from the final visit of the core study.

A listing of abnormal Psychiatric and Mental Status findings will be provided; no summaries of Psychiatric and Mental Status findings are planned.

8.4.6 Vagus nerve stimulation (VNS) status

VNS status is recorded at the ScrV, and EV (DE subjects only), MEV, FEV, YEV, FV and at the EDV and the SV. For LTFU subjects at the EV, VNS status is obtained from the final visit of the core study.

A listing of VNS status will be provided; no summaries of VNS data are planned (with the exception of VNS information recorded on medication pages, see section 6.4).

8.4.7 Neuro-imaging procedures

A brain MRI or brain CT scan (except in Germany) may be recorded prior to the date of the first dose of BRV and used as Baseline if no previous report was available within the 2 years prior to study entry into N01266. A listing of neuro-imaging findings will be provided; no summaries of neuro-imaging findings are planned. Neuro-imaging procedures are only applicable for LTFU subjects.

8.4.8 Assessment of suicidality

Suicidality is assessed by trained study personnel using the C-SSRS (Columbia-Suicide Severity Rating Scale) for subjects ≥ 6 years of age. This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study.

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 subsets of subjects with suicidal ideation and the subset of subjects with actual suicide attempts

Suicide ideation includes a “yes” answer to any 1 of the 5 suicidal ideation questions on the C-SSRS:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

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

- [redacted]
- [redacted]
- [redacted]

8.4.9 Reproductive potential and birth control

A listing of reproductive potential and birth control measures for female as well as male subjects will be provided; no summaries of these findings are planned.

9 EFFICACY ANALYSES

All presentation for efficacy parameters will be based on the FAS and will be summarized by age group (<2 years and ≥2 years of age) and seizure category as categorized in Section 4.8, and overall.

Efficacy variables will be assessed using the seizure count information recorded on the DRC and EEG data. Endpoints derived from the DRC will be summarized separately from those derived from the EEG. EEG data collected from 24-hour EEG and 1-hour EEG will be presented separately.

Details of the derivations for all efficacy variables are provided in Section 3.10.3.1.

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

All seizure data and derived endpoints will be listed. Data from Up-Titration Period (DE subjects only) and Down-Titration Period will be listed only, if not otherwise mentioned.

9.1 Seizure based variables based on EEG data

EEG summaries will be presented by age group (< 2 years (24 hour EEG), ≥2 years (1 hour EEG)) and by seizure category. Outputs will explicitly restrict the analyses on 24 hour EEG to subjects < 2 years of age. If we have 1 hour EEG assessments for subjects categorized as < 2 years of age according to the Baseline age, we will perform sensitivity analyses in which we present results only by age group (< 2 years, ≥2 years), irrespective of the type of EEG performed. The POS and PGS* results for subjects ≥2 years will be missing, because EEG is only performed for subjects within Typical Absence seizure category there.

All analyses will be based on data assessed in Evaluation Period only.

Absolute and percent change in ADF will be summarized by age group and seizure category. Additionally, absolute and percent change in POS ADF will be summarized similarly.

Number of responders based on all seizure categories and the corresponding responder rate will be presented. Same will be presented for response based on POS only.

The number and percentage of seizure free subjects (Seizure freedom) will be presented.

Absolute and percent worsening based on PGS seizure types will be summarized.

All raw EEG seizure counts and derived efficacy variables will be listed.

9.2 Seizure based variables based on DRC data

Absolute and percent change in 28-day adjusted seizure frequency and in 28-day adjusted POS seizure frequency will be summarized for the Evaluation Period by seizure category. This summary will present both age groups to be consistent with EEG summary and worsening based on DRC. The corresponding number and percentage of responder in reduction of 28-day adjusted seizure frequency and 28-day adjusted POS seizure frequency will be presented separately.

For subjects < 2 years of age or ≥ 2 years of age with typical absence seizures, absolute and percent worsening will be presented. Additionally, the ADF will be summarized by age group, seizure category and visit/time period.

The proportion of seizure free days over Evaluation Period will be summarized using quantitative statistics. This summary will be repeated for proportion of seizure free days by visit and by 3-month time interval (including only subjects < 2 years of age or >= 2 years of age with typical absence seizures).

Number and percentages of Seizure freedom will be presented over Evaluation Period. This summary will be repeated for seizure freedom by visit and by 3-month time interval (including only subjects < 2 years of age or >= 2 years of age with typical absence seizures).

Shift tables presenting the incidences of new seizures will be prepared to show actual occurrences of new seizures as well as the percentages based on subjects under risk (subjects without particular seizure type at Baseline).

All raw DRC data and derived efficacy variables will be listed.

9.3 Direct cost parameters

Direct costs will be assessed based on concomitant medications, concurrent medical procedures, health care provider consultations not foreseen by protocol, hospital stays, and ER visits.

All direct cost parameters will be summarized for the SS.

All direct cost parameters will be listed.

9.3.1 Concomitant medications

The analysis of concomitant medications is described in Section 6.4.7 and Section 6.4.8.

9.3.2 Concurrent medical procedures

The number of concurrent medical procedures per subject will be summarized by 6-month time intervals for the corresponding 6-month Exposure Duration Cohorts. Additionally, the number of concurrent medical procedures will be summarized for subjects with < 6 months of exposure to BRV. The number of concurrent medical procedures per subject will be summarized using the categories 0, 1, 2, 3, 4, and 5 or more. Summaries will be provided for the SS.

Medical procedures are defined to be concurrent, if they start after first dose of BRV and will be attributed to 6-month time intervals based on the date of the procedure. For subjects with < 6 months of exposure to BRV, all medical procedures on or after the first dose of BRV will be counted.

9.3.3 Additional healthcare provider consultations

The number of additional healthcare provider visits per subject will be summarized by 6-month time intervals for the corresponding 6-month Exposure Duration Cohorts. Additionally, the number of additional healthcare provider visits will be summarized for subjects with < 6 months of exposure to BRV. The number of additional healthcare provider visits will be summarized using the categories 0, 1, 2, 3, 4, and 5 or more. Summaries will be provided for the SS.

Additional healthcare provider visits will be attributed to 6-month time intervals based on the date of the procedure. For subjects with < 6 months of exposure to BRV, all additional healthcare provider visits on or after the first dose of BRV will be counted.

The number of additional healthcare provider visits will be summarized by type of provider (General Practitioner, Specialist Physician, Nurse, or Other) and by 6-month time intervals for the corresponding 6-month Exposure Duration Cohorts, and for subjects with < 6 months of exposure to BRV. Percentages will be relative to the total number of health care provider visits within each 6-month time interval (for summaries by exposure duration cohorts) or the total number of healthcare provider visits for subjects with < 6 months of exposure to BRV. As above, this summary will be provided for the SS.

9.3.4 Hospital stays

The number of hospital stays per subject will be summarized by 6-month time intervals for the corresponding 6-Month Exposure Duration Cohorts. Additionally, the number of hospital stays will be summarized for subjects with < 6 months of exposure to BRV. The number of hospital stays will be summarized using the categories 0, 1, 2, 3, 4, and 5 or more. Summaries will be provided for the SS.

Hospital stays will be attributed to 6-month time intervals based on the date of the admission. For subjects with < 6 months of exposure to BRV, all hospital stays on or after the first dose of BRV will be counted.

The number and percentage of subjects with specified categories of duration of hospital stays will be summarized by 6-month time intervals and the 6-Month Exposure Duration Cohorts. Additionally, the number and percentage of specified categories of hospital stays will be summarized for subjects with < 6 months of exposure to BRV. Duration of hospital stays will be summarized descriptively for the SS.

The number and percentage of subjects with hospitals stays by duration categories as defined in Section 3.10.4.4 will be summarized by 6-month time intervals for the corresponding 6-Month Exposure Duration Cohorts. Additionally, this table will be produced for subjects with < 6 months of exposure to BRV.

9.3.5 Emergency room visits

The number of ER visits per subject will be summarized by 6-month time intervals for the corresponding 6-month Exposure Duration Cohorts, and for subjects with < 6 months of exposure to BRV. The number of ER visits per subject will be summarized using the categories 0, 1, 2, 3, 4, and 5 or more. Summaries will be provided for the SS.

ER visits will be attributed to 6-month time intervals based on the date of the ER visit. For subjects with < 6 months of exposure to BRV, all ER visits on or after the first dose of BRV will be counted.

9.4 Achenbach Child Behavior Checklist

The Achenbach CBCL is completed at the ScrV (DE subjects only), FEV, YEV, FV, and at the EDV in the case of early discontinuation. For LTFU subjects (except for those from core studies EP0065 and N01349), at the EV, the Achenbach CBCL score is obtained from the Baseline of the core study and should not be recorded in the eCRF for N01266. For DE subjects, the Achenbach CBCL completed at the ScrV and for EP0065 LTFU subjects the Achenbach CBCL completed at the EV, will be the Baseline assessment. For LTFU subjects from core study N01349 Achenbach CBCL Baseline assessment is not available, as this questionnaire was not performed in core study N01349 and not recorded at EV in N01266 study.

Calculated T-score values and raw score values and the corresponding change from Baseline for each CBCL/1½-5 syndrome (aggressive behavior, anxious / depressed, attention problems, emotionally reactive, sleep problems, somatic complaints, withdrawn) will be summarized for each scheduled visit during the Evaluation Period if available.

Calculated T-score and raw score values and corresponding change from Baseline for each CBCL/6-18 syndrome (aggressive behavior, anxious / depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, and withdrawn / depressed) will be summarized for each scheduled visit during the Evaluation Period if available.

Additionally, for all CBCL/1½-5 syndromes as well as CBCL/6-18 syndromes, shift tables for T-scores will be done. These shift tables are based on T-score legacy categorization “Normal”, Borderline” or “Clinical Significant” and the dichotomous approach “Normal” or “Borderline or Clinical Range” as described in Section 3.10.5.1 and will summarize the shift from Baseline for each visit during the Evaluation Period if available and for the last assessment. These shift tables will not include LTFU subjects from core studies N01349 as Baseline values are not available from this study.

All Achenbach CBCL data will be listed. Data assessed on unscheduled visits will be included in listings only.

9.5 BRIEF-P and BRIEF assessment

The BRIEF-P/BRIEF assessments are completed at the ScrV (DE subjects only), FEV, YEV, FV, and at the EDV in the case of early discontinuation. For LTFU subjects (except those coming from core studies N01349, EP0065 and N01263), at the EV of N01266, the BRIEF-P/BRIEF score will be obtained from Baseline of the core study and should not be recorded in the eCRF for N01266. For DE subjects and LTFU subjects from core study EP0065, the Baseline BRIEF-P/BRIEF should be completed at the ScrV. As BRIEF-P/BRIEF questionnaires have not been recorded in core studies N01263 and N01349 and as this data was not collected at EV of N01266, no Baseline values are available for those LTFU subjects within N01266.

The BRIEF-P or BRIEF appropriate for each subject’s age should be completed, with the following exception: For subjects who completed the BRIEF-P at the Baseline assessment and

turn 5 years of age between that assessment and the initial YEV, the BRIEF-P should be completed through and including the initial YEV, and subsequently the BRIEF should be completed.

Calculated T-score and raw score values and corresponding change from Baseline (if available) for the 3 indexed scores (Inhibitory Self-Control, Flexibility and Emergent Metacognition) and the GEC for the BRIEF-P questionnaire will be summarized for each visit during the Evaluation Period where the questionnaire is entered.

Calculated T-score and raw score values and corresponding change from Baseline (if available) for the 2 indexed scores (Behavioral Regulation and Metacognition) and the GEC for the BRIEF questionnaire will be summarized for each visit during the Evaluation Period where the questionnaire is entered.

In addition, for all indexed scores and GEC for BRIEF as well as BRIEF-P questionnaire, shift tables for T-scores will be done. These shift tables are based on T-score legacy categorization "Normal", Borderline" or "Clinical Significant" and the dichotomous approach "Normal" or "Potentially Clinically Significant" as described in Section 3.10.5.2 and Section 3.10.5.3 respectively and will summarize the shift from Baseline for each visit during the Evaluation Period where the questionnaire is entered. These shift tables will not include LTFU subjects from core studies N01349 and N01263 as Baseline values are not available from these studies,

All BRIEF-P and BRIEF assessment data (including validity scores negativity and inconsistency) will be listed.

9.6 Bayley Scales of Infant and Toddler Development, Third Edition

Bayley-III scales are completed within the core study (except for EP0065) if the subject is enrolled in an English-speaking country or a country where a validated translation is available, and data should not be recorded in the eCRF in N01266. If not stated otherwise, the EV data from core study will be obtained as EV data for N01266. For LTFU subjects coming from N01349, the Bayley-III data recorded at FV of N01349 will be obtained as EV data for N01266. Subjects that have been rolled-over from core study EP0065 will complete the Bayley-III questionnaire at the EV of N01266. For N01263 LTFU subjects, the Baseline Bayley-III questionnaire data of the core study will be obtained as EV data for N01266. Directly enrolled subjects will not have data of this type as they are enrolled at an older age than the cohort of ≥ 18 to ≤ 42 months covered by this assessment.

The Bayley-III scales will be completed for LTFU subjects at the FEV, YEV, FV, and at the EDV in the case of early discontinuation.

The sum of scaled scores entered on the eCRF, and change from Baseline for the cognitive scale, language composite scale, motor composite scale, and social-emotional scales, as well as the adaptive behavior scale, will be summarized at Baseline and each visit during the Evaluation Period, if available. All recorded raw scores, scaled scores, composite scores, percentile rank and growth scores will be listed.

9.7 PedsQL assessment

The PedsQL is completed at the ScrV (DE subjects only), FEV, YEV, FV, and the EDV in the case of early discontinuation. For LTFU subjects (except those from core studies EP0065,

N01349 and N01263), at the EV, the PedsQL score will be obtained from Baseline of the core study for subjects ≥ 2 years and is not recorded in the eCRF in N01266. For DE subjects the Baseline PedsQL is completed at the ScrV, for LTFU subjects from core study EP0065 the Baseline PedsQL is completed at the EV of N01266. Within core studies N01349 and N01263 PedsQL assessment was not performed. Furthermore, PedsQL assessment was not done at the EV of N01266 for N01263 and N01349 LTFU subjects. Therefore, Baseline PedsQL is not available for those LTFU subjects.

For subjects <5 years of age only parent-report-scores for PedsQL are available, for subjects >=5 years of age self-reporting scores as well as parent-reporting scores for PedsQL might be available. Self-reporting and parent-reporting scores will be summarized separately. Complete score-related data will be listed.

Calculated values and change from Baseline (if available) for the total scale score, psychosocial health score and each of the 4 scale scores will be summarized for each visit during the Evaluation Period where the questionnaire is entered. Subgroup summaries by age will be performed using the age groupings for which different questionnaires are entered; ≥ 2 to ≤ 4 years, ≥ 5 to ≤ 7 years, ≥ 8 to ≤12 years, and ≥ 13 to ≤ 18 years.

All PedsQL data will be listed.

10 PHARMACOKINETICS

Pharmacokinetic samples will be taken for determination of BRV plasma concentration on FEV and on FV or EDV. In addition to the scheduled assessments, it should be obtained whenever a subject experience an SAE.

Subjects receiving phenytoin as a concomitant AED during the study will have blood samples collected at the ScrV (DE subjects only), FEV, YEV, FV, or at the EDV in the case of early discontinuation and Safety Visit (SV) to monitor phenytoin plasma concentrations. The PK samples will also be taken for determination of phenytoin plasma concentration, if applicable.

The plasma concentrations data will only be listed.

11 REFERENCES

National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion. 2000. http://www.cdc.gov/growthcharts (accessed 23 Dec 2013).

J W Varni The PedsQL: measurement model for the pediatric quality of life inventory https://www.pedsql.org/index.html

12 APPENDICES

12.1 PCST Criteria for Hematology and Biochemistry Parameters

Parameter	Age Range	UNIT	Abnormality Criteria
Hematology			
Hematocrit	<2y	%	≤27 >45
	≥2y - <18y		≤29 >47
Hemoglobin	<2y	g/dL	≤9.0 >15.0
	≥2y - <18y		≤9.5 >16.0
WBC/Leukocytes	<12y	10^9/L	<3.5 >15.0
	≥12y		<3.0 >12.0
Lymphocytes	<6m	%	≤30.0
	≥6m - <6y		≤22.0
	≥6y - <18y		≤12.0 ≥80.0
Basophils	>1m	%	≥3.0
Eosinophils	>1m	%	≥10.0
Monocytes	>1m	%	≥20.0
Platelets	>1m	10^9/L	≤100 >600
RBC/ Erythrocytes	<2y	10^{12}/L	<3.0
	≥2y		<3.5
Biochemistry			
AST (SGOT)	<14y	U/L	>180
	≥14y		>144
ALT (SGPT)	1y - <18y	U/L	>90
Alkaline Phosphatase	<4y	U/L	>690

Parameter	Age Range	UNIT	Abnormality Criteria
	≥4y - <10y		>834
	≥10y - <17y		>1174
GGT	<6m	U/L	>522
	≥6m - <1y		>279
	≥1y - <13y		>66
	≥13y - <18y		>126
Total Bilirubin	>1m	mg/dL	≥1.5
Total Protein	2m-<1y	g/dL	<3.0 >10.0
	≥1y		<4.3 >10.0
Albumin	<1y	g/dL	<1.6 >6.0
	≥1y		<2.4 >7.0
BUN	<1y	mg/dL	>21
	≥1y		>30
Urea	<1y	mg/dL	>42
	≥1y		>60
Creatinine	1y - <10y	mg/dL	>0.9
	≥10y - <16y		>1.4
Creatinine Clearance[a]	All	mL/min	<70
Calcium	<1y	mg/dL	<6.9 >12.2
	1y - <18y		<7.4 >11.7
Phosphorous	<1y	mg/dL	<1.8 >8.2
	≥1y		<1.8 >7.4
Potassium	<1y	mEq/L	<3.0 >6.5
	≥1y		<3.0 >5.8

Parameter	Age Range	UNIT	Abnormality Criteria
Sodium	>1m	mEq/L	≤130 ≥150
Glucose	>1m	mg/dL	<50 >180
Total Cholesterol	1y - <18y	mg/dL	>250
LDL (calculated)	1y - <18y	mg/dL	>140
HDL	≤2y	mg/dL	<10
	>2y		<20
Triglycerides	<1y	mg/dL	>750
	≥1y		>250
Uric Acid	<1y	mg/dL	>7.7
	1y - <13y		>6.5
	≥13y - <18y		>8.6
Thyroxine (T4)	<1y	ug/dL	≤4.3 ≥18.4
	≥1y		≤3.8 ≥13.5
Globulin	<1y	g/dL	<1.0 >3.8
	≥1y		<1.2 >4.4

m=month; y=year.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CrCl=creatinine clearance; dL=deciliter; GGT= gamma-glutamyltransferase; HDL=high density lipoprotein; LDL=low density lipoprotein; L=liter; µg=microgram; m=month (defined as 30 days); mg=milligram; PCST=possibly clinically significant treatment-emergent; U=unit; y=years (defined as 365.25 days)
[a]Schwartz equation (subjects <12): CrCl ml/min=[Height (cm) * 0.55] / serum creatinine
Cockroft equation (subjects ≥12): Male: CrCl ml/min=[(140-age) x body weight (kg)] / (72 x serum creatinine); Female: CrCl ml/min=[(140-age) x body weight (kg)] / (72 x serum creatinine)] x 0.85
Note: A month is defined as 30 days; a year is defined as 365.25 days.

12.2 PCST Criteria for Urinalysis

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

Conversion of results in a five-point scale into a four-point scale

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

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

Urinalysis 4-point scales for PCST criteria

PARAMETER	Negative	1+	2+	3+
Protein	Negative	Trace, 30 mg/dL	100 mg/dL	≥300 mg/dL, ≥1000 mg/dL
Glucose	Negative	100 mg/dL, 250 mg/dL	500 mg/dL	≥1000 mg/dL
Ketones	Negative	Trace, 15 mg/dL	40 mg/dL	≥80 mg/dL, ≥160 mg/dL
Hemoglobin (Occult blood)	Negative	Trace, Small	Moderate	Large
Leukocyte Esterase	Negative	Trace, Small	Moderate	Large
Erythrocytes or Leukocytes	1-5 6-10	11-20	21-25	>25

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

12.3 PCST Criteria for Vital Signs

Parameter (Unit)	Age Range	Abnormality criteria
Pulse Rate (beats/minute)	<6m	<100 >180
	≥6m - <3y	<90 >150
	≥3y - <12y	<60 >130

Parameter (Unit)	Age Range	Abnormality criteria
	≥12y - <17y	<50 >120
Systolic Blood Pressure (mmHg)	<6m	<60 >100
	≥6m - <3y	<70 >120
	≥3y - <12y	<80 >140
	≥12y - <17y	<90 >160
Diastolic Blood Pressure (mmHg)	<6m	<40 >65
	≥6m - <3y	<45 >75
	≥3y - <12y	<50 >80
	≥12y - <17y	<50 >105
Body Weight	1m - <17y	<3% or >97% of the normal body weight growth curve ranges based on gender and the age of subject on date of weight assessment
	≥17y	A decrease/increase from Baseline of ≥ 10%
m=month, y=year. Note: A month is defined as 30 days; a year is defined as 365.25 days.		

13 AMENDMENTS TO THE SAP

SAP amendment 1

SAP amendment 1 includes changes based on Protocol amendment 5 and Protocol amendment 6:

Changes based on Protocol amendment 5 (PA05):

- Duration of study at least 3 years (no longer approx. 3 years)
- Subjects will receive oral solution or tablets, as appropriate (independent if they are < 7 years or ≥ 7 years of age).
- Reference to serious AEs added
- Reference to AEs of interest added
- "Core study" terminology: "previous BRV study" has been changed to "core study"
- Subjects ≥ 2 years of age with typical absence seizures have at least a 24-hour EEG, instead of a 1-hour EEG

Changes based on Protocol amendment 6 (PA06):

- PedsQL for LTFU subjects will only be assessed for subjects with ≥2 years of age at Baseline of core study (no longer for subjects < 2 years)
- Bayley Scale for LTFU subjects will be assessed in English-speaking countries **and** countries where a validated translation is available

Changes not based on PA05/PA06:

- Add descriptions and derivation rules for seizure categories at ScrV used for efficacy and safety analysis in Section 3.10.3
- Update of descriptions and derivation rules of Efficacy variables in Section 2.2.2, Section 3.9 and Section 9.1.
- Update of derivation rules for EV and Baseline values for LTFU subjects based on data availability in core studies and N01266, for example for EEG, ECG, vital signs as well as questionnaire data
- Clarification for subgroup analyses (by age group, by cohort, by core study, by geographic region, by dose group, by seizure category)

SAP amendment 2

SAP amendment 2 includes following changes:

- SAP is based on Protocol Amendment 8, 25 Jun 2020.
- According to the update in the specification of important protocol deviations, the maximum allowable BRV dose is 5.0mg/kg/day, not to exceed a dose of 200mg/day for all subjects. Body weight condition has been deleted.
- The end of study possibility because of subject's transition to another BRV study has been added.

- Study variables have been organized in primary, secondary and other variables according to protocol amendment 8.
- The section 3.10.3 Seizures and seizure categories has been updated to give more details on how subjects are categorized into seizure categories. Description has been specified to explain in which subjects will be categorized if requirements for more than one category would be fulfilled.
- Absence Seizure category has been renamed to Typical Absence Seizure category according to the data evaluation meeting 2 decisions.
- For the efficacy EEG data, it has been clarified which data to use if central reader and site investigator interpretation of EEG differ. Moreover, the number of interpretable hours of 24 hours EEG will be considered in ADF calculation.
- Reduction has been renamed in "Change" according to protocol amendment 8.
- Worsening as categorical variable is not needed anymore as per protocol and has been deleted.
- In Section 3.10.4.1 Medications (AED and non-AED), it has been added that the AED outputs will reflect AED evaluation result of concomitant Benzodiazepine from the data review meetings.
- In Section 3.10.5.1 the Achenbach CBCL T-score categories have been corrected.
- Clarification of the definition of prior medications and medication at study entry for LTFU subjects has been added.
- Within the age groups the group ≥ 2 to < 12 years of age has been split into ≥ 2 to < 4 years of age, ≥ 4 to < 12 years of age.
- Overall subject disposition will be presented by core study.
- The grouping of similar AEDs is applicable to all analyses by preferred term and not limited to history of prior AED use only.
- Concomitant Non-AEDs will be summarized by anatomical main group, therapeutic group and preferred drug name.
- In Section 8.2.2 Incidences of TEAEs, tables by geographical region have been added.
- In Section 9.1 Seizure based variables based on EEG data the sensitivity analyses have been added in case of subjects received 1 hour and 24 hours EEG.
- In Section 9.2 Seizure based variables based on DRC data corrections have been made according to data evaluation meeting 2 decisions.
- Analyses of pharmacokinetics have been deleted in Section 10 according to data evaluation meeting 2 decisions.

SAP amendment 3

SAP amendment 3 includes following changes:

- Dichotomous approach for clinically significant ranges for T-scores added for BRIEF, BRIEF-P, and CBCL questionnaires
- Raw score values and change from baseline for BRIEF, BRIEF-P, and CBCL questionnaires added
- Age calculation added
- Term “special” removed from AE of interest
- PedSQL missing data clarification added

SAP amendment 4

SAP amendment 4 includes following changes:

- In Section 3.10.3 added a description of how subjects with UNC seizure category should be displayed in tables and listings
- In section 3.10.3.1 Derivation of efficacy variables has been updated to give more details on how N01349 subjects should be analyzed.
- Age calculation updated

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