PROTOCOL N01266 AMENDMENT 8

OPEN-LABEL, SINGLE-ARM, MULTICENTER, LONG-TERM STUDY TO EVALUATE SAFETY AND EFFICACY OF BRIVARACETAM USED AS ADJUNCTIVE TREATMENT IN PEDIATRIC SUBJECTS WITH EPILEPSY

PHASE 3

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
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LIST OF ABBREVIATIONS

ADF	average daily frequency
AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
Bayley-III®	Bayley Scales of Infant and Toddler Development®, Third Edition
bid	bis in die (twice daily)
BRIEF®	Behavior Rating Inventory of Executive Function®
BRIEF®-P	Behavior Rating Inventory of Executive Function®-Preschool Version
BRV	brivaracetam
BSID-II™	Bayley Scales of Infant Development™, Second Edition
CBCL	Child Behavior Checklist
CPM	Clinical Project Manager
CDMS	clinical data management system
COVID-19	coronavirus (SARS-CoV-2) disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
DRC	daily record card
DTV	Down-Titration Visit
ECG	electrocardiogram
eCRF	electronic case report form
EDV	Early Discontinuation Visit
EEG	electroencephalogram
EV	Entry Visit
FDA	Food and Drug Administration
FEV	Full Evaluation Visit
FV	Final Visit
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HRQoL	health-related quality of life
ICH	International Council for Harmonisation

IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IRB	Institutional Review Board
iv	intravenous
IVRS	interactive voice response system
LEV	levetiracetam
LFT	liver function test
LTFU	long-term follow-up
M	Month
MEV	Minimal Evaluation Visit
PDCO	European Paediatric Committee
PDILI	potential drug-induced liver injury
PedsQL™	Pediatric Quality of Life Inventory™
PK	pharmacokinetics
POS	partial-onset seizures
PP	polypropylene
PPR	photoparoxysmal response
PS	Patient Safety
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
ScrV	Screening Visit
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	Standard Operating Procedure
SS	Safety Set
SV	Safety Visit
SV2A	synaptic vesicle protein 2A
TEAE	treatment-emergent adverse event
TV	Titration Visit
ULN	upper limit of normal
UV	Unscheduled Visit
V	Visit

YEV	Yearly Evaluation Visit

1 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 POS who had not previously enrolled in a pediatric BRV study (herein referred to as "directly enrolled 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 directly enrolled 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 directly enrolled 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 directly enrolled 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 directly enrolled 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.

Brivaracetam (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 directly enrolled subjects must be able to tolerate at least 1mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266, as indicated in Section 7.2.

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 directly enrolled 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-glutamyltransferase [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 INTRODUCTION

2.1 Background regarding targeted disease

Epilepsy is the second most prevalent neurological disorder in the world. It is estimated that almost 70 million people suffer from epilepsy (Ngugi et al, 2011). Epilepsy affects about 4 to

6 out of 1,000 children aged less than 20 years old, and the overall annual incidence rates of epilepsy for all seizure types for all children aged less than 19 years range between 45 and 86 out of 100,000 children. Long-term prognosis of epilepsy varies across several factors such as types of syndromes, etiology, and presence of co-morbidities.

The existing treatment options for epilepsy in childhood generally follow the treatment options for adults, and clinical experience demonstrates that children may benefit from the administration of conventional AEDs for the treatment of partial-onset seizures (POS) with comparable results to adults. Despite the availability of new AEDs, more than 25% of pediatric patients have inadequate seizure control on currently available AEDs, or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007). Thus, there remains a need for potent AEDs with a positive benefit-risk profile in this population.

Diagnosis of epilepsy is based on the recurrence of seizures. Seizures may be caused by an underlying brain disorder or lesion or due to genetic conditions. Characterization of the epileptic syndrome has profound implications for treatment and prognosis. The major dichotomy for the diagnosis of epilepsy is the differentiation between focal epilepsies (ie, related to a focal brain dysfunction) which are the most frequent and account for approximately 60 to 70% of all cases, and generalized epilepsy syndromes, which represent approximately 25 to 30% of all epilepsy syndromes. In about 10% of cases, other specific syndromes are classified or the classification remains uncertain.

For the purposes of this study, the seizure type classification will follow the 1981 International League Against Epilepsy (ILAE) classification of epileptic seizures, which classifies partial seizures as simple partial seizures (no alteration of consciousness), complex partial seizures (with alteration of consciousness), and secondarily generalized seizures, and, on the other hand, classifies generalized seizure types, referred to as absence seizures (typical and atypical), myoclonic seizures, clonic seizures, tonic seizures, tonic-clonic seizures, and atonic seizures. Apart from myoclonic seizures, consciousness is almost invariably impaired from the onset of the seizure (Commission on Classification and Terminology of the ILAE, 1981).

Likewise, the classification of epilepsy syndromes will be used according to the 1989 ILAE publication (Commission on Classification and Terminology of the ILAE, 1989).

2.2 Background information regarding product

Brivaracetam ((2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1*H*-pyrrol-1-yl]butanamide) displays a high and selective affinity for the synaptic vesicle protein 2A (SV2A) in the brain. Binding to SV2A is believed to be the primary mechanism for BRV anticonvulsant activity. In 2016, marketing authorization for the use of oral and iv BRV as adjunctive treatment of partial-onset seizures (POS) in patients 16 years of age and older with epilepsy was granted in the EU, US, Australia, and Switzerland, and in Canada for patients 18 years and older with epilepsy.

More detailed information regarding the nonclinical and clinical development programs for BRV, including all completed and ongoing studies, is provided in the Investigator's Brochure.

2.3 Rationale for the study

N01266 is designed for pediatric subjects ≥1 month to <17 years of age who have completed core studies (LTFU subjects) and for at least 100 subjects ≥4 years to <17 years of age with POS who have not participated in a core study (directly enrolled subjects). The total enrollment planned for N01266 is approximately 600 subjects.

N01266 will provide long-term safety and tolerability data on BRV in pediatric subjects with epilepsy, while providing access to BRV for subjects who may benefit from long-term treatment. The enrollment of directly enrolled subjects is intended to provide both long-term safety and tolerably data and efficacy data for subjects 4 years to <17 years of age with POS to supplement data collected for subjects with POS in N01263.

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.

Subjects already enrolled in N01266 may participate in EP0065, if eligible, and then resume participation in N01266.

3 STUDY OBJECTIVES

3.1 Primary objective

- To document the long-term safety and tolerability of BRV

3.2 Secondary objective

- To assess the efficacy of BRV during long-term exposure

3.3 Other objectives

- 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 scales 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 PedsQL in subjects ≥ 2 years of age

4 STUDY VARIABLES

4.1 Primary variables

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

4.2 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)

4.3 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 absence seizures based on the 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 seizures (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 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 absence seizures:

- Number and type of nonabsence seizure

For all subjects:

- Physical (including Tanner staging, if applicable depending on subject's developmental status)
- Neurological examinations
- Psychiatric and mental status
- Laboratory tests (hematology, biochemistry including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT, 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) (See Section 9.2.1)
- 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 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 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 the 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 in 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)

5 STUDY DESIGN

5.1 Study description

This is a Phase 3, open-label, single-arm, multicenter, long-term study to evaluate the safety and efficacy of BRV in up to 600 subjects with epilepsy. Subjects who enroll in N01266 from a core study (ie, LTFU subjects) must have been <16 years of age upon entry in the core study; eligible subjects who have POS and enroll in N01266 without having participated in a core study (ie, directly enrolled subjects) must be ≥4 years to <17 years of age.

Upon enrollment, eligible LTFU subjects will enter the Evaluation Period and continue their BRV treatment in accordance with their individualized dose at the completion of the core study. Directly enrolled subjects will be screened and participate in up to 3 weeks of an Up-Titration Period. If a directly enrolled subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than the minimum specified dose) for 7±2 days during the Up-Titration Period, the subject will attend the EV and enter the Evaluation Period on that dose. The subjects already enrolled in N01266 who then participate in EP0065 will resume dosing in N01266 in accordance with the individualized dose they received at the completion of EP0065.

Brivaracetam (tablet and oral solution) should be administered bid in 2 equally divided doses. All LTFU subjects must be able to tolerate the minimum BRV dose specified in the core study to be eligible for entry into the Evaluation Period of N01266. All directly enrolled subjects must be able to tolerate at least 1mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266, as indicated in Section 7.2.

For all subjects enrolled in N01266, the maximum 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 oral tablets, as appropriate. Dose adjustments of BRV and/or concomitant AEDs are allowed at any time based on clinical judgment; however, during the Up-Titration Period, dose adjustments for BRV should be made only as specified in Section 7.2.1. Additional information on BRV administration is presented in Section 7.2.

For LTFU subjects, the EV is the first study visit. For directly enrolled subjects, the EV is the visit at which subjects enter the Evaluation Period and occurs after subjects have completed the ScrV and at least 1 Titration Visit (TV). For subjects who continue in the study until it ends, the Evaluation Period will extend from the EV to the FV. For subjects who prematurely discontinue the study, the Evaluation Period will last from the EV until the EDV. Following the EDV, or following the FV for subjects who complete the study but do not continue BRV treatment, subjects will have their BRV dose reduced by a maximum of half the dose every week for a maximum of 4 weeks until a dose of 1mg/kg/day (50mg/day for subjects with

body weights >50kg) is reached. After 2 weeks free of study drug (Safety Period), subjects will complete the SV.

During the Evaluation Period, MEVs and FEVs will be performed alternatively every month during the first 3 months and every 3 months thereafter, with a YEV every 12 months. The sequence of these visits is presented in Section 5.3. Enrolled subjects who participate in EP0065 and then resume participation N01266 will maintain the visit schedule established for them in N01266 before participation in EP0065.

Both safety data and efficacy data (seizure data) will be collected during the study. Lists of the study assessments performed at each of the visits are presented in Section 5.2.

No formal interim analysis is planned; however, data may be reported prior to the completion of this study (see Section 12.8).

5.1.1 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 directly enrolled subjects.

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

5.1.2 Planned number of subjects and sites

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

5.1.3 Anticipated regions and countries

The LTFU subjects will be enrolled in regions and countries participating in the core studies. Enrollment is planned for Europe, US, and Mexico, with the possibility to extend to other countries and regions if deemed necessary.

Directly enrolled subjects may be enrolled from sites participating in core studies and possibly other sites.

5.2 Schedules of study assessments

Table 5–1 provides a schedule of assessments for the EV (all subjects). Table 5–2 provides a schedule of assessments for the Evaluation, Down-Titration, and Safety (Drug-Free) Periods (all subjects). Table 5–3 provides a schedule of study assessments from the ScrV through the final TV (directly enrolled subjects only).

Table 5–1: Schedule of assessments for the Entry Visit (EV) (all subjects)

Subjects	**LTFU**			**DE**
Core study:	**N01349**	**EP0065**	**Other[a]**	**Not applicable**
Assessment				
Written informed consent	X	X	X	
Assent form (if applicable, according to age and local requirements)		X	X	
Subject identification card dispensing	X	X	X	
Childbearing potential		X	X	X
Verification inclusion/exclusion criteria	X	X	X	
Demographic data	X	X	X	
General medical history	X[c]	X[c]	X[c]	
Procedure history	X	X[c]	X[c]	
Epilepsy history		X	X[c]	
AED history	X	X[c]	X[c]	
Physical and neurological examinations	X[b]	X[b]	X[b]	X
Psychiatric and mental status	X	X	X[b]	X
Vital signs[d]	X	X[b]	X[b]	X
Body weight	X	X[b]	X[b]	X
Height	X[c]	X	X[c]	X
Head circumference	X[c]	X	X[b]	X
ECG	X	X[b]	X[b]	X
DRC dispensed	X	X	X	X

Table 5–1: Schedule of assessments for the Entry Visit (EV) (all subjects)

Subjects	LTFU			DE
Core study:	N01349	EP0065	Other[a]	Not applicable
DRC retrieved				X
Seizure count	X	X[c]	X[b]	X
Recording of medications[e]	X[b]	X[b]	X[b]	X
Recording of procedures	X	X	X[b]	X
Recording of AEs[f]	X[b]	X[b]	X[b]	X
IVRS call	X	X	X	X
Study drug dispensed	X	X	X	X
Study drug returned[g]				X
Study drug compliance				X
Laboratory assessments for safety[h]	X[b]	X[c]	X[b]	X
Phenytoin plasma concentrations, if applicable			X[b]	
C-SSRS[i]		X[b]	X[b]	X
Bayley-III scales[j]	X[b]	X	X[c]	
Achenbach CBCL[k]		X	X[c]	
BRIEF-P/BRIEF[l]		X	X[c]	
PedsQL[m]		X	X[c]	
Health care provider consultations not foreseen by protocol			X[b]	X
Hospital stays			X[b]	X

AE=adverse event; AED=antiepileptic drug; ALP=alkaline phosphatase; ALT=alanine aminotransferase; 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; C-SSRS=Columbia-Suicide Severity Rating Scale; DE=directly enrolled; DRC=daily record card; ECG=electrocardiogram; eCRF=electronic case report

Table 5–1: Schedule of assessments for the Entry Visit (EV) (all subjects)

Subjects	LTFU			DE
Core study:	N01349	EP0065	Other[a]	Not applicable

form; EDV=Early Discontinuation Visit; EEG=electroencephalogram; EV=Entry Visit; GGT=gamma-glutamyltransferase; IVRS=interactive voice response system; LTFU=long-term follow-up; PedsQL=Pediatric Quality of Life Inventory; SAE=serious adverse event

[a] Other" core studies include those other than EP0065 and N01349.

[b] To be obtained from the final visit of the core study and not recorded in the N01266 eCRF.

[c] To be obtained from baseline of the core study and not recorded in the N01266 eCRF.

[d] Vital sign measurements include blood pressure, pulse rate, and body temperature.

[e] Any ongoing concomitant medication at the time the subject completed the core study should not be recorded in the N01266 eCRF. Changes in ongoing concomitant medications should be recorded in the N01266 eCRF.

[f] Any ongoing AEs at the time the subject completed the core study should not be recorded in the N01266 eCRF. Worsening of the AE should be recorded in the N01266 eCRF as a new AE. A pharmacokinetic sample for determination of BRV plasma concentration should be taken whenever a subject experiences an SAE.

[g] Drug return includes study medication intake recording and accountability.

[h] Full laboratory assessments for safety include hematology and biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT) for all subjects, endocrinology for LTFU subjects, and urinalysis for all subjects for whom sample collection is feasible as described in Section 9.2.1. Female subjects of childbearing potential will have a urine pregnancy test done at the site.

[i] The C-SSRS will be administered to subjects ≥6 years of age. The "Since Last Visit" version of the C-SSRS will be used. If a subject turns 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be completed at the first visit after the sixth birthday.

[j] The Bayley-III is applicable to subjects enrolled in English-speaking countries and in countries where a validated translation is available only and as follows:

- Core study N01349: all subjects
- Core study EP0065: subjects <18 months of age at baseline (Screening)
- Other core studies: subjects <18 months of age at baseline for the core study (as indicated in footnote c)

[k] The version of the Achenbach CBCL (CBCL/1½-5 or CBCL/6-18) should be in accordance with the subject's age.

[l] The BRIEF-P should be used for subjects ≥2 years to <5 years of age and the BRIEF should be used for subjects ≥5 years of age.

[m] The version of the PedsQL used should be consistent with the subject's age.

Table 5–2: Schedule of all study assessments for the Evaluation, Down-Titration, and Safety (Drug-Free) Periods (all subjects)

Period	Evaluation					Down-Titration	Safety (Drug-Free)
Visit	Minimal Evaluation Visit (MEV)	Full Evaluation Visit (FEV)	Yearly Evaluation Visit/Final Visit (YEV/FV[a])	Unscheduled Visit (UV)	Early Discontinuation Visit (EDV)	Down-Titration Visit (DTV)[b]	Safety Visit (SV)
Assessment							
Childbearing potential	X	X	X		X		
Physical and neurological examinations		X	X		X		X
Psychiatric and mental status		X	X		X		X
Vital signs[c]	X	X	X		X	X	X
Body weight, height, and head circumference	X	X	X		X		X
ECG[d]			X		X		X[e]
EEG[f]		X	X		X		
DRC dispensed	X	X	X[g]		X	X	
DRC retrieved	X	X	X		X	X	X
Seizure count	X	X	X		X	X	X

Table 5–2: Schedule of all study assessments for the Evaluation, Down-Titration, and Safety (Drug-Free) Periods (all subjects)

Period	Evaluation					Down-Titration	Safety (Drug-Free)
Visit	Minimal Evaluation Visit (MEV)	Full Evaluation Visit (FEV)	Yearly Evaluation Visit/Final Visit (YEV/FV[a])	Unscheduled Visit (UV)	Early Discontinuation Visit (EDV)	Down-Titration Visit (DTV)[b]	Safety Visit (SV)
Assessment							
Assessment of seizure types[h]		X	X				
Recording of medications[i]	X	X	X	X	X	X	X
Recording of procedures	X	X	X	X	X	X	X
Recording of AEs[j]	X	X	X	X	X	X	X
IVRS	X	X	X	X	X	X	X
Study drug dispensed	X	X	X[g]		X		
Study drug returned[k]	X	X	X		X	X	
Study drug compliance	X	X	X		X	X	
Laboratory assessments for safety[l]	X[m]	X	X		X		X[e]
BRV plasma concentrations[n]		X	X		X		

Table 5–2: Schedule of all study assessments for the Evaluation, Down-Titration, and Safety (Drug-Free) Periods (all subjects)

Period	Evaluation					Down-Titration	Safety (Drug-Free)
Visit	Minimal Evaluation Visit (MEV)	Full Evaluation Visit	Yearly Evaluation Visit/Final Visit	Unscheduled Visit	Early Discontinuation Visit	Down-Titration Visit	Safety Visit
		(FEV)	(YEV/FV[a])	(UV)	(EDV)	(DTV)[b]	(SV)
Assessment							
Phenytoin plasma concentrations, if applicable		X	X		X		X[e]
C-SSRS[o]	X	X	X	X[p]	X	X	X
Bayley-III scales[q]		X	X		X		
Achenbach CBCL[r]		X	X		X		
BRIEF-P/BRIEF[s]		X	X		X		
PedsQL[t]		X	X		X		
Health care provider consultations not foreseen by protocol	X	X	X	X	X	X	X
Hospital stays[u]	X	X	X	X	X	X	X
End of study status			X[v]				X

AE=adverse event; AED=antiepileptic drug; ALP=alkaline phosphatase; ALT=alanine aminotransferase; 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; C-SSRS=Columbia-Suicide Severity Rating Scale; DE=directly enrolled; DRC=daily record card; DTV=Down-Titration Visit; ECG=electrocardiogram; eCRF=electronic case report form; EDV=Early Discontinuation Visit; EEG=electroencephalogram; EV=Entry Visit; FEV= Full Evaluation Visit; FV=Final

Table 5–2: Schedule of all study assessments for the Evaluation, Down-Titration, and Safety (Drug-Free) Periods (all subjects)

Period	Evaluation					Down-Titration	Safety (Drug-Free)
Visit	Minimal Evaluation Visit (MEV)	Full Evaluation Visit	Yearly Evaluation Visit/Final Visit	Unscheduled Visit	Early Discontinuation Visit	Down-Titration Visit	Safety Visit
		(FEV)	(YEV/FV[a])	(UV)	(EDV)	(DTV)[b]	(SV)
Assessment							

Visit; GGT=gamma-glutamyltransferase; IVRS=interactive voice response system; LTFU=long-term follow-up; M=Month; MEV=Minimal Evaluation Visit; PedsQL=Pediatric Quality of Life Inventory; SAE=serious adverse event; SV=Safety Visit; TV=Titration Visit; UV=Unscheduled Visit; V=Visit; YEV=Yearly Evaluation Visit

[a] For subjects staying in the study until it ends, the same procedures as for a YEV should be performed at the subject's FV.

[b] Visit should be scheduled at the end of the Down-Titration Period. The duration of the Down-Titration Period will depend on when the final dose of the study drug was taken during the Evaluation Period, with a maximum duration of 4 weeks.

[c] Vital sign measurements include blood pressure, pulse rate, and body temperature.

[d] An ECG has to be scheduled once a year at the YEV and at the EDV in the case of early discontinuation.

[e] At the SV, ECGs, laboratory assessments for safety, and determination of phenytoin plasma concentration will be performed only if abnormal at the EDV.

[f] EEG (for LTFU subjects only)

- For subjects ≥2 years of age at V5 who have typical absence seizures, an EEG of at least 1 hour that includes hyperventilation and intermittent photic stimulation must be performed at V5 and yearly thereafter. For subjects prematurely discontinuing from the study, an at least 1-hour EEG may be performed at the EDV at the Investigator's discretion.
- For subjects <2 years of age at V5, an EEG of at least 24 hours must be performed for efficacy assessment at V5 and yearly thereafter until subjects reach 2 years of age. For subjects prematurely discontinuing from the study, an at least 24-hour EEG may be performed at the EDV at the Investigator's discretion.

[g] No DRC or study drug will typically be dispensed at the FV. However, for subjects who complete the study but do not continue BRV treatment, study drug for down-titration will be dispensed.

[h] The assessment of seizure types will be done at 6-monthly intervals (at the FEV and the YEV) for subjects <2 years of age.

[i] For subjects enrolled in N01266 who volunteered to participate in EP0065 and then returned to N01266, changes to ongoing concomitant medications during EP0065 will be recorded in the N01266 eCRF.

[j] For subjects enrolled in N01266 who volunteered to participate in EP0065 and then returned to N01266, ongoing AEs that stop during EP0065 will be recorded in the N01266 eCRF.

[k] Drug return includes study medication intake recording and accountability.

[l] Full laboratory assessments for safety include hematology, biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT), and

Table 5–2: Schedule of all study assessments for the Evaluation, Down-Titration, and Safety (Drug-Free) Periods (all subjects)

Period	Evaluation					Down-Titration	Safety (Drug-Free)
Visit	Minimal Evaluation Visit (MEV)	Full Evaluation Visit	Yearly Evaluation Visit/Final Visit	Unscheduled Visit	Early Discontinuation Visit	Down-Titration Visit	Safety Visit
		(FEV)	(YEV/FV[a])	(UV)	(EDV)	(DTV)[b]	(SV)
Assessment							

endocrinology for all subjects and urinalysis for subjects for whom sample collection is feasible as described in Section 9.2.1. Female subjects of childbearing potential should have a urine pregnancy test done at the site at all laboratory assessment visits. Endocrinology testing will be performed at the YEV/FV.

[m] Additional hepatic monitoring laboratory assessments (ALT, AST, ALP, total bilirubin, and GGT only) are to be done only at the MEV at V4 (M3) and V6 (M9). Urine pregnancy tests are to be done at the site for female subjects of childbearing potential at all visits.

[n] In addition to the scheduled assessments, a pharmacokinetic sample for determination of BRV plasma concentration should be taken whenever a subject experiences an SAE.

[o] The C-SSRS will be administered to subjects ≥6 years of age. The "Since Last Visit" version of the C-SSRS will be used, with the following exception: If a subject turns 6 years of age during N01266, the "Already Enrolled" version of the C-SSRS should be completed at the first visit after the sixth birthday, and the "Since Last Visit" version of the C-SSRS should be completed at subsequent visits.

[p] If an unscheduled visit is conducted due to safety or efficacy reasons, the C-SSRS will be performed for subjects ≥6 year of age.

[q] The Bayley-III is applicable to subjects who meet all of the following criteria: are enrolled in English-speaking countries and in countries where a validated translation is available, were <18 months of age at baseline of the core study, and are <42 months of age.

[r] The version of the Achenbach CBCL (CBCL/1½-5 or CBCL/6-18) should be in accordance with the subject's age, 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.

[s] The BRIEF-P should be used for subjects ≥2 years to <5 years of age and the BRIEF should be used for subjects ≥5 years of age, with the following exception: For subjects who completed the BRIEF-P at the Baseline assessment and turns 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.

[t] The version of the PedsQL used should be consistent with the subject's age at each visit when it is administered with the following exception: If a subject ages up to the next PedsQL between the Baseline assessment and the initial YEV, the PedsQL that was used at the Baseline assessment should be completed through and including the initial YEV, and subsequently the PedsQL consistent with the age at the time of assessment should be completed.

[u] This refers to any hospital stay that occurs during the study. Data recorded in the eCRF include the reason for the hospitalization, the admission ward, transfers, and length of stay.

[v] End of study status only for subjects who continue in the study until it ends and for whom the visit corresponds to the final evaluation visit or FV.

Table 5–3: Schedule of study assessments from the ScrV through the final TV (directly enrolled subjects only)

Period	Screening[a]	Up-Titration		
Visit	Screening	Titration Visit 1	Titration Visit 2	Titration Visit 3
	(ScrV)	(TV1)	(TV2)	(TV3)
Assessment				
Written informed consent/assent	X			
Subject identification card dispensing	X			
Demographic data	X			
Childbearing potential	X			
Verification inclusion/exclusion criteria	X	X		
Physical and neurological examinations	X			
Psychiatric and mental status	X			
General medical and procedures history	X			
Epilepsy and AED history	X			
Vital signs[b]	X	X	X	X
Body weight, height, and head circumference[c]	X	X	X	X
ECG	X	X	X	X
EEG[d]	X			
Neuro-imaging procedure[e]	X			
DRC dispensed[f]	X	X	X	X
DRC retrieved		X	X	X
Seizure count		X	X	X
Recording of medications	X	X	X	X

Table 5–3: Schedule of study assessments from the ScrV through the final TV (directly enrolled subjects only)

Period	Screening[a]	Up-Titration		
Visit	Screening	Titration Visit 1	Titration Visit 2	Titration Visit 3
	(ScrV)	(TV1)	(TV2)	(TV3)
Assessment				
Recording of procedures	X	X	X	X
Recording of AEs[g]	X	X	X	X
IVRS call	X	X	X	X
Study drug dispensed		X	X	X
Study drug returned[h]			X	X
Study drug compliance			X	X
Laboratory assessments for safety[i]	X		X	X
Phenytoin plasma concentrations	X			
C-SSRS[j]	X	X	X	X
Achenbach CBCL[k]	X			
BRIEF-P/BRIEF[l]	X			
PedsQL[m]	X			
Health care provider consultations not foreseen by protocol		X	X	X
Hospital stays[n]		X	X	X

AE=adverse event; AED=antiepileptic drug; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BRIEF=Behavior Rating Inventory of Executive Function; BRIEF-P=Behavior Rating Inventory of Executive Function-Preschool Version; BRV=brivaracetam; CBCL=Child Behavior Checklist; C-SSRS=Columbia-Suicide Severity Rating Scale; DRC=daily record card; ECG=electrocardiogram; eCRF=electronic case report form; EEG=electroencephalogram; EV=Entry Visit; GGT=gamma-glutamyltransferase; IVRS=interactive voice response system; PedsQL=Pediatric Quality of Life Inventory; POS=partial-onset seizure; SAE=serious adverse event; ScrV=Screening Visit; TV=Titration Visit

[a] The Screening Period will serve as the Baseline Period for directly enrolled subjects. Directly enrolled subjects will begin receiving BRV at TV1 after all

Table 5–3: Schedule of study assessments from the ScrV through the final TV (directly enrolled subjects only)

Period	Screening[a]	Up-Titration		
Visit	Screening	Titration Visit 1	Titration Visit 2	Titration Visit 3
	(ScrV)	(TV1)	(TV2)	(TV3)
Assessment				

inclusion and exclusion criteria are met.

[b] Vital sign measurements include blood pressure, pulse rate, and body temperature.

[c] Height and head circumference will be recorded only at the ScrV.

[d] A previous EEG documenting the diagnosis of POS must be available at the ScrV. If an EEG is not available at the ScrV, it must be scheduled during the Screening Period.

[e] A neuro-imaging procedure (brain magnetic resonance imaging/brain computerized tomography scan [except in Germany]/ultrasounds or any other imaging test) should be performed if no report is available within the previous 2 years.

[f] Seizure counts are collected in the subject's DRC on a daily basis.

[g] A pharmacokinetic sample for determination of BRV plasma concentration should be obtained whenever a subject experiences an SAE.

[h] Drug return includes study medication intake recording and accountability.

[i] The ScrV laboratory assessments for safety will include hematology, biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT), urinalysis (for subjects for whom sample collection is feasible), endocrinology, and a urine pregnancy test at the site (for female subjects of childbearing potential). The TV laboratory assessments for safety will include only hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT. Laboratory samples should be collected at TV2 only if the Investigator anticipates that it will be the final TV before the subject advances to the EV. The decision for treatment at TV1 will include the results of the laboratory sample collected at the ScrV.

[j] The C-SSRS will be administered to subjects ≥6 years of age. The "Since Last Visit" version of the C-SSRS is to be used with the following exceptions: 1) the "Baseline/Screening" version of the C-SSRS should be used at the ScrV, and 2) if a subject turns 6 years of age during N01266, the "Already Enrolled" version of the C-SSRS should be completed at the first visit after the sixth birthday, and the "Since Last Visit" version of the C-SSRS should be completed at subsequent visits.

[k] The version of the Achenbach CBCL (CBCL/1½-5 or CBCL/6-18) used at the ScrV should be in accordance with the subject's age at this visit.

[l] The BRIEF-P should be used for subjects <5 years of age at the ScrV. The BRIEF should be used for subjects ≥5 years of age at the ScrV.

[m] The version of the PedsQL used should be consistent with the subject's age at the ScrV.

[n] This refers to any hospital stay that occurs during the study. Data recorded in the eCRF include the reason for the hospitalization, the admission ward, transfers, and length of stay.

5.3 Visit sequence

Study visits are to be scheduled in the order presented in the following table:

Table 5–4: Visit sequence

Directly enrolled 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

Table 5–4: Visit sequence

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 at 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 directly enrolled subjects must participate in at least TV1, but may participate in fewer than 3 TVs as described in Section 7.2.1.
[b] For directly enrolled subjects, the EV represents the point of entry into the Evaluation Period.
[c] Hepatic monitoring tests only will be performed as described in Section 9.2.1.
[d] Subsequent years will follow the same visit schedule.

5.4 Rationale for study design and selection of dose

N01266 will allow BRV long-term safety and tolerability data to be collected from pediatric subjects with epilepsy who will have participated in core studies and now have the opportunity to continue BRV treatment, and from directly enrolled subjects with POS. The safety and efficacy data collected in this study will support the applications for BRV indications in pediatric patients.

Each LTFU subject will begin treatment in N01266 at the individualized BRV dose he/she was receiving at the completion of the core study. Enrolled subjects who volunteer to participate in EP0065 will resume dosing in N01266 in accordance with the individualized dose they received at the completion of EP0065. Directly enrolled subjects will participate in up to 3 weeks of an Up-Titration Period. If a subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV for 7±2 days during the Up-Titration Period, the subject will be allowed to enter the Evaluation Period (subject must be able to tolerate the minimum dose of 1mg/kg/day; see Section 7.2).

A physiologically-based PK model (N01313) was developed to predict the doses to be tested in N01263. The same doses that were used for up-titration in N01263 will be used for the 3 consecutive weeks that comprise the Up-Titration Period of N01266. Based on the PK analyses performed on the plasma samples collected in N01263, the plasma concentrations approximating the concentrations for adults receiving BRV 200mg/day were not achieved by the dosing scheme initially included in N01266; as a result, it was recommended that the same doses are to be administered in all pediatric subgroups, ≥1 month to ≤16 years of age. For all subjects, the approximate doses to be administered are 0.5, 1, and 2mg/kg bid (1, 2, and 4mg/kg/day, respectively), with the daily doses not exceeding the maximums of 50mg/day, 100mg/day, and 200mg/day for Weeks 1, 2, and 3 of up-titration, respectively. The dose selection was based on the following observations:

- The PK of BRV is linear and of low variability in adults up to 1 order of magnitude above the therapeutic dose range.
- Efficacious doses in adults are expected to be from 50mg/day up to 200mg/day.
- In N01263, BRV was eliminated more rapidly in pediatric subjects than in adult subjects, resulting in a lower plasma concentration. Therefore, clearance of BRV was shown to be higher in pediatric subjects than in adult subjects.

Brivaracetam (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 directly enrolled subjects must be able to tolerate at least 1mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266, as indicated in Section 7.2.

The maximum allowable BRV dose in N01266 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.

The maximum BRV dose allowed in this study will be 200mg/day (100mg bid), which is the maximum allowed dose for those subjects dosed as adults.

5.5 Study conduct due to coronavirus (severe acute respiratory syndrome coronavirus-2) disease 2019

The following applies where normal study conduct is impacted by coronavirus (severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2]) disease 2019 (COVID-19). The protocol visit schedule should be followed to the extent possible, considering the individual benefit-risk assessment by the Investigator. If necessary, remote visits may be conducted and the subjects or caregivers will be contacted by telephone or videoconference. Remote follow-up, at minimum with a telephone call after 3 months, must be done (preferably more frequently and as needed to follow-up on subject safety assessments).

If a subject needs to be discontinued and cannot come into the study site, then appropriate down-titration instructions will be provided, and a visit will be scheduled to perform safety assessments as soon as possible (see Section 7.2.3 for down-titration instructions).

In situations where a subject is unable to return to the study site, Investigators will assess and document the subject's safety via telephone contact. Based on information gathered from the telephone contact, Investigators will confirm whether the subject could continue the current study treatment based upon the outcome of the safety assessment. Subjects' agreement to implement this procedure should be obtained and documented prior to implementing any changes. Changes in the study treatment supply in this situation are described in Section 7.2.4.

Ad hoc subject contact may be warranted to understand the current health status of the subjects, follow up on AEs and inform them of any protective measures taken by the study site as a result of the COVID-19 pandemic (eg, any measures which may limit access to the site or may require additional actions by the subject prior to entry to the site).

Investigators and study coordinators may use discretion when determining the need to perform a home visit (eg, for safety laboratory parameters or PK samples).

If subjects are unable to return to the study site, protocol deviations will occur (even if the study visit is replaced by a home visit or remote visit) (Section 12.6). Investigators must carefully document the occurrence of these and any other deviations, clearly noting deviations which occurred during and in accordance to the COVID-19 pandemic.

If a subject visits another facility for a medical issue (or has to switch sites for some COVID-19-related reason), the Investigator should request contact with the physician providing care to provide a detailed explanation of the subject's condition and his/her participation in the study. Subjects or caregivers shall be reminded to completely collect and keep records of this visit.

In case laboratory assessments cannot be conducted via central laboratory vendor due to restricted site access or home visits by Investigators are not an option, local laboratory safety assessment may need to be conducted, in a format that allows the Investigator to receive and review these results and include as source documentation.

Deviations to data collection including inability to perform some assessments such as EEG, ECG or blood collection for safety laboratory assessments and PK, or alternative methods of assessment such as phone calls should be recorded in the source documentation and notated as "not done" in the electronic case report form (eCRF).

In cases where subjects cannot return to the study site, and it will not be possible to dispense a new DRC, subjects will be instructed to continue recording of seizures in a manner that is mutually agreed with the Investigator (eg, hand-written notes, taking notes on a smart device). Any recording of seizures in a manner outside of the study DRC must be carefully documented in the source medical records (copies or printouts of these recordings will be brought to and retained at site).

6 SELECTION AND WITHDRAWAL OF SUBJECTS

The nonconsecutive numbering and application of letters to some numbers in this section reflect changes that have occurred with protocol amendments.

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met as specified.

6.1.1 Inclusion criteria for all subjects

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the parent(s) or legal representative(s). The Consent form or a specific Assent form, where required, will be signed and dated by minors.

2a. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake (including BRV oral solution or tablets) according to the judgment of the Investigator.

14. For female subjects, the subject is

- Not of childbearing potential

-OR-

- Of childbearing potential, and
  - Is not sexually active
  - Has a negative pregnancy test

-OR-

- Of childbearing potential, and
  - Is sexually active
  - Has a negative pregnancy test
  - Understands the consequences and potential risks of inadequately protected sexual activity, understands and properly uses contraceptive methods, and is willing to inform the Investigator of any contraception changes. Medically acceptable contraceptive methods for the study include, but are not limited to:
    - Oral or depot contraceptive treatment with at least ethinylestradiol 30µg per intake or ethinylestradiol 50µg per intake if also taking one of the following: carbamazepine, phenobarbital, primidone, phenytoin, oxcarbazepine, St. John's Wort, or rifampicin
    - Barrier contraception: intrauterine device, diaphragm with spermicide, male or female condom with spermicide

6.1.2 Inclusion criteria for LTFU subjects only

3a. Male or female subjects having participated in a core study with a confirmed diagnosis of epilepsy and for whom a reasonable benefit from long-term administration of BRV is expected.

6.1.3 Inclusion criteria for directly enrolled subjects only

8. Subject is a male or female ≥4 years to <17 years of age.
9. Subject has a clinical diagnosis of POS according to the ILAE classification.
10. Subject has an EEG compatible with the clinical diagnosis of POS.
11. Subject has been observed to have uncontrolled POS after an adequate course of treatment (in the opinion of the Investigator) with at least 1 AED (concurrently or sequentially).
12. Subject had at least 1 seizure (POS) during the 3 weeks before the ScrV.
13. Subject is taking at least 1 AED. All AEDs need to be at a stable dose for at least 7 days before the ScrV. Vagal nerve stimulator-stable for at least 2 weeks before the ScrV is allowed and will be counted as a concomitant AED. Benzodiazepines taken more than once a week (for any indication) will be considered as a concomitant AED.

6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria are met as specified. Criteria that were in place before Protocol Amendment 3 have retained the previous numbering.

6.2.1 Exclusion criteria for all subjects

1. Subject is a pregnant or nursing female.

3. Subject has severe medical, neurological, or psychiatric disorders or laboratory values, which may have an impact on the safety of the subject.

5. Subject has planned participation in any clinical study of another investigational drug or device.

6. Subject has any medical condition, which in the Investigator's opinion, warrants exclusion.

29. Subject has >1.5x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >1.0xULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

    N01349 subjects with a total bilirubin > ULN may be considered for the study if benign unconjugated hyperbilirubinemia is suspected in the context of prolonged neonatal jaundice, after discussion with the medical monitor.

    For randomized subjects with a baseline result >ULN for ALT, AST, ALP, or total bilirubin, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the eCRF.

    If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at the baseline referenced in Table 5–1 for LTFU subjects and at the Screening Visit for directly enrolled subjects, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes re-screening.

30. Subject has chronic liver disease.

6.2.2 Exclusion criteria for LTFU subjects only

2a. Subject had hypersensitivity to BRV or excipients or comparative drugs as stated in this protocol during the course of the core study.

4a. Subject had poor compliance with the visit schedule or medication intake in the core study.

7a. Subject ≥6 years of age has a lifetime history of suicide attempt (including actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at the EV. If a subject has active suicidal ideation without a specific plan as indicated by a positive response ("Yes") to Question 4 of Columbia-Suicide Severity Rating Scale (C-SSRS) at the EV, the subject should be referred immediately to a Mental Healthcare Professional and may be excluded from the study based upon the Investigator's judgment of benefit/risk of continuing the subject in the study/on study medication.

6.2.3 Exclusion criteria for directly enrolled subjects only

8. Subject has previously received BRV.
9. Subject had concomitant use of LEV at the ScrV. In addition, the use of LEV is prohibited for at least 4 weeks prior to the ScrV.
10. Subject has epilepsy secondary to a progressive cerebral disease or tumor, or any other progressively neurodegenerative disease. Stable arteriovenous malformations, meningiomas or other benign tumors may be acceptable according to Investigator's opinion.
11. Subject has a history of primary generalized epilepsy.
12. Subject has a history of status epilepticus in the month immediately prior to the ScrV or during the Up-Titration Period.
13. Subject has a history or presence of pseudoseizures.
14. Subject is suffering only from febrile seizures.
15. Subject is on felbamate with less than 18 months continuous exposure. Subject who has taken felbamate for a combined duration of treatment and wash out of <18 months before the ScrV.
16. Subjects treated with vigabatrin who have visual field defects.
17. Subject has an allergy to pyrrolidone derivatives or investigational product excipients or a history of multiple drug allergies.
18. Subject has any clinically significant acute or chronic illness as determined during the physical examination or from other information available to the Investigator (eg, bone marrow depression, chronic hepatic disease, severe renal impairment, psychiatric disorder).
19. Subject has an underlying disease or is receiving a treatment that may interfere with the absorption, distribution, metabolism, and elimination of the study drug.
20. Subject has any medical condition that might interfere with his/her study participation (eg, serious infection or scheduled elective surgery).
21. Subject has a terminal illness.
22. Subject has any clinically significant deviations from reference range values for laboratory parameters as determined by the Investigator.
23. Subject has a clinically relevant ECG abnormality according to the Investigator.
24. Subject had major surgery within 6 months prior to the ScrV.
25. Subject received any investigational drug or device within the 30 days prior to the ScrV. The use of AEDs marketed for adults but not approved for pediatric use is not considered to be "investigational" for the purposes of this study.
26. Investigators' and co-Investigators' children may not be included as subjects in the study.
28. Subject has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a

positive response ("Yes") to either Question 4 or Question 5 of the C-SSRS-Baseline/Screening at the ScrV.

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care. Withdrawal criteria are provided as follows, with criteria for potential drug-induced liver injury provided in Section 6.3.1.

Subjects must be withdrawn from the study if any of the following events occurs:

1. Subject develops an illness that, in the opinion of the Investigator, would interfere with his/her continued participation or would potentially be detrimental to his/her physical/mental health.
4. Subject takes prohibited concomitant medications as defined in the protocol.
5. Subject/parent(s)/legal representative(s) withdraws his/her/their consent.
6. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
7. The Sponsor or a regulatory agency requests withdrawal of the subject.

8a. Subject has an episode of convulsive status epilepticus, a prolongation of seizure duration, a worsening of seizure frequency, or emergence of a new type, that is considered by the Investigator to require intervention.

12. Investigator decides that withdrawal from further participation would be in the subject's best interest.
13. Subject is unwilling or unable to continue, or the parent/legal guardian is unwilling or unable to allow the subject to continue in this study.
14. If subject is ≥6 years of age, subject has active suicidal ideation with a specific plan as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" or "Already Enrolled Subjects" (as applicable) version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and **must** be withdrawn from the study.

Subjects may be withdrawn from the study if any of the following events occurs:

15. If subject is ≥6 years of age, subject has active suicidal ideation without a specific plan as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" or "Already Enrolled Subjects" version of C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and *may* be withdrawn from the study based on the Investigator's judgment of benefit/risk of continuing with the subject in the study/on study medication.

If a subject from N01266 enrolls in EP0065 and either withdraws consent solely due to route of BRV administration (iv) or if the subject requires more than 10 iv doses of BRV, the subject may be allowed to return to N01266 after discussion with and agreement from the Medical Monitor. If a subject from N01266 is advised to withdraw from N01266 after participation in EP0065, the subject will be required to return to the N01266 to complete the required EDV, DTV, and SV assessments.

Investigators should attempt to obtain information on subjects, in the case of withdrawal or discontinuation. In case of discontinuation, the Investigator will complete a full evaluation documented as an EDV. For subjects considered as lost to follow-up the Investigator should make an effort (at least 1 phone call and 1 written message to the subject/parent[s]/legal representative[s]), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents) to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reasons for removing or discontinuing the subject, must be recorded in the source documents. The main reason for terminating the study will be reported in the eCRF.

Subjects who are withdrawn from the study should have their BRV dose down titrated weekly as described in Section 7.2. Refer to Table 5–2 for procedures to be performed at the time of withdrawal.

Investigators should contact the Medical Monitor whenever possible to discuss the withdrawal of a subject in advance.

6.3.1 Potential drug-induced liver injury investigational medicinal product discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if the investigational medicinal product (IMP) must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the Investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 9.2.2. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and

observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

7 STUDY TREATMENTS

7.1 Description of investigational medicinal products

Immediate-release BRV oral solution and immediate-release, film-coated BRV oral tablets will be provided during the study.

Brivaracetam oral solution at a concentration of 10mg/mL will be supplied in 300mL glass bottles.

Brivaracetam oral tablets will be provided in the following strengths; 10mg, 25mg, and 50mg.

There is no placebo or reference product.

7.2 Treatments to be administered

Brivaracetam (tablet and oral solution) should be administered bid approximately 12 hours apart in 2 equally divided doses. Subjects should be dosed with either oral tablets or oral solution and not a combination of both. The mg dosage for the oral tablet treatment should be calculated to match as closely as possible the mg/kg based dosage and should be a combination of the BRV 10mg, 25mg, and 50mg tablets. Only the following exact dosages are allowed for the oral tablet administration: BRV 20, 40, 50, 70, 100, 150, and 200mg/day.

The dose of oral solution will be measured using the appropriate syringes (1mL, 3mL, and/or 10mL) with an adaptor able to fit both bottle sizes. Oral solution should not be mixed with other liquids prior to administration.

Subjects should take their BRV treatment according to instructions provided by the Investigator. Dose adjustments for concomitant AEDs are allowed at any time based on clinical judgment.

Dispensation of IMP will be done by an interactive voice response system (IVRS).

7.2.1 Up-Titration Period for directly enrolled subjects

Beginning with Protocol Amendment 3, at TV1, eligible directly enrolled subjects will initiate treatment with BRV (oral solution or tablet, as appropriate).

The BRV dose will be titrated to optimize tolerability and seizure control. Table 7–1 provides the recommended titration steps for the oral solution and tablet formulations. Subjects must be on the same daily dose for 7±2 days before the dose is titrated to the next dosing level. 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. Fewer than 3 TVs may be needed before entry into the Evaluation Period, depending on the BRV dose at which acceptable tolerability and seizure control is demonstrated.

Based on tolerability and seizure control, a subject's BRV dose may be reduced to no lower than the designated minimum dose indicated in Table 7–1. If a subject had previously received the

reduced BRV dose for 7±2 days with acceptable tolerability and seizure control, then the subject may enter directly into the Evaluation Period.

Table 7–1: Recommended BRV dosing schedule for directly enrolled subjects during the Up-Titration Period

Visit (Week)	BRV 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.

7.2.2 Evaluation Period for all subjects

The maximum BRV dose will be 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day. Subjects may receive oral solution or oral tablets, as appropriate.

The LTFU subjects will ordinarily start dosing in N01266 on the individualized BRV dose they were receiving at the completion of the core study; enrolled subjects who volunteer to participate in EP0065 should resume dosing in N01266 on the individualized BRV dose they were receiving at the completion of EP0065. Subjects must be able to tolerate the minimum BRV dose specified in the core study to be eligible for entry into the Evaluation Period of N01266.

Dose can be adjusted at any time as considered necessary by the Investigator and required by the subject's medical condition. The newly adjusted dose must not exceed the maximum allowed dose (5mg/kg/day [2.5mg/kg bid], not to exceed a dose of 200mg/day).

7.2.3 Down-Titration Period

All subjects who prematurely discontinue the study should complete an EDV and have their BRV dose down titrated by a maximum of half the dose every week for a maximum of 4 weeks until a dose of 1mg/kg/day (50mg/day for subjects with body weights >50kg) is reached. Equally, all subjects completing the study but switching to treatment other than BRV should have their BRV dose down titrated.

7.2.4 Alternative study treatment supply due to COVID-19

When a subject can no longer return to the study site but will continue in the study, the following methods may be used to provide study treatment:

- Site to subject: In instances where site staff can ship study treatment dispensed from the site or pharmacy supply directly to the subject, or
- Depot to subject: In instances where it is not possible for the site staff to access study treatment and/or ship study treatment dispensed from the site or pharmacy supply directly to the subject.

7.3 Packaging

Oral solution (10mg/mL) will be packaged in 300mL type III amber glass bottles with child-resistant tamper evident polypropylene (PP) screw closures. Measuring devices, 1mL, 3mL, and 10mL syringes, will be provided as necessary with an adaptor able to fit all the bottle sizes.

Oral tablets of BRV 10mg, 25mg, and 50mg will be packaged in high-density PP bottles with child-resistant PP screw closures.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

The labels will be adapted to the size of the IMP bottles.

7.5 Handling and storage requirements

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access, according to the storage conditions mentioned in the label.

Appropriate storage conditions must be ensured either by the temperature (eg, room, refrigeration unit) or by completion of a temperature log in accordance with local requirements on a regular basis (eg, once a week), showing actual and minimum/maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be reported as per instructions contained in the IMP Handling Manual.

The Investigator (or designee) will instruct the subject to store the IMP following the instructions on the label.

7.6 Drug accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms.

All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used bottles of IMP until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the IMP is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB SOPs or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

The IMP (oral solution or oral tablets) will be supplied to the subject/parent(s)/legal representative(s) at the TV(s) (directly enrolled subjects only), EV, MEV, FEV, YEV, and at the EDV in the case of early discontinuation. The IMP for down-titration will be dispensed at the FV for subjects who complete the study but do not continue BRV treatment.

The Investigator will instruct the subject/parent(s)/legal representative(s) to bring back at each visit the bottles (even empty) dispensed at the previous visit and containing all the remaining tablets or oral solution.

Drug accountability must be done in the parent(s)/legal representative(s), and when possible, the subject's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

If a subject is found to be persistently noncompliant in the Investigator's opinion, the Sponsor in conjunction with the Investigator will make a decision as to whether the subject should be withdrawn from the study.

Study drug compliance will be assessed at the TV(s) and EV (directly enrolled subjects only), MEV, FEV, YEV, FV, and at the EDV and the Down-Titration Visit (DTV) in the case of early discontinuation.

The number of tablets and the quantity of the oral solution dispensed and returned must be recorded in the source documents.

7.8 Concomitant medications/treatments

For any treatment other than the IMP, including over-the-counter products, an accurate record must be kept in the clinic chart (source documentation) and in the eCRF.

For LTFU subjects, ongoing medications at the time the subject completed the core study should not be recorded in the eCRF at the EV, or any subsequent visit. Changes in ongoing concomitant medications should be recorded in the N01266 eCRF. For directly enrolled subjects, all concomitant medications should be recorded in the eCRF at the ScrV and subsequently be recorded only if there is a change regarding the administration of the medication. For all subjects, new medications should be recorded in the eCRF at only the first visit at which they are reported and subsequently only if there is a change. For any change, the start date corresponding to the date of change in administration should be recorded in the eCRF.

For all subjects, all changes in concomitant AEDs and non-AEDs will be recorded on the AED or non-AED concomitant medication page, respectively, in the eCRF. This record should include the name of the drug (preferably the brand name), the dose, the date(s) of administration, and the indication for use.

Please contact the study physician or designee before initiating or stopping any medication during the study unless it is a medical emergency.

7.8.1 Permitted concomitant treatments (medications and therapies)

All concomitant AEDs, except the ones specified in Section 7.8.2, are permitted during the study.

7.8.1.1 Permitted concomitant medications

Benzodiazepines are allowed. If taken more than once a week, for any indication, a benzodiazepine will be considered as an AED. Each intake for as needed use must be listed individually in the eCRF, either on the concomitant AED medication page or on the concomitant non-AED medication page, according to the indication.

Levetiracetam is allowed after the EV.

Felbamate is allowed as follows:

- LTFU subjects:
  - At the established dose if a stable dose was maintained during the core study
- Directly enrolled subjects:
  - At a stable dose during the Screening and Up-Titration Periods
  - At the established dose from the EV onwards if a stable dose was maintained during the Screening and Up-Titration Periods

7.8.1.2 Permitted concomitant therapy

Vagal nerve stimulation is allowed and will be counted as a concomitant AED. Ketogenic diet is allowed.

7.8.2 Prohibited concomitant medications

The following concomitant AED medication is prohibited during the study:

- LTFU subjects:
  - Felbamate (except if on a stable dose during the core study)
- Directly enrolled subjects:
  - Felbamate (except if on a stable dose during the Screening and Up-Titration Periods)
  - LEV (from the ScrV until the EV)

7.8.3 Rescue medication

No rescue medication will be provided.

7.9 Blinding

This is an open-label study and therefore, no blinding is required.

7.10 Randomization and numbering of subjects

Subjects will not be randomized in this study, as each LTFU subject will start on the individualized BRV dose that he/she was receiving at the completion of the core study, and directly enrolled subjects will start the Evaluation Period on the dose established during the Up-Titration Period.

To enroll a LTFU subject (EV, V1), the Investigator will call the IVRS and provide brief details about the subject to be enrolled. Subjects will continue with the 5-digit subject number assigned by the IVRS in the core study.

Directly enrolled subjects will be assigned unique numbers for the purpose of study and subject identification, as well as for subject confidentiality. To enroll these subjects, at the ScrV, the Investigator will call the IVRS and provide information about the subject to be enrolled. Subjects will then be assigned a 5-digit subject number by the IVRS.

For all subjects, the subject number will be required in all communication between the Investigator (or designee) and the IVRS regarding a particular subject. Subjects' status and the dispensing of IMP (bottle numbers) will be tracked via the IVRS.

8 STUDY PROCEDURES BY VISIT

Prior to any study activities, the parent(s)/legal representative(s) will be asked to read and sign an Informed Consent form that has been approved by an IRB/IEC and which complies with regulatory requirements. The parent(s)/legal representative(s) will be given adequate time to consider any information concerning the study, given to them by the Investigator or designee. As part of the informed consent procedure, the subject/parent(s) or legal representative(s) will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study. Additionally, if applicable (according to subject's age and local requirements), the subject will sign an IRB/IEC-approved Assent form.

8.1 Screening Visit for directly enrolled subjects only

The ScrV is applicable only to directly enrolled subjects (ie, subjects ≥4 years to <17 years of age with POS who have not participated in a core study). The Screening Period will serve as the Baseline Period for directly enrolled subjects. The ScrV is not applicable for LTFU subjects; the first N01266 visit for LTFU subjects is the Entry Visit (Section 8.3.1).

The ScrV assessments will be conducted 7±2 days prior to the first administration of BRV. It is acceptable for the ScrV assessments to be conducted on more than 1 day.

The ScrV assessments are as follows:

- Signing and dating of written Informed Consent by parent(s)/legal representative(s)
- Signing and dating of Assent form by the subject (if applicable, according to age and local requirements)
- Subject identification card dispensing
- Demographic data
- Childbearing potential

- Verification of inclusion/exclusion criteria
- Physical (including Tanner Scale, as applicable) and neurological examinations
- Psychiatric and mental status
- General medical and procedures history
- Epilepsy and AED history
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight, height, and head circumference
- ECG
- EEG (A previous EEG documenting the POS diagnosis must be available at the ScrV for directly enrolled subjects. If an EEG is not available at the ScrV, it must be scheduled during the Screening Period.)
- Neuro-imaging procedure (brain magnetic resonance imaging/brain computerized tomography scan [except in Germany]/ultrasounds or any other imaging test) should be performed if no report is available within the previous 2 years
- DRC dispensed
- Recording of medications
- Recording of procedures
- Recording of AEs
- IVRS call
- Laboratory assessments for safety including:
  - Hematology
  - Biochemistry including hepatic monitoring
  - Urinalysis (for subjects for whom sample collection is feasible)
  - Endocrinology
  - Urine pregnancy test (see Section 9.2.1)
- Phenytoin plasma concentrations (if applicable)
- Suicidality assessment (C-SSRS-Baseline/Screening) (for subjects ≥6 years of age)
- Achenbach CBCL (version consistent with age at the visit)
- BRIEF-P (<5 years of age)/BRIEF (≥5 years of age) (version consistent with age at the visit)
- PedsQL (version consistent with age at the visit)
- Appointment for the next visit (TV1) 7±2 days later

8.2 Titration Visit(s) (TV1, TV2, and TV3) for directly enrolled subjects only

Directly enrolled subjects will initiate treatment with BRV at TV1 (see Section 7.2.1 for dosing information). The TVs are not applicable for LTFU subjects; the first visit in N01266 for these subjects is the EV (Section 8.3.1).

The first dose of BRV at each titration level will be administered at the clinic during the TV. Subjects will remain on the BRV dose administered at the clinic for 7±2 days before titrating up to the next dose. The BRV up-titration schedule is provided in Section 7.2.1.

A total of up to 3 TVs may be required; however, based on tolerability and seizure control, a subject's BRV dose may be titrated to a lower dose level and 3 TVs would not be needed.

The following assessments are required at each TV:

- Verification of inclusion/exclusion criteria (TV1 only)
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight
- ECG
- DRC dispensed
- DRC retrieved
- Seizure count
- Recording of medications
- Recording of procedures
- Recording of AEs
- IVRS call
- Hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT (TV3 only unless the Investigator anticipates that TV2 will be the final TV, in which case hepatic monitoring assessments are to be done at TV2)
- Study drug dispensed
- Study drug returned (TV2 and TV3 only)
- Study drug compliance (TV2 and TV3 only)
- Suicidality assessment (C-SSRS) (for subjects ≥6 years of age)
- Healthcare provider consultation not foreseen by the protocol
- Hospital stays
- Appointment for the next visit 7±2 days later

8.3 Entry Visit

At the EV, the progress of directly enrolled subjects will become aligned with LTFU subjects; for all subjects, the EV is the time of entry into the Evaluation Period. For LTFU subjects, the EV is the first visit in N01266. For directly enrolled subjects, the EV will occur after subjects have attended the ScrV and at least 1 TV and achieved, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than the minimum specified dose) for 7±2 days.

8.3.1 LTFU subjects

8.3.1.1 Core study: N01349

The following assessments will be performed at this visit:

- Signing and dating of written Informed Consent by parent(s)/legal representative(s)
- Subject identification card dispensing
- Verification of inclusion/exclusion criteria
- Demographic data
- Procedure history
- AED history
- Psychiatric and mental status examination
- Vital signs
- Body weight
- ECG
- DRC dispensed
- Seizure count
- Recording of medications (Any ongoing medications [including AEDs and non-AEDs] at the time the subject completed N01349 should not be recorded in the N01266 eCRF. Changes in ongoing concomitant medications should be recorded in the N01266 eCRF).
- Recording of procedures
- Recording of AEs (Any ongoing AEs at the time the subject completed N01349 should not be recorded in the N01266 eCRF. Worsening of the AE should be recorded as a new AE.)
- IVRS call
- Study drug dispensed
- Bayley-III scales (subjects enrolled in English-speaking countries and in countries where a validated translation is available)

Other assessments listed in Table 5–1 will be obtained from N01349 (as footnoted in Table 5–1) and are not to be recorded in the N01266 eCRF.

8.3.1.2 Core study: EP0065

The following assessments will be performed at this visit:

- Signing and dating of written Informed Consent by parent(s)/legal representative(s)
- Signing and dating of the Assent form by the subject (if applicable, according to age and local requirements)
- Subject identification card dispensing
- Childbearing potential
- Verification of inclusion/exclusion criteria
- Demographic data
- Epilepsy history
- Psychiatric and mental status examination
- Height
- Head circumference
- DRC dispensed
- Recording of medications (Any ongoing medications [including AEDs and non-AEDs] at the time the subject completed EP0065 should not be recorded in the N01266 eCRF. Changes in ongoing concomitant medications should be recorded in the N01266 eCRF.)
- Recording of procedures
- Recording of AEs (Any ongoing AEs at the time the subject completed EP0065 should not be recorded in the N01266 eCRF. Worsening of the AE should be recorded as a new AE.)
- IVRS call
- Study drug dispensed
- Bayley-III scales (subjects enrolled in English-speaking countries and in countries where a validated translation is available, and <18 months of age)
- Achenbach CBCL (see Section 10.3.3)
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (see Section 9.3.8)
- PedsQL (see Section 10.3.5)

Other assessments listed in Table 5–1 will be obtained from EP0065 (as footnoted in Table 5–1) and are not to be recorded in the N01266 eCRF.

8.3.1.3 Core study: Other (not N01349 or EP0065)

The following assessments will be performed at this visit:

- Signing and dating of written Informed Consent by parent(s)/legal representative(s)
- Signing and dating of Assent form by the subject (if applicable, according to age and local requirements)
- Subject identification card dispensing
- Childbearing potential
- Verification of inclusion/exclusion criteria
- Demographic data
- DRC dispensed
- Recording of medications (Any ongoing medications [including AEDs and non-AEDs] at the time the subject completed the core study should not be recorded in the N01266 eCRF. Changes in ongoing concomitant medications should be recorded in the N01266 eCRF.)
- Recording of AEs (Any ongoing AEs at the time the subject completed the core study should not be recorded in the N01266 eCRF. Worsening of the AE should be recorded as a new AE.)
- IVRS call
- Study drug dispensed

Other assessments listed in Table 5–1 will be obtained from the core study (as footnoted in Table 5–1) and are not to be recorded in the N01266 eCRF.

8.3.2 Directly enrolled subjects

Directly enrolled subjects will finish the Up-Titration Period and attend the EV when the same BRV dose (no lower than the minimum specified dose) has been maintained for 7±2 days at a level that, in the opinion of the Investigator, achieves acceptable tolerability and seizure control.

- Childbearing potential
- Physical examination
- Neurological examination
- Psychiatric and mental status
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight, height, and head circumference
- DRC dispensed
- DRC retrieved
- Recording of medications

- Recording of procedures
- Recording of AEs
- ECG
- Seizure count
- IVRS call
- Study drug dispensed
- Study drug returned
- Study drug compliance
- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects for whom sample collection is feasible)
  - Urine pregnancy test (see Section 9.2.1)
- Suicidality assessment (C-SSRS) (for subjects ≥6 years of age)
- Health care provider consultations not foreseen by the protocol
- Hospital stays
- Appointment for the next visit according to the schedule described in Section 5.3

8.4 Minimal Evaluation Visit (all subjects)

- Childbearing potential
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight, height, and head circumference
- Hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT (performed only at V4 [M3] and V6 [M9])
- DRC dispensed
- DRC retrieved
- Seizure count
- Recording of medications
- Recording of procedures
- Recording of AEs
- Suicidality assessment (C-SSRS) (for subjects ≥6 years of age)

- IVRS call
- Study drug dispensed
- Study drug returned
- Study drug compliance
- Urine pregnancy test (see Section 9.2.1)
- Health care provider consultations not foreseen by the protocol
- Hospital stays
- Appointment for the next visit according to the schedule described in Section 5.3

8.5 Full Evaluation Visit (all subjects)

- Childbearing potential
- Physical examination
- Neurological examination
- Psychiatric and mental status
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight, height, and head circumference
- EEG (for LTFU subjects only)
  - For subjects ≥2 years of age at V5 who have typical absence seizures, an EEG of at least 1 hour that includes hyperventilation and intermittent photic stimulation must be performed only at V5 and yearly thereafter.
  - For subjects <2 years of age at V5, an EEG of at least 24 hours of recording must be performed at V5 and yearly thereafter.
- DRC dispensed
- DRC retrieved
- Seizure count
- Assessment of seizure types for subjects <2 years of age
- Recording of medications
- Recording of procedures
- Recording of AEs
- Suicidality assessment (C-SSRS) (for subjects ≥6 years of age)
- IVRS call
- Study drug dispensed
- Study drug returned

- Study drug compliance
- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects for whom sample collection is feasible)
  - Urine pregnancy test (see Section 9.2.1)
- BRV plasma concentrations
- Phenytoin plasma concentrations (if applicable)
- Bayley-III scales (for LTFU subjects enrolled in English-speaking countries and in countries where a validated translation is available, <18 months of age at baseline of the core study, and <42 months of age)
- Achenbach CBCL (see Section 10.3.3)
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (see Section 9.3.8)
- PedsQL (see Section10.3.5)
- Health care provider consultations not foreseen by the protocol
- Hospital stays
- Appointment for the next visit according to the schedule described in Section 5.3

8.6 Yearly Evaluation Visit (all subjects)

- Childbearing potential
- Physical examination
- Neurological examination
- Psychiatric and mental status
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight, height, and head circumference
- ECG
- DRC dispensed
- DRC retrieved
- Seizure count
- Recording of medications
- Recording of procedures
- Assessment of seizure types for subjects <2 years of age

- Recording of AEs
- Suicidality assessment (C-SSRS) (for subjects ≥6 years of age)
- IVRS call
- Study drug dispensed
- Study drug returned
- Study drug compliance
- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects for whom sample collection is feasible)
  - Urine pregnancy test (see Section 9.2.1)
  - Endocrinology
- BRV plasma concentrations
- Phenytoin plasma concentrations (if applicable)
- Bayley-III scales (for LTFU subjects enrolled in English-speaking countries and in countries where a validated translation is available, <18 months of age at baseline of the core study, and <42 months of age)
- Achenbach CBCL (see Section 10.3.3)
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (see Section 9.3.8)
- Peds QL (see Section 10.3.5)
- Health care provider consultations not foreseen by the protocol
- Hospital stays
- Appointment for the next visit according to the schedule described in Section 5.3.

8.7 Unscheduled Visit (all subjects)

At any time, the subject may have an Unscheduled Visit (UV) if the Investigator or the subject and/or parent(s)/legal representative(s) consider it necessary.

- Recording of medications
- Recording of procedures
- Recording of AEs
- IVRS call (if applicable)
- Health care provider consultations not foreseen by the protocol

- Hospital stays

If an Unscheduled Visit is conducted due to safety or efficacy reasons, a suicidality assessment (C-SSRS) will be performed with subjects ≥6 years of age during the visit. If an Unscheduled Visit is conducted for reasons other than safety or efficacy concerns (eg, replacement of lost medication, repeated collection of a laboratory specimen due to collection or analysis issues), a C-SSRS will not be required at these visits.

8.8 Early Discontinuation Visit (all subjects)

- Childbearing potential
- Physical examination
- Neurological examination
- Psychiatric and mental status
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight, height, and head circumference
- ECG
- EEG (LTFU subjects only)
  - For subjects ≥2 years of age at V5 who have typical absence seizures, a 1-hour EEG may be performed at the Investigator's discretion.
  - For subjects <2 years of age at V5, a 24-hour EEG may be performed at the Investigator's discretion.
- DRC dispensed
- DRC retrieved
- Seizure count
- Recording of medications
- Recording of procedures
- Recording of AEs
- Suicidality assessment (C-SSRS) (for subjects ≥6 years of age)
- IVRS call
- Study drug dispensed
- Study drug returned
- Study drug compliance
- Laboratory assessments for safety
  - Hematology

  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects for whom sample collection is feasible)
  - Urine pregnancy test (see Section 9.2.1)
- BRV plasma concentrations
- Phenytoin plasma concentrations (if applicable)
- Bayley-III scales (for LTFU subjects enrolled in English-speaking countries and in countries where a validated translation is available, <18 months of age at baseline of the core study, and <42 months of age)
- Achenbach CBCL (see Section 10.3.3)
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (see Section 9.3.8)
- PedsQL (see Section 10.3.5)
- Health care provider consultations not foreseen by the protocol
- Hospital stays
- Appointment for the next visit should be scheduled for the end of the 4-week Down-Titration Period (maximum)

8.9 Down-Titration Visit (all subjects)

- Vital signs (blood pressure, pulse rate, and body temperature)
- DRC dispensed
- DRC retrieved
- Seizure count
- Recording of medications
- Recording of procedures
- Recording of AEs
- Suicidality assessment (C-SSRS) (for subjects ≥6 years of age)
- IVRS call
- Study drug returned
- Study drug compliance
- Health care provider consultations not foreseen by the protocol
- Hospital stays
- Appointment for the next visit according to the schedule described in Section 5.2.

8.10 Safety Visit (all subjects)

The SV will be performed after the subject has been free of study drug for 2 weeks (Safety Period).

- Physical examination
- Neurological examination
- Psychiatric and mental status
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight, height, and head circumference
- ECG performed only if abnormal at the EDV
- DRC retrieved
- Seizure count
- Recording of medications
- Recording of procedures
- Recording of AEs
- Suicidality assessment (C-SSRS) (for subjects ≥6 years of age)
- IVRS call
- Laboratory assessments for safety (to be performed only if abnormal at the EDV)
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects for whom sample collection is feasible)
  - Urine pregnancy test (see Section 9.2.1)
- Phenytoin plasma concentrations (if applicable) only if abnormal at the EDV
- Health care provider consultations not foreseen by the protocol
- Hospital stays
- End of study status

8.11 Final Visit (all subjects)

Subjects who continue in the study until it ends should complete a FV.

- Childbearing potential
- Physical examination
- Neurological examination

- Psychiatric and mental status
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight, height, and head circumference
- ECG
- EEG (for LTFU subjects only)
  - For subjects ≥2 years of age at V5 who have typical absence seizures, an EEG of at least 1 hour that includes hyperventilation and intermittent photic stimulation must be performed
  - For subjects <2 years of age at V5, an EEG of at least 24 hours must be performed
- DRC retrieved
- Seizure count
- Recording of medications
- Recording of procedures
- Recording of AEs
- Suicidality assessment (C-SSRS) (for subjects ≥6 years of age)
- IVRS call
- Study drug returned
- Study drug compliance
- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects for whom sample collection is feasible)
  - Urine pregnancy test (see Section 9.2.1)
  - Endocrinology
- BRV plasma concentrations
- Phenytoin plasma concentrations (if applicable)
- Bayley-III scales (for LTFU subjects enrolled in English-speaking countries and in countries where a validated translation is available, <18 months of age at baseline of the core study, and <42 months of age)
- Achenbach CBCL (see Section 10.3.3)
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (see Section 9.3.8)

- PedsQL (see Section 10.3.5)
- Health care provider consultations not foreseen by the protocol
- Hospital stays
- End of study status
- Appointment for the next visit should be scheduled for the end of the 4-week Down-Titration Period (maximum) if BRV treatment is not continued after study completion (FV), and study drug for down-titration should be dispensed

9 ASSESSMENT OF SAFETY

The safety variables will be evaluated during the Up-Titration Period (directly enrolled subjects only) and the Evaluation Period. For subjects who continue in the study until it ends, the Evaluation Period will include the EV through the FV. For subjects who prematurely discontinue the study, the Evaluation Period will include the EV through the EDV, followed by a 4-week Down-Titration Period (maximum), and a 2-week Safety (Drug-Free) Period.

9.1 Adverse events

9.1.1 Definitions

9.1.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after signing the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no investigational product was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs, which recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the investigational product is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or the Baseline Period.

9.1.1.2 Serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious

  (Important medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

  (A patient admitted to a hospital, even if released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

  Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE since there is no AE upon which to assess the serious criterion. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

9.1.1.2.1 Anticipated serious adverse events

The following Anticipated SAEs are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 9.1.2.3.

Table 9–1: Anticipated serious adverse events for the pediatric epilepsy population

MedDRA SOC	MedDRA PT
Congenital, familial and genetic disorders	Teratogenicity
General disorders and administration site conditions	Sudden unexpected death in epilepsy
Nervous system disorders	Convulsion[a]
	Status epilepticus
Pregnancy, puerperium and perinatal disorders	Abortion spontaneous
Psychiatric disorders	Psychotic behavior
	Abnormal behavior
	Anxiety
	Sleep disorder

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class
[a] Convulsion if consistent with the seizure type known for the subject.

9.1.1.3 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound. For this study, the AEs of special interest include:

- Autoimmune nephritis
- Nephritis
- Nephritis allergic
- Tubulointerstitial nephritis
- Tubulointerstitial nephritis and uveitis syndrome
- Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

9.1.2 Procedures for reporting and recording adverse events

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs, for example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the Investigator should review any self-assessment procedures (eg, diary cards) employed in the study.

For LTFU subjects, AEs ongoing at the time the subject completed the core study should not be recorded in the eCRF at the EV, or any subsequent visit. Worsening of the AE should be recorded as a new AE. For all subjects, new AEs should be recorded in the eCRF at only the first visit at which they are reported and subsequently only if there is a change.

9.1.2.1 Description of adverse events

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event in the eCRF (including judgment of relationship to study medication) are described in the eCRF Completion Guidelines.

Occurrence of COVID-19 in subjects should be reported as either "suspected COVID-19" or "confirmed COVID-19." For subjects where COVID-19 is still suspected despite a negative viral test, please report as "suspected COVID-19."

9.1.2.2 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- the outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening",
- the AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one.

9.1.2.3 Additional procedures for reporting adverse events

A blood sample for determination of BRV plasma concentration should be obtained for any subject who has an SAE.

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact numbers for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed Investigator SAE Report form provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE Report form will be provided to the Investigator. The Investigator SAE Report form must be completed in English.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE Report form.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the investigational product), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the Investigator of any SAE within this period. Any SAEs that the Investigator thinks may be associated with the investigational product must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the Investigator's Brochure.

9.1.3 Follow-up on adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up.

If an AE is still ongoing at the end of the study for a subject, follow-up should be provided until resolution/stable level of sequelae, the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow-up. If no follow-up is provided, the Investigator must provide a justification. The follow-up will usually be continued for 30 days after the subject has discontinued their IMP.

Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

9.1.4 Pregnancy

Should a subject become pregnant after the first intake of any IMP, UCB's PS department should be informed immediately. The subject should be withdrawn from the study as soon as the pregnancy is known and the following should be completed:

- The subject should return for an EDV.
- The subject should immediately stop the intake of the IMP or be down titrated as instructed at the EDV.
- A SV should be scheduled 2 weeks after the subject has discontinued their IMP.

The Investigator must inform the subject/parent(s)/legal representative(s) of information currently known about potential risks and about available treatment alternatives.

The Investigator will complete the Pregnancy Report and Outcome form for any pregnancy and send it to UCB's PS department (for contact details see SAE reporting information at the beginning of this protocol).

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. Those SAEs must be additionally reported using the Investigator SAE Report form.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/contract research organization contract monitor for the study.

If the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form, the Pregnancy Report and Outcome form will be completed. UCB's PS department is the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow-up.

9.1.5 Suspected transmission of an infectious agent via a medicinal product

A suspected transmission of infectious agent is defined as any infection that is temporally related to the administration of the medicinal product with no other likely cause. The Medical Monitor should be contacted immediately. No further medicinal product from that specific batch should be administered. Infections should be treated according to normal clinical practice.

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

9.1.6 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded on the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other serious or nonserious AE. These events may be symptomatic, in that the excessive dosing results in clinical signs and symptoms, or the excessive intake may itself be a symptom.

9.1.7 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that Investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Patient Safety representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (examples: AEs, vital signs, laboratory, or ECG results) for which data will be periodically reviewed during the course of the study.

9.2 Laboratory measurements

9.2.1 Laboratory assessments for safety

Laboratory assessments for safety (including hematology, biochemistry, and endocrinology for all subjects, and urinalysis for subjects for whom sample collection is feasible) will be conducted using standard methods at a central laboratory. The central laboratory will provide the Investigator with dedicated, standardized sampling equipment (labels, needles, tubes) and a study-specific laboratory manual, which will explain how to use the equipment and how to ship the samples to the central laboratory.

For blood samplings, methods to minimize pain are recommended (eg, topical anesthetic and microsamplings will be used).

The total blood volume drawn for clinical laboratory assessments in subjects ≥2 years of age will be a maximum of 11mL per sampling, which includes up to 3mL for hematology and up to 8mL for biochemistry. For subjects <2 years of age, the blood volume drawn will be typically much smaller and in the range of 1mL to 2.5mL. Further details will be provided in the laboratory manual.

The following laboratory parameters will be measured:

Hematology	**Biochemistry**	**Urinalysis[a]**	**Pregnancy**	**Endocrinology**
WBC	Glucose	Glucose	β-hCG[d]	FSH
RBC	Sodium	Ketones		LH
Hemoglobin	Potassium	Occult blood		TSH
Hematocrit	Calcium	Protein		T3
MCV	Chloride	Nitrites		T4
MCH	Bicarbonate	Leukocytes		
MCHC	Phosphorus (inorganic)	Microscopic examination[c]		
Platelet count	Total protein			
Lymphocytes (number, %)	Albumin			
Monocytes (number, %)	Total bilirubin[b]			
Neutrophils (number, %)	ALP[b]			
Eosinophils (number, %)	AST (SGOT)[b]			
Basophils (number, %)	ALT (SGPT)[b]			
	GGT[b]			
	Uric acid			
	Urea			
	Creatinine			
	Triglycerides			
	Cholesterol			

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=beta-human chorionic gonadotropin; FSH=follicle-stimulating hormone; GGT=gamma-glutamyltransferase; LH=luteinizing hormone; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; ScrV=Screening Visit; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; T3=triiodothyronine; T4=tetraiodothyronine; TSH=thyroid-stimulating hormone; TV=Titration Visit; WBC=white blood cell

[a] Urinalysis will be performed for subjects for whom sample collection is feasible.
[b] This assessment is used for hepatic monitoring.
[c] Includes bacteria, cells, casts, and crystals for all samples.
[d] Urine pregnancy tests should be conducted at the site for all female subjects of childbearing potential.

The creatinine clearance will be calculated over time by the central laboratory using their current methods. The subject's age, body weight and height, and gender must be recorded on the laboratory requisition form.

All female subjects of childbearing potential should have urine pregnancy tests. A serum pregnancy test will be performed as backup if a urine sample is not available. A urine pregnancy test should be performed at any time during the study if a pregnancy is suspected. All urine pregnancy tests should be conducted at the site.

Results for hematology, biochemistry, urinalysis, pregnancy tests, and endocrinology measurements will be provided by fax to the Investigator within 72 hours after sample receipt.

9.2.2 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and Sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 9.1.1.3), and, if applicable, also reported as an SAE (see Section 9.1.2.3).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 9–2 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 9.2.2.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 9.2.2.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and Sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

Table 9–2: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 9.2.2.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥5xULN (and ≥2x baseline)	<2xULN	No	Discussion with Medical Monitor required. Hepatology consult required if ALT/AST ≥8x ULN.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 9.2.2.3).	

Table 9–2: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 9.2.2.2). IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase • Liver chemistry values remain ≥3xULN (and ≥2x baseline) after 2 weeks of monitoring without stabilization or evidence of resolution.	Not required unless otherwise medically indicated (at discretion of Investigator).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[d] Immediate IMP discontinuation required if : • Liver chemistry values continue to increase • Liver chemistry values remain ≥3xULN (and ≥2x baseline) after 2 weeks of monitoring without stabilization or evidence of resolution Continue to monitor until values normalize, stabilize, or return to within baseline values. [d]

Table 9–2: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 9.2.2.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the Investigator and UCB responsible physician. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

9.2.2.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 9.2.2.3) and SAE report (if applicable).

9.2.2.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 9–2 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The Investigator should also consider dose reduction of medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

9.2.2.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 9–3 (laboratory measurements) and Table 9–4 (additional information). Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

Table 9–3: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥2xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	Serum pregnancy test[b]
	PK sample[c]

CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] Determined only for female subjects of childbearing potential.

[c] Blood sample for determination of plasma concentrations of BRV.

The following additional information is to be collected:

Table 9–4: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use, if applicable
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

9.2.2.4 Follow-up evaluation

Potential drug-induced liver injury events will require follow-up monitoring as described in Table 9–2. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

9.2.3 Plasma concentration measurements

9.2.3.1 BRV plasma concentrations

Blood samples for the analysis of BRV concentrations will be collected at the visits designated in Table 5–2. Additionally, a blood sample for determination of BRV plasma concentration should be taken whenever the subject experiences an SAE.

Brivaracetam will be assayed in batch runs at the bioanalytical laboratory. Plasma levels will be reported to the central laboratory after the batch run is performed, according to laboratory

methodology. Results will be reported by the central laboratory to the Investigator as exact values, with a flag to those values that are outside the therapeutic range.

9.2.3.2 Phenytoin plasma concentrations (if applicable)

Subjects receiving phenytoin as a concomitant AED during the study will have blood samples collected at the visits designated in Table 5–1, Table 5–2, and Table 5–3 to monitor phenytoin plasma concentrations.

Phenytoin plasma levels will be determined by the central laboratory. Further details on sample collection, bioanalytical method, and shipping of the samples will be provided in the central laboratory manual.

9.3 Other safety measurements

Other safety measurements will be performed at the visits indicated in Table 5–1, Table 5–2, and Table 5–3.

9.3.1 ECG

A standard 12-lead ECG will be performed. The Investigator will determine whether the results of the ECG are normal or abnormal and assess the clinical significance of any abnormalities.

The original ECG tracing will be signed or initialed and dated by the Investigator, and retained as part of the source documentation.

9.3.2 Vital signs

Vital signs, including measurements of blood pressure, supine or sitting pulse rate, and body temperature, will be performed after 5 minutes of rest. Vital signs measurements will be repeated after 30 minutes if unusual values are observed at the initial reading.

9.3.3 Body weight, height, and head circumference

Body weight (subject wearing light clothing without shoes), height (length may be used for this measure, as appropriate), and head circumference (occipital-frontal circumference) will be measured.

9.3.4 Physical examination

A standard physical examination will be performed. Clinically significant new or worsened abnormalities discovered at the physical examination must be reported as AEs.

The Investigator or qualified designee will evaluate the subject's physical development using the 3-item Tanner scale. The Investigator should use clinical judgment in deciding which subjects are selected for evaluation of Tanner Stage (ie, those subjects who are pubescent at Baseline).

9.3.5 Neurological examination

A standard neurological examination will be performed. Clinically significant new or worsened abnormalities in the neurological examination must be reported as AEs.

9.3.6 Psychiatric and mental status

Psychiatric and mental status will be reported by recording the presence or absence of psychiatric symptoms, mental impairment, and behavioral problems. Clinically significant new or worsened abnormalities must be reported as AEs.

9.3.7 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS 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. The C-SSRS will be completed according to the tabular schedules of study procedures, Section 5.2.

The "Since Last Visit" version of the C-SSRS will be used, with the following exceptions:

- For directly enrolled subjects, the "Baseline/Screening" version of the C-SSRS should be completed at the ScrV.

If a subject turns 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be completed at the first visit after the sixth birthday.

The C-SSRS is not validated for subjects <6 years of age and will not be used for this population. Subjects should be monitored for any changes in mood, ideas, or behavior for warning signs of depression. The Investigator should be aware of common warning signs that might be a signal for risk of depression. For common signs and symptoms of depression in children younger than 6 years old, reference should be made to the current version of the Diagnostic and Statistical Manual of Mental Disorders. Parents and caregivers should also be advised accordingly and effort should be made at clinic visits to specifically assess potential depression.

9.3.8 BRIEF-P and BRIEF

The BRIEF-P and the BRIEF are validated tools that will be used for the evaluation of subjects ≥2 years to <5 years of age and ≥5 years of age, respectively. The BRIEF-P and BRIEF include rating forms used by parents 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-P rating form consists of items that measure various aspects of executive functioning: Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize. The clinical scales form 3 broad indexes (Inhibitory Self-Control, Flexibility, and Emergent Metacognition) and 1 composite score (Global Executive Composite).

The BRIEF rating form contains items in nonoverlapping clinical scales. These theoretically and statistically derived scales form 2 broader Indexes: Behavioral Regulation (3 scales) and Metacognition (5 scales), as well as a Global Executive Composite score.

Both the BRIEF-P and the BRIEF include validity scales to measure negativity and inconsistency of responses.

10 ASSESSMENT OF EFFICACY

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 directly enrolled 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.

10.1 Efficacy assessments for seizure data based on DRC

At each visit, the subject/parent(s)/legal representative(s) will receive a DRC, which has to be filled in daily by the 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 ILAE codes and record the seizure types and frequency on the 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.

The DRC will be considered as source documentation. The subject/parent(s)/legal representative(s) should be educated to complete the DRC on a daily basis (eg, when taking evening dose of BRV). Substantial noncompliance with diary completion (seizures recording) may result in subject discontinuation from the study at any time by the Investigator or the Sponsor.

10.2 Efficacy assessments for seizure data based on EEG

All EEGs specific to this study will be recorded in the eCRF modules specifically designed for this purpose.

10.3 Other assessments

Other assessments will be performed at the visits indicated in Table 5–1, Table 5–2, and Table 5–3.

10.3.1 Direct cost parameters

Direct cost parameters include the following: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays.

10.3.1.1 Concomitant medications/treatments

Concomitant medication information will be collected and recorded.

For LTFU subjects, any ongoing medications (including AEDs and non-AEDs) at the time the subject completed the core study should not be recorded in the N01266 eCRF. Changes in ongoing concomitant medications should be recorded in the N01266 eCRF. In this event, the medication should be recorded in the eCRF for N01266 with the start date corresponding to the date of change in administration.

Details of the concomitant medications and therapy are provided in Section 7.8.

10.3.1.2 Medical procedures

Data on medical procedures (surgery, therapeutic and/or diagnostic, hospitalizations) undertaken during the study will be collected and recorded in the eCRF. Electrocardiograms specific to this study will not be recorded on the medical procedures page of the eCRF, but in the modules specifically designed for this purpose.

10.3.1.3 Health care provider consultations not foreseen by the protocol

Data collected for health care provider consultations not foreseen by the protocol will include the type of provider (general practitioner, specialist physician, nurse), the site of care (office-private, office-hospital, home, emergency room), and the reason leading to the consultation.

10.3.1.4 Hospital stays

Data collected for hospital stays will include the reason leading to the hospitalization, the admission ward, transfers, and length of stay.

10.3.2 Bayley Scales of Infant and Toddler Development, Third Edition

The Bayley-III scales are validated as a tool for assessment of neurological development in young children and recognized internationally as one of the most comprehensive developmental assessment instruments (Sattler and Hoge, 2006) used to examine the major facets of a young child's development (Bayley, 2006). The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) are a standardized individually administered adaptive assessment that measures the developmental functioning of infants and young children from 1 month to 42 months of age (Bayley, 2006). The Bayley-III scales measure cognitive, language, motor, social-emotional, and adaptive development and are a revision of the predecessor, the Bayley Scales of Infant Development, Second Edition (BSID-II) (Bayley, 1993). The Bayley-III scales are a technically sound instrument, with strong internal consistency, as well as test-retest stability. The Bayley-III scales are provided in English and in countries where a validated translation is available.

The Bayley-III scales are an individually administered adaptive assessment that presents children with situations and tasks designed to produce an observable set of behavioral responses. They consist of a cognitive scale, a language composite scale with receptive and expressive language subscales, and a motor composite scale with fine and gross motor subscales to be completed by the Investigator or designee, and of a social-emotional scale, comprising social-emotional competence and sensory processing, and an adaptive behavior scale, which assesses the attainment of skills necessary for the development of independence, to be completed by the child's parent or caregiver.

The completion of the Bayley-III scales will require approximately 50 minutes for children who are 12 months old or younger and 90 minutes for children aged 13 months and older.

The Bayley-III scales will be applied to subjects as described in Table 5–1 and Table 5–2. The Bayley-III scale is not applicable to directly enrolled subjects due the age of these subjects (≥4 years of age) at entry into N01266.

10.3.3 Achenbach Child Behavior Checklist

The Achenbach CBCL is a widely used validated questionnaire to evaluate a child's competencies and behavioral/emotional problems. Behavioral problems will be scored by the parent(s) or legal representative(s). Depending on the subject's age, 2 versions of the Achenbach CBCL will be 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 <16 years, the Achenbach CBCL/6-18 version will be used. The Achenbach CBCL will not be applied to children below 18 months of age.

The Achenbach CBCL should be completed by the same parent(s)/legal representative(s) who completed the CBCL in the core study, when possible. The completion of the Achenbach CBCL will require approximately 45 minutes.

In both questionnaires, the occurrence of certain problems and behaviors in the past 6 months will be scored on the following scale:

0=not true (as far as known)

1=somewhat or sometimes true

2=very true or often true

Eight syndrome scores will be calculated from these questions, which will in turn be summarized by 2 composite scores. Additionally, for each score on the question, syndrome, and total level, categorizations based on a normative sample will be used to evaluate normal, borderline, or clinically relevant behavior.

In addition, the Achenbach CBCL/6-18 includes ratings related to performance in school, activities in leisure time, and special interests.

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.

10.3.4 Assessment of seizure types

The assessment of seizure types will be done at 6-monthly intervals (at the FEV and the YEV) for subjects <2 years of age.

10.3.5 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. Self-report is measured for pediatric subjects ≥5 years to ≤18 years of age, and parent proxy report of child HRQoL is measured for pediatric subjects ≥2 years to ≤18 years of age.

The multidimensional PedsQL generic core scales encompass the essential core domains for pediatric HRQoL measurement: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. The PedsQL assessment is retrospective to the prior 4 weeks, and individual items are scored using a 5-point Likert scale (never, almost never, sometimes, often, or always). A total health summary score ranging between 0 and 100 is calculated from the sum of the raw scores, with higher scores indicating higher HRQoL.

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.

11 STUDY MANAGEMENT AND ADMINISTRATION

11.1 Adherence to protocol

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator may use his/her medical judgment and may remove a study participant from immediate hazard before notifying UCB (or its representative) and the IRB/IEC in writing regarding the type of emergency and the course of action taken.

11.2 Monitoring

UCB (or designee) will monitor the study to meet the Sponsor's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a contract research organization or a contract monitor. Remote monitoring visits may be conducted during the COVID-19 pandemic or under other exceptional circumstances as deemed appropriate to ensure subjects' safety.

The Investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The Investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

11.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments

(such as removable self-stick notes). Photocopies and/or printouts of eCRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECGs, or other printouts, or completed scales, for example. Source documents should be kept in a secure, limited access area.

Original laboratory results, ECGs, and EEGs are considered as source documents and should be placed and stored with the subject's study information.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the subject's source documents. The Investigator will authorize the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as Holter monitor records or EEG records must be saved and stored as instructed by UCB (or designee).

11.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 11.2.1.

11.3 Data handling

11.3.1 Case report form completion

This study will be performed using electronic data capture.

The Investigator is responsible for prompt reporting of accurate and complete data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

11.3.2 Database entry and reconciliation

External electronic data will be loaded in a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. Data are entered into the eCRFs once and are subsequently verified.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data has been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

11.3.3 Subject Selection and Enrollment log/Subject Identification Code list

The subject's selection and enrollment will be recorded in the Subject Selection and Enrollment Log. The Investigator will keep a Subject Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each subject. The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

11.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused investigational products and other material in accordance with UCB procedures for the study.

11.5 Archiving and data retention

The Investigator will maintain adequate records for the study including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002, [Section 4.9.5]). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

11.6 Audit and inspection

The Investigator will permit study-related audits mandated by UCB and inspections by domestic or foreign regulatory authorities, after reasonable notice.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH/GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform UCB (or designee).

11.7 Good Clinical Practice

Noncompliance with the protocol, ICH/GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

12 STATISTICS

A description of statistical methods is presented below and will be described in more detail in the statistical analysis plan (SAP).

12.1 Definition of analysis sets

Analysis sets will be defined as follows:

- The Safety Set (SS) will consist of all enrolled subjects who took at least 1 dose of study medication in this long-term study. All safety analyses will be performed on the SS.
- The Full Analysis Set 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.

12.2 General statistical considerations

Descriptive statistics, such as the mean, standard deviation, median, 25th percentile, 75th percentile, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, will be provided. Key supporting data will be provided in data listings. Data collected during the Up-Titration Period for directly enrolled subjects will be summarized separately.

Analyses may also be summarized for direct enrollers, as well as by core study (eg, EP0065 and N01349).

12.3 Planned safety analyses

The long-term safety of BRV at individualized doses will be evaluated by means of the safety analyses. Summary tables will be presented over the Evaluation Period by 3-month periods and by categories of total duration of exposure.

All safety variables will be analyzed by descriptive methods on the Safety Set. Treatment-emergent adverse events will be summarized by categories of total duration of exposure, 3-month period, Medical Dictionary for Regulatory Activities (MedDRA®) Primary

System Organ Class and Preferred Term in incidence tables. Separate tables will be provided by categories of total duration of exposure for AEs leading to withdrawal from the study and SAEs.

Laboratory values, vital signs, and weight will be summarized by 3-month period and visit. Possibly clinically significant treatment-emergent abnormalities for laboratory values, vital signs, and weight will be listed and summarized by 3-month period and visit. ECG abnormalities, as well as physical and neurological abnormalities, will also be listed by 3-month periods and visit.

12.4 Planned efficacy analyses

Efficacy parameters related to seizures will be summarized descriptively and will be reported individually using data listings. Subgroup analyses based on seizure types and other characteristics may be conducted, depending on the number of subjects enrolled per seizure type and epilepsy syndrome. Additional details will be provided in the SAP.

12.5 Other analyses

Descriptive statistics will be also presented for the number of medical resources used (medications, consultations, procedures, hospitalizations, and length of hospital stays).

The Achenbach CBCL, the Bayley-III scores (LTFU subjects only), BRIEF-P/BRIEF, PedsQL, and change from Baseline scores (core study for LTFU subjects and ScrV for directly enrolled subjects) will be analyzed in a descriptive manner.

12.6 Handling of 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. To the extent feasible, the rules for identifying protocol deviations will be defined without review of the data and without the 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 database lock to confirm exclusion from analysis sets.

Protocol deviations (eg, missing assessments or visits) related to COVID-19 will be documented.

12.7 Handling of dropouts or missing data

No specific procedure is foreseen for handling dropouts or missing data.

12.8 Planned interim analysis and data monitoring

No formal interim analysis is planned; however, data may be reported prior to the completion of this study to support ongoing data cleaning, annual reports, regulatory submissions, and publications.

12.9 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 directly enrolled subjects, with no change in the assumption regarding core study completion.

13 ETHICS AND REGULATORY REQUIREMENTS

13.1 Informed consent

Informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable in both oral and written form by the Investigator (or designee). Parent(s), legal representative(s), and subject if applicable will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the Informed Consent form should be signed and personally dated by the subject's parent(s)/legal representative(s), and by the person who conducted the informed consent discussion (Investigator [or designee]). The subject/parent(s)/legal representative(s) must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject/parent(s)/legal representative(s) must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection. In addition, a Consent form or a specific Assent form, where required, will be signed and dated by minors. Any subject who is over 16 years of age during N01266 must sign and date the Informed Consent form according to local regulations.

If the Informed Consent form is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB/IEC and use of the amended form.

All studies conducted at centers in the United States must include the use of a Health Insurance Portability and Accountability Act (ie, HIPAA) Authorization form.

The subject/parent(s)/legal representative(s) may withdraw his/her/their consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she or parent(s)/legal representative(s) has signed the Informed Consent form. An eCRF must not be started nor may any study specific procedure be performed for a given subject without having obtained his/her written consent to participate in the study.

13.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject's parent(s) or legal representative(s) will be provided with a subject identification card in the language of the subject. The Investigator will fill in the name of the study and medical emergency contact information. The Investigator will instruct the subject to keep the card with them at all times.

13.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, Informed Consent form, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The Investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on the Committee's requirements), at intervals appropriate to the degree of subject risk involved but no less than once per year. The Investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

13.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at selection.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital

admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

13.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

14 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the Investigator and/or CRO agreements as applicable.

15 REFERENCES

Bayley N. Bayley Scales of Infant and Toddler Development. 3rd ed. San Antonio: Pearson Education Inc; 2006.

Bayley N. Bayley Scales of Infant Development. 2nd ed. San Antonio: The Psychological Corporation; 1993.

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia. 1989;30:389-99.

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia. 1981;22:489-501.

CPMP/ICH/135/95 Note for guidance on Good Clinical Practice (EMEA) Jul 2002.

Hadjiloizou SM, Bourgeois BF. Antiepileptic drug treatment in children. Expert Rev Neurother. 2007;7:179-93.

Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: a systematic review and meta-analysis. Neurology. 2011; 77(10): 1005–12.

Sattler JM, Hoge RD. Assessment of children: behavioral, social, and clinical foundations. 5th ed. La Mesa: Jerome M Sattler; 2006.

Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care. 1999;37:126-39.

16 APPENDICES

16.1 Protocol Amendment 1

Rationale for the amendment

The BSID-II was included in order to assess the cognitive development of children <18 months at Baseline in response to the PDCO request. Withdrawal criteria have been extended to include the consequences of any findings related to the results of LFTs. Procedures for reporting SAEs were updated to implement the Food and Drug Administration (FDA) Final Rule requirements. The C-SSRS was added to address the request of the FDA that prospective assessments for suicidality should be included in clinical studies involving all drugs for neurological indications. Some operational updates are also considered.

Administrative changes include the update of the SAE reporting and CRO contact details. A few changes of editorial nature are not listed in the specific changes section.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Addition of a new Section 9.6.7 (Assessment of suicidality) to introduce the C-SSRS for subjects ≥6 years of age. Respective exclusion and withdrawal criteria possibly resulting from the individual C-SSRS assessment were added to the list of withdrawal criteria.
- Addition of a new Section 9.4 (Anticipated SAEs) to account for the FDA Final Rule implementation.
- Addition of a cognition scale (Section 10.3.2; BSID-II) for subjects <18 months of age at Baseline of N01263.
- Addition of an assessment of seizure types at 6-monthly intervals for subjects <2 years of age.
- Update of the withdrawal criteria in order to clarify the withdrawal of subjects with findings in LFT results above the references ranges.
- Clarification of the age limit (subjects >2 years) for the 1-hour EEG including hyperventilation and intermittent photic stimulation for subjects with typical absence seizures.

Specific changes

Change #1, TITLE PAGE

The title page was updated to reflect the current amendment.

Change #2, SPONSOR DECLARATION

The following signature was added to the list of signatures:

Exploratory Development Director

[redacted]

Date/Signature

Change #3, Clinical Monitoring Contract Research Organization

The empty table was updated as follows:

Name:	**Pharma-Research Associates (UK) Ltd.**
Address:	**Imperial Way** **Reading, Berkshire** **RG2 OTD** **United Kingdom**
Phone:	**+44 118 918 1000**
Fax:	**+44 118 918 1001**

Change #4, SERIOUS ADVERSE EVENT REPORTING

The original table:

Serious adverse event reporting (24h), safety related issues		
Fax	**Europe and Rest of the World (except Japan):** +32 2 386 2421 **USA and Canada:** +1 800 880 6949 or +1 866 890 3175	
Phone	**During business hours:**	**Outside business hours:**
	Europe and Rest of the World (except Japan): +32 2 386 2468 **USA and Canada:** +1 919 767 2627	**Europe and Rest of the World (except Japan):** +32 2 386 2468 **USA and Canada:** +1 404 895 0794

Has been changed to:

Serious adverse event reporting (24h), safety related issues, and emergency unblinding		
Fax	**Europe and Rest of the World (except Japan):** +32 2 386 2421 **USA:** +1 800 880 6949 **Canada:** +**1 877 582 8842**	
Phone	**During business hours:**	**Outside business hours:**
	Europe and Rest of the World (except Japan): +32 2 386 2468 **USA and Canada:** +1 **404 895 0794**	**Europe and Rest of the World (except Japan):** +32 2 386 2468 **USA and Canada:** +1 404 895 0794

Change #5, LIST OF ABBREVIATIONS

The following abbreviations were added to the list:

ADF	**average daily frequency**
ALT	**alanine aminotransferase**
AST	**aspartate aminotransferase**
BSID-II™	**Bayley Scales of Infant Development-II**
C-SSRS	**Columbia-Suicide Severity Rating Scale**
FDA	**Food and Drug Administration**

ADF	**average daily frequency**
LFT	**liver function test**
PDCO	**European Pediatric Committee**
ULN	**upper limit of normal**

Change #6, Section 1, SUMMARY, paragraph 1

The original text:

This is a Phase 3, open-label, single-arm, multicenter, long-term follow-up (LTFU) study to evaluate the safety and efficacy of brivaracetam (BRV) in children with epilepsy. 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 and the other objectives are to explore direct cost parameters and to assess the effect of BRV on behavior using the age-appropriate Achenbach Child Behavior Checklist (CBCL/1½-5 or CBCL/6-18).

Has been changed to:

This is a Phase 3, open-label, single-arm, multicenter, long-term follow-up (LTFU) study to evaluate the safety and efficacy of brivaracetam (BRV) in children with epilepsy. 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 and the other objectives are to explore direct cost parameters and to assess the effect of BRV on behavior **and cognition** using the age-appropriate Achenbach Child Behavior Checklist (CBCL/1½-5 or CBCL/6-18) **for subjects ≥18 months of age at Baseline of the previous study N01263 or the Bayley Scales of Infant Development-II (BSID-II™) for subjects <18 months of age at Baseline of the previous study N01263.**

Change #7, Section 1, SUMMARY, paragraph 8

The original text:

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) scores over time.

Has been changed to:

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) **and BSID-II** scores over time.

Change #8, Section 2.4, Safety with BRV, paragraph 2

The original text:

In addition, there are 3 ongoing open-label LTFU studies (N01125, N01199, and N01315) that include subjects with POS, primary generalized seizures, or ULD who completed 1 of the above Phase 2/3 well-controlled studies. As of 20 Sep 2010, 1628 subjects have been enrolled in these

studies. The most frequently reported TEAEs based on interim safety monitoring review include headache, dizziness, nasopharyngitis, convulsion, somnolence, and fatigue. Overall, 227 subjects (14.0%) reported SAEs. The only SAE occurring at a frequency >1% was convulsion (2.3%). Overall, 130 subjects (8.0%) discontinued due to TEAEs.

Has been changed to:

In addition, there are 3 ongoing open-label LTFU studies (N01125, N01199, and N01315) that include subjects with POS, primary generalized seizures, or ULD who completed 1 of the Phase 2/3 well-controlled studies. As of **04 Jan 2011, 1629** subjects have been enrolled into these studies and **1624 subjects** have received study medication. The median duration of BRV exposure in LTFU studies was **91** weeks. The most **common** TEAEs based on interim safety monitoring review include headache, dizziness, nasopharyngitis, convulsion, somnolence, and fatigue. Overall, **234** subjects reported SAEs. The only SAE occurring at a frequency >1% was convulsion (**2.4**%). Overall, **132** subjects discontinued due to TEAEs. The most **common** TEAEs leading to premature discontinuation were convulsion and depression.

Change #9, Section 3.3, Other objectives

The original text:

- To explore direct cost parameters
- To assess the effect of BRV on behavior using the Achenbach CBCL

Has been changed to:

- To explore direct cost parameters
- To assess the effect of BRV on behavior using the Achenbach CBCL **in subjects ≥18 months of age**
- **To assess the effect of BRV on cognition using the BSID-II in subjects <18 months of age**

Change #10, Section 4.1, Safety variables

The original text displayed below has been removed.

At a later stage in the study, new variables (such as tests to assess cognitive functions) may be added in order to continue to gather additional information from the subjects who will enter this LTFU study from future pediatric studies.

Change #11, Section 4.2, Efficacy variables

The original text:

Due to the wide range in age, epilepsy syndromes and conditions of subjects who will be eligible to enroll in this LTFU study, all efficacy variables will be considered exploratory in nature. Seizure count information will be measured using appropriate methods based on the subject's age and type of epilepsy, taking into account the potential evolution of the disease as the subject ages over the course of the study. Appropriate descriptive statistics will be presented for variables related to seizure counts based on the types of measurements obtained (DRCs or EEGs) and disease characteristics of each subject.

Has been changed to:

The efficacy variables planned for analysis of subjects ≤2 years of age or subjects with absence seizures will be based on EEG data and will include the following:

- **Responder rate for total POS defined as the percentage of subjects with a ≥50% reduction in ADF (average daily frequency) of POS recorded on EEG**
- **Absolute and percent reduction in ADF of POS**
- **50% responder rate for total seizures (all types)**
- **Absolute and percent reduction in ADF of total seizures (all types)**

The efficacy variables planned for analysis of subjects ≥2 years of age will be based on DRC data and will include the following:

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

Change #12, Section 4.3, Other variables

The original text:

The other variables include the following:

- Direct cost parameters: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays
- Change over time from previous study 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.

Has been changed to:

The other variables include the following:

- Direct cost parameters: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays
- Change over time from previous study 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.

- **Change over time from previous study Baseline in the BSID-II score for children <18 months of age**

Change #13, Section 5.2, Schedule of study assessments

The following assessments have been added:

Period	Evaluation						Down-Titration	Safety (Drug-free)
Visit	Entry Visit	Minimal Evaluation Visit	Full Evaluation Visit	Yearly Evaluation Visit/Final Visit	Unscheduled Visit	Early Discontinuation Visit	Down-Titration Visit	Safety Visit
	(EV)[a]	(MEV)	(FEV)	(YEV/FV[b])	(UV)	(EDV)	(DTV)[c]	(SV)
Assessment								
Assessment of seizure types[i]			X	X				
C-SSRS[o]	X	X	X	X		X	X	X
BSID-II score[p]			X	X		X		

All subsequent footnote indices have been updated accordingly and the following abbreviations have been added below the table:

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BSID-II=Bayley Scales of Infant Development-II; C-SSRS=Columbia-Suicide Severity Rating Scale; LFT=liver function test;

Change #14, Section 5.2, Schedule of study assessments, footnotes

The original text:

a. The following data will be obtained from the previous pediatric study and should not be recorded on the eCRF for N01266: general medical and procedure history, epilepsy history, AED history, seizure count, absence seizure count (1-hour EEG for subjects suffering from absences), ECG, laboratory assessments for safety, including phenytoin plasma concentrations (if applicable), the Achenbach CBCL score, vital signs, body weight and height, physical and neurological examinations, psychiatric and mental status, recording of epileptic seizures, and data on health care provider consultations not foreseen by the protocol and hospital stays. The EV is also the final evaluation visit of the previous pediatric study.

Has been changed to:

a. The following data will be obtained from the previous pediatric study and should not be recorded on the eCRF for N01266: general medical and procedure history, epilepsy history, AED history, seizure count, **EEG**, ECG, laboratory assessments for safety, including phenytoin plasma concentrations (if applicable), the Achenbach CBCL score, **BSID-II score**, vital signs, body weight and height, physical and neurological examinations, psychiatric and mental status, recording of epileptic seizures, and data on health care provider consultations not foreseen by the protocol and hospital stays. The EV is also the final evaluation visit of the previous pediatric study.

The original text:

g. EEG

- For subjects with typical absence seizures: every 3 months during the first 6 months (starting at V4), and then yearly thereafter: a 1-hour EEG including hyperventilation and intermittent photic stimulation must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, a 1-hour EEG should also be performed at the EDV.
- For subjects ≥1 month to ≤2 years: every 3 months during the first 6 months (starting at V4), then yearly thereafter: a 24-hour EEG including sleeping and awakening periods must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, a 24-hour EEG should also be performed at the EDV.

Has been changed to:

g. EEG

- For subjects **>2 years** with typical absence seizures: every 3 months during the first 6 months (starting at V4), and then yearly thereafter: a 1-hour EEG including hyperventilation and intermittent photic stimulation must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, a 1-hour EEG should also be performed at the EDV.
- For subjects ≥1 month to ≤2 years: every 3 months during the first 6 months (starting at V4), then yearly thereafter: a 24-hour EEG including sleeping and awakening periods must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, a 24-hour EEG should also be performed at the EDV.

Change #15, Section 5.2, Schedule of study assessments, footnotes

The following footnotes have been added:

i. The assessment of seizure types will be done at 6-monthly intervals (at the FEV and the YEV) for subjects <2 years of age.

o. The C-SSRS will be administered to subjects ≥6 years of age.

p. The cognition scale (BSID-II) to be used in this study for subjects <18 months of age will be the same as the one used in the previous pediatric study. If the subject reaches 18 months of age in this LTFU study, the subject will still be assessed using the BSID-II to allow for an evaluation of the change from Baseline even if their age increases to ≥18 months.

Change #16, Section 6.2, Exclusion criteria

The following exclusion criterion has been added to the list:

7. Subject has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at the EV.

Change #17, Section 6.3, Withdrawal criteria

The following withdrawal criteria have been added to the list:

9. Subject has the following findings based on liver function tests (LFT):

- **If the subject has LFT results of transaminases (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]) ≥3x the upper limit of normal (ULN) to <5xULN or total bilirubin ≥2xULN, the measurements will be repeated within a few days. If the repeat testing confirms the abnormality (eg, transaminases are ≥3xULN to <5xULN), then monitoring of LFTs should continue at subsequent study visits until resolved (eg, <3xULN or stable condition). The Investigator is to decide whether or not to stop the study medication.**

- **If the subject has LFT results of transaminases (AST and/or ALT) ≥5xULN, study medication should be tapered off immediately and the subject must be withdrawn from the study.**

10. Criteria for subjects who completed a C-SSRS assessment at the EV:

- **Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Children's Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.**

11. Criteria for already enrolled subjects who did not complete a C-SSRS assessment at the EV:

- **Subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt) of the "Children's Baseline/Screening" version of the C-SSRS. The Investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional.**
- **Subject had active suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Children's Baseline/Screening" version of the C-SSRS. The Investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the subject from the study.**
- **Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Children's Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.**

Change #18, Section 7.2, Treatments to be administered, paragraph 1

The original text:

At study entry (EV), subjects will start on the individualized BRV dose that they had reached at the completion of the previous study.

Has been changed to:

At study entry (EV), subjects will **ordinarily** start on the individualized BRV dose that they had reached at the completion of the previous study.

Change #19, Section 7.2, Treatments to be administered, paragraph 4

The original text:

The mg dosage for the oral tablet treatment should be calculated to match as closely as possible the mg/kg oral solution treatment and should be a combination of the BRV 10mg, 25mg, and 50mg tablets (given bid in 2 equally divided doses). Subjects should be dosed with either oral tablets or oral solution and not a combination of both.

Has been changed to:

The mg dosage for the oral tablet treatment should be calculated to match as closely as possible the mg/kg oral solution treatment and should be a combination of the BRV 10mg, 25mg, and 50mg tablets (given bid in 2 equally divided doses). **Only the following exact dosages are allowed for the oral tablet administration: BRV 20, 40, 50, 70, 100, 150, and 200mg/day.** Subjects should be dosed with either oral tablets or oral solution and not a combination of both.

Change #20, Section 8, STUDY PROCEDURES BY VISIT

The C-SSRS assessment has been added to the bulleted lists for all visits except for the Unscheduled Visit.

- **Suicidality assessment (C-SSRS) for subjects ≥6 years of age**

Change #21, Section 8.1, Entry Visit

The original text:

The following data will be obtained from the previous pediatric study and should not be recorded on the eCRF for N01266:

- General medical and procedures history
- Epilepsy history
- AED history
- Seizure count
- Absence seizure count (a 1-hour EEG for subjects suffering from absences)
- ECG
- Laboratory assessments for safety
- Phenytoin plasma concentrations (if applicable)
- Achenbach CBCL score
- Vital signs
- Body weight and height
- Physical examination
- Neurological examination
- Psychiatric and mental status
- Recording of epileptic seizures
- Health care provider consultations not foreseen by the protocol
- Hospital stays

Has been changed to:

The EV is also the final evaluation visit of the previous pediatric study. The following data will be obtained from the previous pediatric study and should not be recorded on the eCRF for N01266:

- General medical and procedures history
- Epilepsy history
- AED history
- Seizure count
- **EEG**
  - **For subjects >2 years with typical absence seizures: a 1-hour EEG (including hyperventilation and intermittent photic stimulation) must be performed**
  - **For subjects ≥1 month to ≤2 years: a 24-hour EEG (including sleeping and awakening periods) must be performed**
- ECG
- Laboratory assessments for safety
- **Suicidality assessment (C-SSRS) for subjects ≥6 years of age**
- Phenytoin plasma concentrations (if applicable)
- **BSID-II score for subjects <18 months of age at Baseline of N01263**
- Achenbach CBCL score **for subjects ≥18 months of age at Baseline of N01263**
- Vital signs
- Body weight and height
- Physical examination
- Neurological examination
- Psychiatric and mental status
- Recording of epileptic seizures
- Health care provider consultations not foreseen by the protocol
- Hospital stays

Change #22, Section 8.2 to Section 8.4, Section 8.6, and Section 8.9, bullet on the 1-hour EEG

The original text:

- EEG
  - For subjects with typical absence seizures: a 1-hour EEG (including hyperventilation and intermittent photic stimulation) must be performed

Has been changed to:

- EEG
  - For subjects **>2 years** with typical absence seizures: a 1-hour EEG (including hyperventilation and intermittent photic stimulation) must be performed

Change #23, Section 8.3 and Section 8.4

The following bullet has been added to the list.

- **Assessment of seizure types for subjects <2 years of age**

Change #24, Section 8.3, Section 8.4, Section 8.6, and Section 8.9

The following bullet has been added to the list.

- **BSID-II score for subjects <18 months of age at Baseline of N01263**

Change #25, Section 8.5, Unscheduled Visit

The following text was added to the section.

- **If an Unscheduled Visit is conducted due to safety or efficacy reasons, a suicidality assessment (C-SSRS) will be performed with the subject during the visit. If an Unscheduled Visit is conducted for reasons other than safety or efficacy concerns (eg, replacement of lost medication, repeated collection of a laboratory specimen due to collection or analysis issues), a C-SSRS will not be required at these visits.**

Change #26, Section 9, ASSESSMENT OF SAFETY

The following Section 9.4 has been added. The subsequent section numbers were updated accordingly.

The following list of Anticipated SAEs has been identified, as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure: convulsion. This original list will remain in effect for the duration of the protocol.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 9.2.3.

Change #27, Section 9.6, Other safety measurements

The following section has been added. The following section numbers were updated accordingly.

9.6.7 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS 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. The C-SSRS will be completed according to the tabular schedule of study procedures, Section 5.2.

Change #28, Section 10.2, Efficacy assessments for seizure data based on EEG, paragraph 1

The original text:

At the EV, data on absence seizure count (a 1-hour EEG for subjects suffering from absences) will be obtained from the previous pediatric study and should not be recorded in the eCRF for N01266.

Has been changed to:

At the EV, data on absence seizure count (a 1-hour EEG for subjects **>2 years** suffering from absences) will be obtained from the previous pediatric study and should not be recorded in the eCRF for N01266.

Change #29, Section 10.2, Efficacy assessments for seizure data based on EEG, paragraph 3, bullet on 1-hour EEG

The original text:

- For subjects with typical absence seizures: a 1-hour EEG (including hyperventilation and intermittent photic stimulation) will be performed starting at V4 and at every 3-month visit for the first 6 months and then yearly thereafter. For subjects prematurely discontinuing from the study, a 1-hour EEG should also be performed at the EDV.

Has been changed to:

- For subjects **>2 years** with typical absence seizures: a 1-hour EEG (including hyperventilation and intermittent photic stimulation) will be performed starting at V4 and at every 3-month visit for the first 6 months and then yearly thereafter. For subjects prematurely discontinuing from the study, a 1-hour EEG should also be performed at the EDV.

Change #30, Section 10.3, Other assessments

The following sections have been added. The following section numbers were updated accordingly.

10.3.2 Bayley Scales of Infant Development-II

The BSID-II™ is a widely used validated questionnaire for children from 1 month up to 42 months of age designed to evaluate a child's developmental function, including cognition, language, personal-social behavior, and motor development.

This scale is accepted as a tool for assessment of neurological development in young children and is therefore considered appropriate for this study. The BSID-II will be used throughout the study for all subjects who were <18 months of age at Baseline (V1) of the previous pediatric study, N01263, by the Investigator or designee. Children started on the BSID-II at Baseline of N01263 will also be assessed using the BSID-II in N01266 even if their age increases to ≥18 months. The completion of the BSID-II will

require approximately 25 to 35 minutes for children below 15 months of age and up to 60 minutes for children above 15 months of age.

The BSID-II includes a mental scale that evaluates sensory/perceptual activities, discriminations, acquisition of object constancy, memory, learning and problem-solving, vocalization, early verbal communication, abstract thinking, habituation, mental mapping, complex language, and mathematical concept formation; a motor scale that evaluates degree of body control, coordination of large muscles, fine manipulation skills, dynamic movement, postural imitations, and stereognosis; and a behavior rating scale that measures attention and arousal, orientation and engagement, emotional regulation, and motor quality (Bayley, 1993).

At the EV, the BSID-II score will be obtained from the previous pediatric study and should not be recorded in the eCRF in N01266. The BSID-II will be completed at the FEV, YEV, FV, and at the EDV in the case of early discontinuation. The BSID-II should be completed by the same person who completed the CBCL in the previous pediatric study.

10.3.4 Assessment of seizure types

The assessment of seizure types will be done at 6-monthly intervals (at the FEV and the YEV) for subjects <2 years of age.

Change #31, Section 10.3, Other assessments, paragraph 3

The original text:

The Achenbach CBCL should be completed by the same parent(s)/legal representative(s) who completed the CBCL in the previous pediatric study.

Has been changed to:

The Achenbach CBCL should be completed by the same parent(s)/legal representative(s) who completed the CBCL in the previous pediatric study. **The completion of the Achenbach CBCL will require approximately 45 minutes.**

Change #32, Section 12.5, Other analyses, paragraph 2

The original text:

The Achenbach CBCL scores and change from previous study Baseline scores will be analyzed in a descriptive manner.

Has been changed to:

The Achenbach CBCL, **the BSID-II scores**, and change from previous study Baseline scores will be analyzed in a descriptive manner.

Change #33, Section 15, REFERENCES

The following reference was added to the list.

Bayley N. Bayley Scales of Infant Development. 2nd ed. San Antonio. The Psychological Corporation; 1993.

16.2 Protocol Amendment 2

Rationale for the amendment

The purpose of this amendment is to replace the children's version of the C-SSRS with the version validated in multiple languages for subjects 6 years of age and older. The BSID-II score was replaced by the Bayley-III scales in order to apply the most recent version of the cognition scale. In addition, it was clarified that the cognition scale will be used only in English-speaking countries, since it is validated only in English. The efficacy variables for subjects <2 years of age and for subjects with absence seizures were updated and amended in response to the PDCO requirements. It was clarified that safety laboratory assessments include hepatic monitoring. Furthermore, an error in the mathematical symbols used for the presentation of the age limits of the EEG assessments was corrected, and the SAE reporting details were updated. Administrative changes include the update of the Clinical Project Manager contact details and typographical corrections.

Few changes of editorial nature are additionally listed in the specific changes section.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- The efficacy variables for subjects <2 years of age and for subjects with absence seizures were amended in response to the PDCO requirements. Additional efficacy variables based on DRC data were added. In addition, the description of the EEGs has changed from "24-hour EEG" and "1-hour EEG" to "an EEG of at least 24 hours of recording" and "an EEG of at least 1 hour of recording". The resulting wording updates were applied to relevant sections for consistency reasons.
- The children's version of the C-SSRS was replaced with the version validated for subjects 6 years and older, since the children's version is validated only in English, and the version for subjects 6 years and older is validated in multiple languages.
- The BSID-II score was replaced by the Bayley-III scales in order to apply the most recent version of the cognition scale. In addition, it was clarified that the cognition scale will be used only in English-speaking countries.
- Data for some assessments at the Entry Visit (as outlined in footnote "a" of Table 5:1) will be obtained from the previous study. The revised footnote specifies which of these data will be taken from the Baseline visit and which data will be taken from the last visit of the previous study. All related sections have been updated accordingly.
- The assessment "recording of epileptic seizures" has been updated to "seizure count" in order to align with the terminology used in N01263.
- All sections referring to biochemistry assessments were updated in order to clarify that tests for hepatic monitoring (ALT, AST, ALP, total bilirubin, and GGT) will be included in safety laboratory assessments.

- An error in the mathematical symbols used for the presentation of the age limits of the EEG assessments was corrected in all respective sections. In addition, it was clarified that the age limits for the EEG assessments are based on the subject's age on the day of the visit.
- A format error in the table footnotes was corrected without any content-related changes.

Specific changes

Change #1, TITLE PAGE

The title page was updated to reflect the current amendment.

Change #2, SPONSOR DECLARATION, Clinical Project Manager and Clinical Program Director

The original text:

Clinical Project Manager

[redacted]

_____
Date/Signature

Associate Clinical Program Director

[redacted]

_____
Date/Signature

Has been changed to:

Clinical Project Manager

[redacted]

_____
Date/Signature

Clinical Program Director

[redacted]

_____
Date/Signature

Change #3, STUDY CONTACT INFORMATION

The original text:

Clinical Project Manager

Name:	[redacted]
Address:	UCB Center Bruxelles Allée de la Recherche 60 B-1070 Bruxelles Belgium
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Clinical Project Manager

Name:	[redacted]
Address:	UCB Center Bruxelles Allée de la Recherche 60 B-1070 Bruxelles Belgium
Phone:	[redacted]
Fax:	[redacted]

Change #4, SERIOUS ADVERSE EVENT REPORTING

The original text:

Serious adverse event reporting (24h), safety related issues, and emergency unblinding		
Fax	**Europe and Rest of the World (except Japan):** +32 2 386 2421 **USA:** +1 800 880 6949 **Canada:** +1 877 582 8842	
Phone	**During business hours:**	**Outside business hours:**
	Europe and Rest of the World (except Japan): +32 2 386 2468 **USA and Canada:** +1 404 895 0794	**Europe and Rest of the World (except Japan):** +32 2 386 2468 **USA and Canada:** +1 404 895 0794

Has been changed to:

Serious adverse event reporting (24h), safety related issues, and emergency unblinding	
Fax	**Europe and Rest of the World (except Japan):** +32 2 386 2421 **US:** +1 800 880 6949 **Canada:** +1 877 582 8842
Phone	**Europe, US, and Rest of the World (except Japan):** +32 2 386 2468
Email	**Europe, US, and Rest of the World (except Japan): GCSP@ucb.com**

Change #5, Section 1, LIST OF ABBREVIATIONS

The following abbreviations were added to the list:

Bayley-III®	**Bayley Scales of Infant and Toddler Development®, Third Edition**
GGT	**gamma-glutamyltransferase**
M	**month**
SGOT	**serum glutamic oxaloacetic transaminase**
SGPT	**serum glutamic pyruvic transaminase**

The following abbreviation was updated:

The original text:

BSID-II™	Bayley Scales of Infant Development-II

Has been changed to:

BSID-II™	Bayley Scales of Infant Development**™, Second Edition**

Change #6, SUMMARY, paragraph 1

The original text:

This is a Phase 3, open-label, single-arm, multicenter, long-term follow-up (LTFU) study to evaluate the safety and efficacy of brivaracetam (BRV) in children with epilepsy. 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 and the other objectives are to explore direct cost parameters and to assess the effect of BRV on behavior and cognition using the age-appropriate Achenbach Child Behavior Checklist (CBCL/1½-5 or CBCL/6-18) for subjects ≥18 months of age at Baseline of the previous study N01263 or the Bayley Scales of Infant Development-II (BSID-II™) for subjects <18 months of age at Baseline of the previous study N01263.

Has been changed to:

This is a Phase 3, open-label, single-arm, multicenter, long-term follow-up (LTFU) study to evaluate the safety and efficacy of brivaracetam (BRV) in children with epilepsy. 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. **T**he other objectives are to explore direct cost parameters and to assess the effect of BRV on behavior and cognition using the age-appropriate Achenbach Child Behavior Checklist (CBCL/1½-5 or CBCL/6-18) for subjects ≥18 months of age at Baseline of the previous study N01263 or **other pediatric studies**. **T**he Bayley Scales of Infant **and Toddler** Development**®, Third Edition (Bayley-III®) will be used to assess** subjects **enrolled in English-speaking**

countries and <18 months of age at Baseline of the previous study N01263 **or other BRV pediatric studies.**

Change #7, Section 1, SUMMARY, paragraph 6

The original text:

Safety variables include adverse events (AEs), safety laboratory assessments (hematology, biochemistry, and endocrinology for all subjects and urinalysis for subjects ≥4 years of age), plasma concentrations of BRV and phenytoin (if applicable), electrocardiograms (ECGs), vital signs, physical and neurological examinations, psychiatric and mental status, body weight, and height.

Has been changed to:

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-glutamyltransferase [GGT],** and endocrinology for all subjects and urinalysis for subjects ≥4 years of age), plasma concentrations of BRV and phenytoin (if applicable), electrocardiograms (ECGs), vital signs, physical and neurological examinations, psychiatric and mental status, body weight, and height.

Change #8, Section 1, SUMMARY, paragraph 8

The original text:

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) and BSID-II scores over time.

Has been changed to:

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) **or the change in Bayley-III** scales over time **for subjects enrolled in English-speaking countries.**

Change #9, Section 3.3, Other objectives, third bullet

The original text:

- To assess the effect of BRV on cognition using the BSID-II in subjects <18 months of age

Has been changed to:

- To assess the effect of BRV on cognition using the **Bayley-III scales** in subjects <18 months of age **(applicable only to subjects enrolled in English-speaking countries)**

Change #10, Section 4.1, Safety variables, bullet on laboratory assessments

The original text:

- Safety laboratory tests (hematology, biochemistry**,** and endocrinology for all subjects and urinalysis for subjects ≥4 years of age)

Has been changed to:

- Safety laboratory tests (hematology, biochemistry **including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT,** and endocrinology for all subjects and urinalysis for subjects ≥4 years of age)

Change #11, Section 4.2, Efficacy variables

The original text:

The efficacy variables planned for analysis of subjects ≤2 years of age or subjects with absence seizures will be based on EEG data and will include the following:

- Responder rate for total POS defined as the percentage of subjects with a ≥50% reduction in ADF (average daily frequency) of POS recorded on EEG
- Absolute and percent reduction in ADF of POS
- 50% responder rate for total seizures (all types)
- Absolute and percent reduction in ADF of total seizures (all types)

The efficacy variables planned for analysis of subjects ≥2 years of age will be based on DRC data and will include the following:

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

Has been changed to:

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

- Responder rate for total POS defined as the percentage of subjects with a ≥50% reduction in ADF (average daily frequency) of POS recorded on EEG
- Absolute and percent reduction in ADF of POS

- 50% responder rate for total seizures (all types)
- Absolute and percent reduction in ADF of total seizures (all types)
- **Seizure freedom (rate and proportion)**
- **Worsening of other types of seizures (absolute and percent)**

In addition, the following efficacy variables will be repeated for subjects <2 years of age or subjects with absence seizures based on the 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 and percent worsening in ADF of total seizures (all types)**

A descriptive summary of seizure frequency by visit based on the DRC data will be also provided for these subjects.

The efficacy variables planned for analysis of subjects ≥2 years of age will be based on DRC data and will include the following:

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

Change #12, Section 4.3, Other variables, third bullet

The original text:

- Change over time from previous study Baseline in the BSID-II score for children <18 months of age.

Has been changed to:

- Change over time from previous study Baseline in the **Bayley-III scales** for children <18 months of age **(applicable only to subjects enrolled in English-speaking countries)**

Change #13, Section 5.2, Schedule of study assessments, Table 5:1

The original text:

Recording of epileptic seizures

Has been changed to:

Seizure count

The original text:

BSID-II score[p]

Has been changed to:

Bayley-III scales[p]

Change #14, Section 5.2, Schedule of study assessments, Table 5:1

The table cell for the C-SSRS at the EV has been unchecked, since the data will be obtained from the previous study.

Change #15, Section 5.2, Schedule of study assessments, Table 5:1, footnotes

The format and content of the original text:

[a.] AE=adverse event; AED=antiepileptic drug; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BRV=brivaracetam; BSID-II=Bayley Scales of Infant Development-II; CBCL=Child Behavior Checklist; C-SSRS=Columbia-Suicide Severity Rating Scale; DRC=daily record card; ECG=electrocardiogram; eCRF=electronic case report form; EEG=electroencephalogram; IVRS=interactive voice response system; M=Month; LFT=liver function test; SAE=serious adverse event; V=Visit

Have been changed to:

AE=adverse event; AED=antiepileptic drug; **ALP=alkaline phosphatase;** ALT=alanine aminotransferase; AST=aspartate aminotransferase; **Bayley-III**=Bayley Scales of Infant **and Toddler** Development, **Third Edition;** BRV=brivaracetam; CBCL=Child Behavior Checklist; C-SSRS=Columbia-Suicide Severity Rating Scale; DRC=daily record card; ECG=electrocardiogram; eCRF=electronic case report form; EEG=electroencephalogram; **GGT=gamma-glutamyltransferase;** IVRS=interactive voice response system; LFT=liver function test; M=Month; SAE=serious adverse event; V=Visit

All subsequent footnote indices have been corrected accordingly.

Change #16, Section 5.2, Schedule of study assessments, Table 5:1, footnote a

The original text:

[b.] The following data will be obtained from the previous pediatric study and should not be recorded on the eCRF for N01266: general medical and procedure history, epilepsy history, AED history, seizure count, EEG, ECG, laboratory assessments for safety, including phenytoin plasma concentrations (if applicable), the Achenbach CBCL score, the BSID-II score, vital signs, body weight and height, physical and neurological examinations, psychiatric and mental status, recording of epileptic seizures, and data on health

care provider consultations not foreseen by the protocol and hospital stays. The EV is also the final evaluation visit of the previous pediatric study.

Has been changed to:

a. The following data will be obtained from **Baseline** of the previous pediatric study and should not be recorded on the eCRF for N01266: general medical and procedure history, epilepsy history, AED history, **height, Bayley-III scales**, and the Achenbach CBCL score. **The following data will be obtained from the last visit of the previous pediatric study and should not be recorded on the eCRF for N01266:** seizure count, EEG, ECG, laboratory assessments for safety, including phenytoin plasma concentrations (if applicable), **the C-SSRS**, vital signs, body weight, physical and neurological examinations, psychiatric and mental status, and data on health care provider consultations not foreseen by the protocol and hospital stays. The EV is also the final evaluation visit of the previous pediatric study.

Change #17, Section 5.2, Schedule of study assessments, Table 5:1, footnotes

The original text and the mathematical symbols:

h. EEG

i. For subjects >2 years with typical absence seizures: every 3 months during the first 6 months (starting at V4), and then yearly thereafter: a 1-hour EEG including hyperventilation and intermittent photic stimulation must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, a 1-hour EEG should also be performed at the EDV.

j. For subjects ≥1 month to ≤2 years: every 3 months during the first 6 months (starting at V4), then yearly thereafter: a 24-hour EEG including sleeping and awakening periods must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, a 24-hour EEG should also be performed at the EDV.

Have been changed to:

g. EEG

- For subjects ≥2 years **of age on the day of the study visit and** with typical absence seizures: every 3 months during the first 6 months (starting at V4), and then yearly thereafter: a**n** EEG **of at least** 1 hour **of recording** including hyperventilation and intermittent photic stimulation must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, a**n** EEG **of at least** 1 hour **of recording** should also be performed at the EDV.
- For subjects ≥1 month to <2 years **of age on the day of the study visit:** every 3 months during the first 6 months (starting at V4), then yearly thereafter: a**n** EEG **of at least 24 hours of recording** including sleeping and awakening periods must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, an EEG **of at least** 24 hours **of recording** should also be performed at the EDV.

All subsequent footnote indices have been corrected accordingly.

Change #18, Section 5.2, Schedule of study assessments, Table 5:1, footnotes

The original text:

p. Laboratory assessments for safety include hematology, biochemistry, and endocrinology for all subjects and urinalysis for subjects ≥4 years of age. Female subjects with a Tanner stage >1 should have a urine pregnancy test performed at all laboratory assessment visits, except for the EDV and the SV, when a serum pregnancy test will be performed. Endocrinology testing will be performed once a year at the YEV. Liver function tests as described in Section 9.5.1 will be performed at the MEVs at V4 [M3] and V6 [M9].

Has been changed to:

m. **Full** laboratory assessments for safety include hematology, biochemistry **(including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)**, and endocrinology for all subjects and urinalysis for subjects ≥4 years of age **as described in Section 9.5.1**. Female subjects with a Tanner stage >1 should have a urine pregnancy test performed at all laboratory assessment visits, except for the EDV and the SV, when a serum pregnancy test will be performed. Endocrinology testing will be performed once a year at the YEV. **In addition,** liver function tests as described in Section 9.5.1 will be performed at the MEVs at V4 (M3) and V6 (M9).

Change #19, Section 5.2, Schedule of study assessments, Table 5:1, footnotes

The original text:

s. The cognition scale (BSID-II) to be used in this study for subjects <18 months of age will be the same as the one used in the previous pediatric study. If the subject reaches 18 months of age in this LTFU study, the subject will still be assessed using the BSID-II to allow for an evaluation of the change from Baseline even if their age increases to ≥18 months.

Has been changed to:

p. The cognition scale (**Bayley-III**) to be used in this study for subjects <18 months of age **and enrolled in English-speaking countries** will be the same as the one used in the previous pediatric study. If the subject reaches 18 months of age in this LTFU study, the subject will still be assessed using the **Bayley-III** to allow for an evaluation of the change from Baseline even if their age increases to ≥18 months.

Change #20, Section 5.3, Visit sequence, Table 5:2, footnotes

The format of the original text and footnote c:

a. EV=Entry Visit; FEV=Full Evaluation Visit; LTFU=long-term follow-up; MEV=Minimal Evaluation Visit; YEV=Yearly Evaluation Visit

b. Note: "-" denotes that no visit is scheduled in that month.

c. The Entry Visit is the final evaluation visit of the previous pediatric study.

d. Subsequent years will follow the same visit schedule.

e. Liver function tests will be performed in addition to the assessments described in Section 9.5.1.

Have been changed to:

EV=Entry Visit; FEV=Full Evaluation Visit; LTFU=long-term follow-up; MEV=Minimal Evaluation Visit; YEV=Yearly Evaluation Visit

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

a. The Entry Visit is the final evaluation visit of the previous pediatric study.

b. Subsequent years will follow the same visit schedule.

c. Liver function tests **only** will be performed **as** described in Section 9.5.1.

Change #21, Section 6.3, Withdrawal criteria, criterion 10

The original text:

10. Criteria for subjects who completed a C-SSRS assessment at the EV:

- Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Children's Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Has been changed to:

10. Criteria for subjects who completed a C-SSRS assessment at the EV:

- Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Change #22, Section 6.3, Withdrawal criteria, criterion 11

The original text:

11. Criteria for already enrolled subjects who did not complete a C-SSRS assessment at the EV:

- Subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt) of the "Children's Baseline/Screening" version of the C-SSRS. The Investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional.
- Subject had active suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Children's Baseline/Screening" version of the C-SSRS. The Investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the subject from the study.
- Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Children's Since Last Visit" version of the

C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Has been changed to:

11. Criteria for already enrolled subjects who did not complete a C-SSRS assessment at the EV:

- Subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt) of the "**Already Enrolled Subjects**" version of the C-SSRS. The Investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional.
- Subject had active suicidal ideation **prior to study entry or since study start** as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "**Already Enrolled Subjects**" version of the C-SSRS. The Investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the subject from the study.
- Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Change #23, Section 8.1, Entry Visit, assessments obtained from the previous study

The original text:

The EV is also the final evaluation visit of the previous pediatric study. The following data will be obtained from the previous pediatric study and should not be recorded on the eCRF for N01266:

- General medical and procedures history
- Epilepsy history
- AED history
- Seizure count
- EEG
  - For subjects >2 years with typical absence seizures: a 1-hour EEG (including hyperventilation and intermittent photic stimulation) must be performed
  - For subjects ≥1 month to ≤2 years: a 24-hour EEG (including sleeping and awakening periods) must be performed
- ECG
- Laboratory assessments for safety
- Suicidality assessment (C-SSRS) for subjects ≥6 years of age

- Phenytoin plasma concentrations (if applicable)
- BSID-II score for subjects <18 months of age at Baseline of N01263
- Achenbach CBCL score for subjects ≥18 months of age at Baseline of N01263
- Vital signs
- Body weight and height
- Physical examination
- Neurological examination
- Psychiatric and mental status
- Recording of epileptic seizures
- Health care provider consultations not foreseen by the protocol
- Hospital stays

Has been changed to:

The EV is also the final evaluation visit of the previous pediatric study. The following data will be obtained from **Baseline of** the previous pediatric study and should not be recorded on the eCRF for N01266:

- General medical and procedures history
- Epilepsy history
- AED history
- **Height**
- **Bayley-III scales** for subjects <18 months of age at Baseline of N01263 **or other pediatric studies and only for subjects enrolled in English-speaking countries**
- Achenbach CBCL score for subjects ≥18 months of age at Baseline of N01263

The following data will be obtained from the last visit of the previous pediatric study and should not be recorded on the eCRF for N01266:

- Seizure count
- EEG
  - For subjects ≥2 years **of age on the day of the study visit and** with typical absence seizures: a**n** EEG **of at least** 1 hour **of recording** (including hyperventilation and intermittent photic stimulation) must be performed
  - For subjects ≥1 month to <2 years **of age on the day of the study visit**: a**n** EEG **of at least** 24 hour**s of recording** (including sleeping and awakening periods) must be performed
- ECG

- Laboratory assessments for safety (**including hepatic monitoring)**
- Suicidality assessment (C-SSRS) for subjects ≥6 years of age
- Phenytoin plasma concentrations (if applicable)
- Vital signs
- Body weight
- Physical examination
- Neurological examination
- Psychiatric and mental status
- Health care provider consultations not foreseen by the protocol
- Hospital stays

Change #24, Section 8.2, Minimal Visit

The original text:

- EEG
  - For subjects >2 years with typical absence seizures: a 1-hour EEG (including hyperventilation and intermittent photic stimulation) must be performed
  - For subjects ≥1 month to ≤2 years: a 24-hour EEG (including sleeping and awakening periods) must be performed
- Recording of epileptic seizures

Has been changed to:

- EEG
  - For subjects **≥**2 years **of age on the day of the study visit and** with typical absence seizures: a**n** EEG **of at least** 1 hour **of recording** (including hyperventilation and intermittent photic stimulation) must be performed **only at V4 (M3) as described in Section 10.2**
  - For subjects ≥1 month to **<**2 years **of age on the day of the study visit**: a**n** EEG **of at least** 24 hour**s of recording** (including sleeping and awakening periods) must be performed **only at V4 (M3) as described in Section 10.2**
- **Seizure count**

Change #25, Section 8.3, Full Evaluation Visit

The original text:

- EEG
  - For subjects >2 years with typical absence seizures: a 1-hour EEG (including hyperventilation and intermittent photic stimulation) must be performed

  - For subjects ≥1 month to ≤2 years: a 24-hour EEG (including sleeping and awakening periods) must be performed

- Recording of epileptic seizures
- Laboratory assessments for safety (hematology and biochemistry for all subjects, and urinalysis for subjects ≥4 years of age)
- BSID-II for all subjects who were <18 months of age at Baseline of N01263

Has been changed to:

- EEG
  - For subjects **≥**2 years **of age on the day of the study visit and** with typical absence seizures: a**n** EEG **of at least** 1 hour **of recording** (including hyperventilation and intermittent photic stimulation) must be performed **only at V5 (M6) as described in Section 10.2**
  - For subjects ≥1 month to **<**2 years **of age on the day of the study visit**: a**n** EEG **of at least** 24 hour**s of recording** (including sleeping and awakening periods) must be performed **only at V5 (M6) as described in Section 10.2**
- **Seizure count**
- Laboratory assessments for safety (hematology and biochemistry **including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT** for all subjects, and urinalysis for subjects ≥4 years of age)
- **Bayley-III** scale**s** for subjects <18 months of age at Baseline of N01263 or other pediatric studies **and only for subjects enrolled in English-speaking countries**

Change #26, Section 8.4, Yearly Evaluation Visit

The original text:

- EEG
  - For subjects >2 years with typical absence seizures: a 1-hour EEG (including hyperventilation and intermittent photic stimulation) must be performed
  - For subjects ≥1 month to ≤2 years: a 24-hour EEG (including sleeping and awakening periods) must be performed
- Recording of epileptic seizures
- Laboratory assessments for safety (hematology, biochemistry, and endocrinology for all subjects, and urinalysis for subjects ≥4 years of age)
- BSID-II for all subjects who were <18 months of age at Baseline of N01263

Has been changed to:

- EEG
  - For subjects ≥2 years **of age on the day of the study visit and** with typical absence seizures: a**n** EEG **of at least** 1 hour **of recording** (including hyperventilation and intermittent photic stimulation) must be performed
  - For subjects ≥1 month to **<**2 years **of age on the day of the study visit**: a**n** EEG **of at least** 24 hour**s of recording** including sleeping and awakening periods) must be performed
- **Seizure count**
- Laboratory assessments for safety (hematology, biochemistry **including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT**, and endocrinology for all subjects, and urinalysis for subjects ≥4 years of age)
- **Bayley-III** scales for subjects <18 months of age at Baseline of N01263 or other pediatric studies **and only for subjects enrolled in English-speaking countries**

Change #27, Section 8.5, Unscheduled Visit, last paragraph

The original text:

- If an Unscheduled Visit is conducted due to safety or efficacy reasons, a suicidality assessment (C-SSRS) will be performed with the subject during the visit. If an Unscheduled Visit is conducted for reasons other than safety or efficacy concerns (eg, replacement of lost medication, repeated collection of a laboratory specimen due to collection or analysis issues), a C-SSRS will not be required at these visits.

Has been changed to:

- If an Unscheduled Visit is conducted due to safety or efficacy reasons, a suicidality assessment (C-SSRS) will be performed with subject**s ≥6 years of age** during the visit. If an Unscheduled Visit is conducted for reasons other than safety or efficacy concerns (eg, replacement of lost medication, repeated collection of a laboratory specimen due to collection or analysis issues), a C-SSRS will not be required at these visits.

Change #28, Section 8.6, Early Discontinuation Visit

The original text:

- EEG
  - For subjects >2 years with typical absence seizures: a 1-hour EEG (including hyperventilation and intermittent photic stimulation) must be performed
  - For subjects ≥1 month to ≤2 years: a 24-hour EEG (including sleeping and awakening periods) must be performed.
- Recording of epileptic seizures

- Laboratory assessments for safety (hematology, biochemistry, and endocrinology for all subjects, and urinalysis for subjects ≥4 years of age)
- BSID-II for all subjects who were <18 months of age at Baseline of N01263

Has been changed to:

- EEG
  - For subjects ≥2 years **of age on the day of the study visit and** with typical absence seizures: a**n** EEG **of at least** 1 hour **of recording** (including hyperventilation and intermittent photic stimulation) must be performed
  - For subjects ≥1 month to <2 years **of age on the day of the study visit**: a**n** EEG **of at least** 24 hour**s of recording** (including sleeping and awakening periods) must be performed.
- **Seizure count**
- Laboratory assessments for safety (hematology, biochemistry **including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT,** and endocrinology for all subjects, and urinalysis for subjects ≥4 years of age)
- **Bayley-III** scale**s** for subjects <18 months of age at Baseline of N01263 or other pediatric studies **and only for subjects enrolled in English-speaking countries**

Change #29, Section 8.7, Down-Titration Visit

The original text:

- Recording of epileptic seizures

Has been changed to:

- **Seizure count**

Change #30, Section 8.8, Safety Visit

The original text:

- Recording of epileptic seizures
- Laboratory assessments for safety (hematology, biochemistry, and endocrinology for all subjects, and urinalysis for subjects ≥4 years of age) performed only if abnormal at the EDV

Has been changed to:

- **Seizure count**
- Laboratory assessments for safety (hematology, biochemistry **including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT,** and endocrinology for all subjects, and urinalysis for subjects ≥4 years of age) performed only if abnormal at the EDV

Change #31, Section 8.9, Final Visit

The original text:

- EEG
  - For subjects >2 years with typical absence seizures: a 1-hour EEG (including hyperventilation and intermittent photic stimulation) must be performed
  - For subjects ≥1 month to ≤2 years: a 24-hour EEG (including sleeping and awakening periods) must be performed.
- Recording of epileptic seizures
- Laboratory assessments for safety (hematology, biochemistry, and endocrinology for all subjects, and urinalysis for subjects ≥4 years of age).
- BSID-II for all subjects who were <18 months of age at Baseline of N01263

Has been changed to:

- EEG
  - For subjects **≥**2 years **of age on the day of the study visit and** with typical absence seizures: a**n** EEG **of at least** 1 hour **of recording** (including hyperventilation and intermittent photic stimulation) must be performed
  - For subjects ≥1 month to **<**2 years **of age on the day of the study visit**: a**n** EEG **of at least** 24 hour**s of recording** (including sleeping and awakening periods) must be performed.
- **Seizure count**
- Laboratory assessments for safety (hematology, biochemistry **including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT**, and endocrinology for all subjects, and urinalysis for subjects ≥4 years of age).
- **Bayley-III** scales for subjects <18 months of age at Baseline of N01263 or other pediatric studies **and only for subjects enrolled in English-speaking countries**

Change #32, Section 9.4, Anticipated SAEs

The section reference in the original text:

The following list of Anticipated SAEs has been identified, as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure: convulsion. This original list will remain in effect for the duration of the protocol.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 9.2.3.

Has been changed to:

The following list of Anticipated SAEs has been identified, as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure: convulsion. This original list will remain in effect for the duration of the protocol.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 9.2.2.

Change #33, Section 9.5.1, Laboratory assessments for safety, table footnotes

The format of the original text and footnote c:

a. ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=beta-human chorionic gonadotropin; FSH=follicle-stimulating hormone; GGT=gamma-glutamyltransferase; LH=luteinizing hormone; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; T3=triiodothyronine; T4=tetraiodothyronine; TSH=thyroid-stimulating hormone; WBC=white blood cell

b. Urinalysis will be performed in subjects ≥4 years of age.

c. Liver function tests will be assessed at the MEVs at V4 [M3] and V6 [M9] during the first year in addition to the full laboratory assessments described in Section 9.5.

d. Includes bacteria, cells, casts, and crystals for all samples.

e. Female subjects with a Tanner stage >1 should have a urine pregnancy test at all laboratory assessment visits, except the EDV and the SV, when a serum pregnancy test will be performed.

f. Endocrinology testing will be performed once a year at the YEV.

Have been changed to:

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=beta-human chorionic gonadotropin; FSH=follicle-stimulating hormone; GGT=gamma-glutamyltransferase; LH=luteinizing hormone; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; T3=triiodothyronine; T4=tetraiodothyronine; TSH=thyroid-stimulating hormone; WBC=white blood cell

a. Urinalysis will be performed in subjects ≥4 years of age.

b. **In addition,** liver function tests will be assessed at the MEVs at V4 **(**M3**)** and V6 **(**M9**)**, as described in Section 9.5.1.

c. Includes bacteria, cells, casts, and crystals for all samples.

d. Female subjects with a Tanner stage >1 should have a urine pregnancy test at all laboratory assessment visits, except the EDV and the SV, when a serum pregnancy test will be performed.

e. Endocrinology testing will be performed once a year at the YEV.

All footnote indices have been corrected accordingly.

Change #34, Section 9.5.1, Laboratory assessments for safety, paragraph 6

The original text:

Laboratory safety assessments at the EV will be obtained from the previous pediatric study and should not be recorded on the eCRF for N01266. Laboratory safety assessments will be performed at the FEV, YEV, FV, and at the EDV in the case of early discontinuation.

Laboratory assessments will also be mandatory at the SV if the laboratory results at the EDV are abnormal. Liver function tests will be performed at the MEVs at V4 (M3) and V6 (M9) during the first year. Endocrinology testing will be performed once a year at the YEV.

Has been changed to:

Laboratory safety assessments at the EV will be obtained from the **last visit of the** previous pediatric study and should not be recorded on the eCRF for N01266. Laboratory safety assessments will be performed at the FEV, YEV, FV, and at the EDV in the case of early discontinuation. Laboratory assessments will also be mandatory at the SV if the laboratory results at the EDV are abnormal. **In addition, l**iver function tests will be performed at the MEVs at V4 (M3) and V6 (M9) during the first year. Endocrinology testing will be performed once a year at the YEV.

Change #35, Section 9.6.1 to Section 9.6.6

It was clarified whether the assessments at the Entry Visit of N01266 are taken from Baseline or from the last visit of the previous study. The clarification applies to the following assessments: ECG, vital signs, body weight and height, physical examination, neurological examination, and psychiatric and mental status.

The original text:

At the EV, ECG data will be obtained from the previous pediatric study and should not be recorded in the eCRF for N01266.

At the EV, vital sign data will be obtained from the previous pediatric study and should not be recorded in the eCRF for N01266.

At the EV, body weight and height data will be obtained from the previous pediatric study and should not be recorded in the eCRF for N01266.

At the EV, physical examination data will be obtained from the previous pediatric study and should not be recorded in the eCRF for N01266.

At the EV, neurological examination data will be obtained from the previous pediatric study and should not be recorded in the eCRF for N01266.

At the EV, psychiatric and mental status data will be obtained from the previous pediatric study and should not be recorded in the eCRF for N01266.

Has been changed to:

At the EV, ECG data will be obtained from the **last visit of the** previous pediatric study and should not be recorded in the eCRF for N01266.

At the EV, vital sign data will be obtained from the **last visit of the** previous pediatric study and should not be recorded in the eCRF for N01266.

At the EV, body weight data will be obtained **from the last visit** and height data will be obtained from **Baseline of the** previous pediatric study and should not be recorded in the eCRF for N01266.

At the EV, physical examination data will be obtained from the **last visit of the** previous pediatric study and should not be recorded in the eCRF for N01266.

At the EV, neurological examination data will be obtained from the **last visit of the** previous pediatric study and should not be recorded in the eCRF for N01266.

At the EV, psychiatric and mental status data will be obtained from the **last visit of the** previous pediatric study and should not be recorded in the eCRF for N01266.

Change #36, Section 10.2, Efficacy assessments for seizure data based on EEG

The original text:

At the EV, data on absence seizure count (a 1-hour EEG for subjects >2 years suffering from absences) will be obtained from the previous pediatric study and should not be recorded in the eCRF for N01266.

All EEGs specific to this study will be recorded in the eCRF modules specifically designed for this purpose.

The EEGs will be performed according to the following specifications:

- For subjects >2 years with typical absence seizures: a 1-hour EEG (including hyperventilation and intermittent photic stimulation) will be performed starting at V4 and at every 3-month visit for the first 6 months and then yearly thereafter. For subjects prematurely discontinuing from the study, a 1-hour EEG should also be performed at the EDV.
- For subjects ≥1 month to ≤2 years: a 24-hour EEG (including sleeping and awakening periods) will be performed every 3 months during the first 6 months of the study, then yearly thereafter, and at the FV or the EDV in the case of early discontinuation.

The EEGs will be recorded at the MEV, FEV, YEV, FV, and at the EDV in the case of early discontinuation.

A central reader will review and assess all EEGs in a standardized manner.

Has been changed to:

At the EV, **seizure data based on an EEG of at least 24 hours of recording (including sleeping and awakening periods) for subjects <2 years of age and** data on absence seizure count (**based on an** EEG **of at least** 1 hour **of recording** for subjects ≥2 years **of age** suffering from absences) will be obtained from the **last visit of the** previous pediatric study and should not be recorded in the eCRF for N01266.

All EEGs specific to this study will be recorded in the eCRF modules specifically designed for this purpose.

The EEGs will be performed according to the following specifications:

- For subjects **≥**2 years **of age on the day of the study visit and** with typical absence seizures: a**n** EEG **of at least** 1 hour **of recording** (including hyperventilation and intermittent photic stimulation) will be performed starting at V4 and at every 3-month

visit for the first 6 months and then yearly thereafter. For subjects prematurely discontinuing from the study, a**n** EEG **of at least** 1 hour **of recording** should also be performed at the EDV.

- For subjects ≥1 month to **<**2 years **of age on the day of the study visit: an** EEG **of at least** 24 hour**s of recording** (including sleeping and awakening periods) will be performed every 3 months during the first 6 months of the study, then yearly thereafter, and at the FV or the EDV in the case of early discontinuation.

A central reader will review and assess all EEGs in a standardized manner.

Change #37, Section 10.3.1.3, Health care provider consultations not foreseen by the protocol, last sentence

The original text:

At the EV, information on the health care provider consultations not foreseen by the protocol will be obtained from the previous pediatric study and should not be recorded in the eCRF for N01266.

Has been changed to:

At the EV, information on the health care provider consultations not foreseen by the protocol will be obtained from **the last visit of** the previous pediatric study and should not be recorded in the eCRF for N01266.

Change #38, Section 10.3.1.4, Hospital stays, last sentence

The original text:

At the EV, information on hospital stays will be obtained from the previous pediatric study and should not be recorded in the eCRF for N01266.

Has been changed to:

At the EV, information on hospital stays will be obtained from **the last visit of** the previous pediatric study and should not be recorded in the eCRF for N01266.

Change #39, Section 10.3.2

The original text:

10.3.2 Bayley Scales of Infant Development-II

The BSID‑II™ is a widely used validated questionnaire for children from 1 month up to 42 months of age designed to evaluate a child's developmental function, including cognition, language, personal social behavior, and motor development.

This scale is accepted as a tool for assessment of neurological development in young children and is therefore considered appropriate for this study. The BSID-II will be used throughout the study for all subjects who were <18 months of age at Baseline (V1) of the previous pediatric study, N01263, by the Investigator or designee. Children started on the BSID-II at Baseline of N01263 will also be assessed using the BSID-II in N01266 even if their age increases to >18 months. The completion of the BSID-II will require approximately 25 to

35 minutes for children below 15 months of age and up to 60 minutes for children above 15 months of age.

The BSID-II includes a mental scale that evaluates sensory/perceptual activities, discriminations, acquisition of object constancy, memory, learning and problem solving, vocalization, early verbal communication, abstract thinking, habituation, mental mapping, complex language, and mathematical concept formation; a motor scale that evaluates degree of body control, coordination of large muscles, fine manipulation skills, dynamic movement, postural imitations, and stereognosis; and a behavior rating scale that measures attention and arousal, orientation and engagement, emotional regulation, and motor quality (Bayley, 1993).

At the EV, the BSID-II score will be obtained from the previous pediatric study and should not be recorded in the eCRF in N01266. The BSID-II will be completed at the FEV, YEV, FV, and at the EDV in the case of early discontinuation. The BSID-II should be completed by the same person who completed the CBCL in the previous pediatric study.

Has been changed to:

10.3.2 Bayley Scales of Infant and Toddler Development, Third Edition

The Bayley-III scales are recognized internationally as one of the most comprehensive developmental assessment instruments (Sattler and Hoge, 2006) used to examine the major facets of a young child's development (Bayley, 2006). The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) are a standardized individually administered adaptive assessment that measures the developmental functioning of infants and young children from 1 month to 42 months of age (Bayley, 2006). The Bayley-III scales measure cognitive, language, motor, social-emotional, and adaptive development and are a revision of the predecessor, the Bayley Scales of Infant Development, Second Edition (BSID-II) (Bayley, 1993). The Bayley-III scales are a technically sound instrument, with strong internal consistency, as well as test-retest stability. The Bayley-III scales are validated only in English.

This scale is validated as a tool for assessment of neurological development in young children and is therefore considered appropriate for N01266. The same scale has been completed by the Investigator or designee at Baseline (V1) of N01263 for children from 1 month to <18 months of age at Baseline enrolled in English-speaking countries. Children started on the Bayley-III scales at Baseline of N01263 will also be assessed using the Bayley-III scales in N01266 even if their age increases to ≥18 months.

The Bayley-III scales are an individually administered adaptive assessment that presents children with situations and tasks designed to produce an observable set of behavioral responses. They consist of a cognitive scale, a language composite scale with receptive and expressive language subscales, and a motor composite scale with fine and gross motor subscales to be completed by the Investigator or designee, and of a social-emotional scale, comprising social-emotional competence and sensory processing, and an adaptive behavior scale, which assesses the attainment of skills necessary for the development of independence, to be completed by the child's parent or caregiver.

The completion of the Bayley-III scales will require approximately 50 minutes for children who are 12 months old or younger and 90 minutes for children aged 13 months and older.

At the EV, the Bayley-III scales will be obtained from Baseline of the previous pediatric study if the subject was enrolled in an English-speaking country, and data should not be recorded in the eCRF in N01266. The Bayley-III scales will be completed at the FEV, YEV, FV, and at the EDV in the case of early discontinuation. The Bayley-III scales should be completed by the same person who completed the Bayley-III scales in the previous pediatric study.

Change #40, Section 10.3.3, Achenbach Child Behavior Checklist, last paragraph

The original text:

At the EV, the Achenbach CBCL score will be obtained from the previous pediatric study and should not be recorded in the eCRF in N01266. The Achenbach CBCL will be completed at the FEV, YEV, FV, and at the EDV in the case of early discontinuation.

Has been changed to:

At the EV, the Achenbach CBCL score will be obtained from **Baseline of** the previous pediatric study and should not be recorded in the eCRF in N01266. The Achenbach CBCL will be completed at the FEV, YEV, FV, and at the EDV in the case of early discontinuation.

Change #41, Section 12.5, Other analyses, last paragraph

The original text:

The Achenbach CBCL, the BSID-II scores, and change from previous study Baseline scores will be analyzed in a descriptive manner.

Has been changed to:

The Achenbach CBCL, the **Bayley-III** scores, and change from previous study Baseline scores will be analyzed in a descriptive manner.

Change #42, Section 15, REFERENCES

The following references have been added:

Bayley N. Bayley Scales of Infant and Toddler Development. 3rd ed. San Antonio: Pearson Education Inc; 2006.

Sattler JM, Hoge RD. Assessment of children: behavioral, social, and clinical foundations. 5th ed. La Mesa: Jerome M Sattler; 2006.

16.3 Protocol Amendment 3

Rationale for the amendment

The primary purpose of the protocol amendment is to allow subjects who have not previously participated in a clinical study of BRV to enroll directly into N01266 (ie, directly enrolled subjects). Up to 100 subjects who are ≥4 years to <17 years of age with POS and meet entry criteria are planned for direct enrollment. The purpose of direct enrollment is to obtain sufficient long-term safety exposure data in subjects in this age group. These data will be included in the planned regulatory submission for BRV as adjunctive therapy for POS in pediatric subjects ≥1 month to ≤16 years of age with epilepsy.

With this amendment, the BRIEF-P/BRIEF and PedsQL were added to the assessments for subjects ≥2 years of age. These assessments were added to provide an additional means of assessing the effect of BRV on cognition and quality of life, respectively, in pediatric subjects ≥2 years of age.

Modifications and changes

Global changes

The following changes that pertain to the inclusion of directly enrolled subjects were made throughout the protocol:

- The study title and protocol text have been updated to reflect that, with the inclusion of eligible direct enrollees, N01266 is no longer exclusively a LTFU study.
- Information has been added throughout the protocol to indicate that up to 100 subjects ≥4 years to <17 years of age with POS who have not previously participated in a clinical study of BRV (ie, directly enrolled subjects) may enroll directly into N01266 provided eligibility criteria are met. Information specific to these subjects was added throughout the protocol as shown in "specific changes."
- A Screening Visit, TV(s), and an EV unique to directly enrolled subjects were added. A schedule of assessments was added to specify the assessments to be performed at these visits, and the text throughout the protocol was modified accordingly.
- The visit sequence table was revised to include visits unique to directly enrolled subjects.
- The inclusion criteria (Section 6.1) and exclusion criteria (Section 6.2) were modified to provide the eligibility requirements for directly enrolled subjects, and make a distinction between the previously existing criteria for LTFU subjects.

The following changes that pertain to all subjects were made:

- Table 5-1 was revised to include directly enrolled subjects and updated to provide additional clarity regarding assessments. The revised table is shown below in "specific changes."
- Introductory information was updated to include background safety data included in the most current Investigator's Brochure (cutoff date 08 Sep 2011).

- Reference to the Global Clinical Safety and Pharmacovigilance department was replaced by reference to Drug Safety, and SAE reporting contact information was updated.
- BRIEF-P/BRIEF and PedsQL assessments were added and included as variables and objectives. Descriptions of these assessments were added.
- The contact information in the section pertaining to serious adverse event reporting was updated.
- The word "active" was replaced with "actual" as a descriptor for suicide attempts in order to match the language used in the C-SSRS scale.
- Laboratory safety assessments done at each visit were clarified, but not changed.
- For subjects who prematurely discontinue, age-based targets were specified for the final down-titration BRV dose.
- Minor editorial changes were made.
- Formatting changes (eg, reduced space between lines in tables, footnote indentation, and table title number formatting) were made to address new technical presentation requirements put in place by UCB. Due to the scope of these changes and the fact that they do not represent content changes, they are not included in "specific changes."
- Minor typographical corrections were made (eg, removal of an extra full stop at the end of a sentence). These changes are not included in "specific changes."

Specific changes

Change #1, TITLE PAGE

The title page was updated to reflect the current amendment.

Change #2, TITLE PAGE

The original title:

Open-label, single-arm, multicenter, long-term follow-up study to evaluate safety and efficacy of brivaracetam used as adjunctive treatment in pediatric subjects with epilepsy

Has been changed to:

Open-label, single-arm, multicenter, long-term study to evaluate safety and efficacy of brivaracetam used as adjunctive treatment in pediatric subjects with epilepsy

Change #3, SPONSOR DECLARATION

The original text:

Clinical Project Manager

[redacted]

_____
Date/Signature

Study Physician

[redacted]

_____
Date/Signature

Senior Clinical Program Director

[redacted]

_____
Date/Signature

Has been changed to:

Clinical Project Manager

[redacted]

_____
Date/Signature

Study Physician

[redacted]

_____
Date/Signature

Change #4, STUDY CONTACT INFORMATION

The original text:

Sponsor Study Physician

Name:	[redacted]
Address:	8010 Arco Corporate Drive, [redacted] Raleigh, NC 27617 United States
Phone:	[redacted]
Fax:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	UCB Center Bruxelles Allée de la Recherche 60 B-1070 Bruxelles Belgium
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Sponsor Study Physician

Name:	[redacted]
Address:	8010 Arco Corporate Drive, [redacted] Raleigh, NC 27617 United States
Phone:	[redacted]
Fax:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	UCB Center Bruxelles Allée de la Recherche 60 B-1070 Bruxelles Belgium
Phone:	[redacted]
Fax:	[redacted]

Change #5, SERIOUS ADVERSE EVENT REPORTING

The original text:

Serious adverse event reporting (24h), safety related issues, and emergency unblinding	
Fax	**Europe and Rest of the World (except Japan):** +32 2 386 2421 **US:** +1 800 880 6949 **Canada:** +1 877 582 8842
Phone	**Europe, US, and Rest of the World (except Japan):** +32 2 386 2468
Email	**Europe, US, and Rest of the World (except Japan):** GCSP@ucb.com

Has been changed to:

Serious adverse event reporting (24h) and safety related issues	
Fax	**Europe and Rest of the World (except Japan):** +32 2 386 2421 **US:** +1 800 880 6949 **Canada:** +1 877 582 8842
Email	**Europe, US, and Rest of the World (except Japan): DS_ICT@ucb.com**

Change #6, LIST OF ABBREVIATIONS

The following abbreviations have been added to the list:

ALP	**alkaline phosphatase**
BRIEF®	**Behavior Rating Inventory of Executive Function®**
BRIEF®-P	**Behavior Rating Inventory of Executive Function®-Preschool Version**
HRQoL	**health-related quality of life**
PedsQL™	**Pediatric Quality of Life Inventory™**
ScrV	**Screening Visit**
TV	**Titration Visit**

The original text for the following abbreviations:

bid	twice daily
M	month
PDCO	European Pediatric Committee
POS	partial onset seizures

Has been changed to:

bid	**bis in die (**twice daily**)**
M	**M**onth
PDCO	European P**a**ediatric Committee
POS	partial-onset seizures

The following abbreviation has been deleted from the list:

GCSP	Global Clinical Safety and Pharmacovigilance

Change #7, SUMMARY, paragraphs 1 through 4

The original text:

This is a Phase 3, open-label, single-arm, multicenter, long-term follow-up (LTFU) study to evaluate the safety and efficacy of brivaracetam (BRV) in children with epilepsy. 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 on behavior and cognition using the age-appropriate Achenbach Child Behavior Checklist (CBCL/1½-5 or CBCL/6-18) for subjects ≥18 months of age at Baseline of the previous study N01263 or other pediatric studies. The Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®) will be used to assess subjects enrolled in English-speaking countries and <18 months of age at Baseline of the previous study N01263 or other BRV pediatric studies.

To enroll in this study, subjects must have completed N01263 or will have completed a future BRV pediatric study. On entering this study, subjects will continue their BRV treatment at the individualized dose that they had reached at the completion of their previous pediatric study. Subjects entering this study from N01263 must be able to tolerate at least 0.4mg/kg of BRV twice daily (bid) if ≥8 years of age or at least 0.5mg/kg bid if <8 years of age. The maximum BRV dose for subjects ≥8 years of age is 3.2mg/kg/day and 4.0mg/kg/day for subjects <8 years of age. Younger subjects (<7 years of age) will be administered BRV oral solution (given bid in 2 equally divided doses). Subjects above 50kg will be dosed as adults, up to a maximum total daily dose not exceeding 200mg/day, and should transition from the oral solution to the equivalent oral tablet dose (given bid in 2 equally divided doses). Dose adjustments of BRV and any concomitant antiepileptic drugs (AEDs) are allowed at any time based on clinical judgment.

Subjects will continue to receive BRV treatment in this study for at least 3 years, or until approval of BRV has been obtained for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor.

For subjects who continue in this study until it ends, the Evaluation Period will extend from the Entry Visit (EV, Visit 1 [V1]) 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 study drug-free Safety Period, and a final Safety Visit (SV).

Has been changed to:

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 was initially designed for pediatric subjects who had completed N01263 or would complete other future pediatric BRV studies (herein referred to as "long-term follow-up" [LTFU] subjects). With Protocol Amendment 3, enrollment was expanded to include up to 100 subjects ≥4 years to <17 years of age with POS who had not previously enrolled in a pediatric BRV study (herein referred to as "directly enrolled 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 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 the previous **BRV** study **and for all directly enrolled subjects. With Protocol Amendment 3, the effect of BRV on cognition will also be assessed using the Behavior Rating Inventory of Executive Function® (BRIEF®)/BRIEF®-Preschool Version (BRIEF®-P) and the effect of BRV on quality of life will be assessed using the Pediatric Quality of Life Inventory™ (PedsQL™) for LTFU subjects ≥1 month of age at the Baseline of the previous BRV study and for all directly enrolled 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 <18 months of age at Baseline of the previous **pediatric**

BRV study; Bayley-III will not be used to access directly enrolled 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 previous pediatric **BRV** 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 directly enrolled subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than the minimum specified dose) for 7±2 days during the Up-Titration Period, the subject will attend the EV and enter the Evaluation Period on that dose.**

Brivaractam (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 previous BRV study to be eligible for entry into the Evaluation Period. This minimum tolerated dose for LTFU subjects from N01263 is **0.8**mg/kg/**day** if ≥8 years of age and **1.0**mg/kg/**day** if <8 years of age. **The same minimums apply to directly enrolled subjects as indicated in Section 7.2.**

The maximum **allowable** BRV dose **is 3.2mg/kg/day** for subjects ≥8 years of age and 4.0mg/kg/day for subjects <8 years of age. Younger subjects (<7 years of age) will be administered BRV oral solution. Subjects above 50kg will be dosed as adults, up to a maximum total daily dose not exceeding 200mg/day, and should transition from the oral solution to the equivalent oral tablet dose, **if 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 **approximately** 3 years, until approval of BRV has been obtained for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor.

For LTFU subjects, the EV is the first study visit. For directly enrolled 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 study drug-free Safety Period, and a final Safety Visit (SV). **At selected sites, subjects may be able to participate in a substudy without withdrawing from N01266.**

Change #8, SUMMARY, paragraphs 8 and 9

The original text:

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) or the change in Bayley-III scales over time for subjects enrolled in English-speaking countries.

Up to 500 subjects may possibly enroll in this study, with the number and location of the sites dependent on those participating in N01263 and in other future pediatric studies that will provide access to this LTFU.

Has been changed to:

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.

Up to 600 subjects may possibly enroll in this study. **The** number and location of the sites **will depend** on those participating in N01263 and other future pediatric **BRV** 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 N01263 and other pediatric BRV studies.**

Change #9, Section 2.3, Efficacy with BRV

The original header text:

Efficacy with BRV

Has been changed to:

Efficacy with BRV (adult studies)

Change #10, Section 2.4, Safety with BRV

The original header text:

Safety with BRV

Has been changed to:

Safety with BRV (adult studies)

Change #11, Section 2.4. Safety with BRV, paragraph 3

The original text:

In addition, there are 3 ongoing open-label LTFU studies (N01125, N01199, and N01315) that include subjects with POS, primary generalized seizures, or ULD who completed 1 of the Phase 2/3 well-controlled studies. As of 04 Jan 2011, 1629 subjects have been enrolled in these studies and 1624 subjects have received study medication. The median duration of BRV exposure in LTFU studies was 91 weeks. The most common TEAEs based on interim

safety monitoring review include headache, dizziness, nasopharyngitis, convulsion, somnolence, and fatigue. Overall, 234 subjects reported SAEs. The only SAE occurring at a frequency >1% was convulsion (2.4%). Overall, 132 subjects discontinued due to TEAEs. The most common TEAEs leading to premature discontinuation were convulsion and depression.

Has been changed to:

In addition, there are 3 ongoing open-label LTFU studies (N01125, N01199, and N01315) that include subjects with POS, primary generalized seizures, or ULD who completed 1 of the Phase 2/3 well-controlled studies. As of **08 Sep** 2011, 1629 subjects have been enrolled into these studies and 1624 subjects have received study medication. The median duration of BRV exposure in LTFU studies was **119** weeks**.** The most common TEAEs**,** based on interim safety monitoring review**,** include headache, dizziness, nasopharyngitis, convulsion, somnolence, and fatigue. Overall, **272** subjects reported SAEs. The only SAE occurring at a frequency >1% was convulsion (2.**5**%). Overall, **142** subjects discontinued due to TEAEs. The most common TEAEs leading to premature discontinuation were convulsion and depression.

Change #12, Section 2.5, Rationale for the study, paragraph 3 and 4

The original text:

UCB is developing BRV as an adjunctive treatment including in subjects <16 years of age suffering from epilepsy. N01263 is the first study of BRV in pediatric subjects. This is an open-label, fixed 3-step up-titration, PK, safety and efficacy study to evaluate BRV as adjunctive therapy in children (aged ≥1 month to <16 years) with epilepsy using an oral solution. The safety and PK data from this study will be used for BRV dose adaptation in pediatric subjects with epilepsy.

This present study (N01266) will give subjects who have completed N01263 or will have completed other future BRV pediatric studies an opportunity to continue BRV treatment for at least 3 years, or until approval of BRV is granted for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor. In addition, N01266 will gather additional long-term safety and tolerability data on BRV in pediatric subjects with epilepsy while providing access to BRV for subjects who may benefit from long-term treatment.

Has been changed to:

N01263 is the first study of BRV in pediatric subjects. This is an open-label, fixed 3-step up-titration, PK, safety and efficacy study to evaluate BRV as adjunctive therapy in children (aged ≥1 month to <16 years) with epilepsy using an oral solution. The safety and PK data from this study will be used for BRV dose adaptation in pediatric subjects with epilepsy.

N01266 was originally designed to give subjects who complete N01263 or other future **pediatric BRV** studies (**ie, LTFU subjects**) an opportunity to continue BRV treatment for **approximately** 3 years, until approval of BRV is granted for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor. **With Protocol Amendment 3, enrollment is expanded to include up to 100 eligible subjects**

≥4 years to <17 years of age with POS who have not participated in another pediatric BRV study (ie, directly enrolled subjects). Thus, N01266 will gather additional long-term safety and tolerability data on BRV in pediatric subjects with epilepsy while providing access to BRV for subjects who may benefit from long-term treatment.

Change #13, Section 3.3, Other objectives

The original text:

- To explore direct cost parameters
- To assess the effect of BRV on behavior using the Achenbach CBCL in subjects ≥18 months of age
- To assess the effect of BRV on cognition using the Bayley-III scales in subjects <18 months of age (applicable only to subjects enrolled in English-speaking countries)

Has been changed to:

- 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 scales in subjects <18 months of age (applicable only to **LTFU** subjects enrolled in English-speaking countries)
- **To explore the effect of BRV on health-related quality of life (HRQoL) using the PedsQL in subjects ≥1 month of age**

Change #14, Section 4.3, Other variables

The original text:

The other variables include the following:

- Direct cost parameters: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays
- Change over time from previous study 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
- Change over time from previous study Baseline in the Bayley-III scales for children <18 months of age (applicable only to subjects enrolled in English-speaking countries)

Has been changed to:

The other variables include the following:

- Direct cost parameters: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays
- Change 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
- **Change from Baseline in the BRIEF-P/BRIEF score for subjects ≥2 years of age**
- Change from previous **BRV** study Baseline in the Bayley-III scales for children <18 months of age (applicable only to **LTFU** subjects enrolled in English-speaking countries)
- **Change from Baseline in PedsQL for subjects ≥1 month of age**

Change #15, Section 5.1, Study description, paragraphs 1 through 5

The original text:

This is a Phase 3, open-label, single-arm, multicenter, LTFU study to evaluate the safety and efficacy of BRV in up to 500 subjects with epilepsy. Subjects had to be <16 years of age upon entry in their previous pediatric study.

To enroll in this LTFU study, subjects must have completed N01263 or will have completed a future BRV pediatric study. On entering the LTFU study, subjects will continue their BRV treatment at the individualized dose that they had reached at the completion of the previous study. Younger subjects (<7 years of age) will be administered BRV oral solution (given bid in 2 equally divided doses). Subjects above 50kg will be dosed as adults, up to a maximum total daily dose not exceeding 200mg/day, and should transition from the oral solution to the equivalent oral tablet dose (given bid in 2 equally divided doses). Dose adjustments of BRV and/or concomitant AEDs are allowed at any time based on clinical judgment. Further information on the treatment administered is presented in Section 7.2.

Subjects will continue to receive BRV treatment in this study for at least 3 years, or until approval for BRV has been obtained for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor.

For subjects who continue in the study until it ends, the Evaluation Period will extend from the EV to the FV. For subjects who prematurely discontinue the study, the Evaluation Period will last from the EV until the EDV. Following the EDV, subjects will have their dose of BRV down titrated over a maximum of 4 weeks (Down-Titration Period). After 2 weeks free of study drug (Safety Period), subjects will complete the SV.

During the Evaluation Period, MEVs and FEVs will be performed alternatively every month during the first 3 months and every 3 months thereafter, with a YEV every 12 months. The sequence of these visits is presented in Section 5.3. Both safety data and efficacy data (seizure data) will be collected during the study. A list of the study assessments performed at each of the visits is presented in Section 5.2.

Has been changed to:

This is a Phase 3, open-label, single-arm, multicenter, **long-term** study to evaluate the safety and efficacy of BRV in up to **600** subjects with epilepsy. Subjects **who enroll in N01266 from N01263 or another pediatric BRV study (ie, LTFU subjects) must have been** <16 years of age upon entry in their previous study**; eligible subjects who have POS and enroll in N01266 without having participated in a previous pediatric BRV study (ie, directly enrolled subjects) must be ≥4 years to <17 years of age.**

Upon enrollment, eligible LTFU subjects will enter the Evaluation Period and continue their BRV treatment in accordance with their individualized dose at the completion of their previous pediatric BRV study. Directly enrolled subjects will be screened and participate in up to 3 weeks of an Up-Titration Period. If a directly enrolled subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than the minimum specified dose) for 7±2 days during the Up-Titration Period, the subject will attend the EV and enter the Evaluation Period on that dose.

Brivaracetam (tablet and oral solution) should be administered bid in 2 equally divided doses. All LTFU subjects must be able to tolerate the minimum BRV dose specified in the previous study to be eligible for entry into the Evaluation Period of N01266. For LTFU subjects from N01263, this minimum tolerated BRV dose is 0.8mg/kg/day if ≥8 years of age and 1.0mg/kg/day if <8 years of age. The same minimums apply to directly enrolled subjects.

For all subjects enrolled in N01266, the maximum BRV dose is 3.2mg/kg/day for subjects ≥8 years of age and 4.0mg/kg/day for subjects <8 years of age. Younger subjects (<7 years of age) will be administered BRV oral solution. Subjects above 50kg will be dosed as adults, up to a maximum total daily dose not exceeding 200mg/day, and should transition from the oral solution to the equivalent oral tablet dose. Dose adjustments of BRV and/or concomitant AEDs are allowed at any time based on clinical judgment**; however, during the Up-Titration Period, dose adjustments for BRV should be made only as specified in Section 7.2.1**. **Additional** information on **BRV administration** is presented in Section 7.2. Subjects will continue to receive BRV treatment in this study for **approximately** 3 years, until approval for BRV has been obtained for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor.

For LTFU subjects, the EV is the first study visit. For directly enrolled subjects, the EV is the visit at which subjects enter the Evaluation Period and occurs after subjects have completed the ScrV and at least 1 Titration Visit (TV). For subjects who continue in the study until it ends, the Evaluation Period will extend from the EV to the FV. For subjects who prematurely discontinue the study, the Evaluation Period will last from the EV until the EDV. Following the EDV, subjects will have their dose of BRV down titrated over a maximum of 4 weeks (Down-Titration Period). After 2 weeks free of study drug (Safety Period), subjects will complete the SV.

During the Evaluation Period, MEVs and FEVs will be performed alternatively every month during the first 3 months and every 3 months thereafter, with a YEV every 12 months. The

sequence of these visits is presented in Section 5.3. Both safety data and efficacy data (seizure data) will be collected during the study. **Lists** of the study assessments performed at each of the visits **are** presented in Section 5.2.

Change #16, Section 5.1.1, Study duration per subject, paragraph 1

The original text:

The maximum duration for subject participation will extend from study entry (EV, V1) for at least 3 years, or until approval of BRV has been obtained for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor.

Has been changed to:

Subject participation will extend from study entry for **approximately** 3 years, until approval of BRV has been obtained for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor. **Study entry is defined as the EV for LTFU subjects and the ScrV for directly enrolled subjects.**

Change #17, Section 5.1.2, Planned number of subjects and sites

The original text:

Up to 500 subjects (<16 years of age upon entry in their previous pediatric study) may possibly enroll in this study during the pediatric development plan, based upon the assumption that 90% of subjects having completed a previous pediatric study with BRV as adjunctive treatment in epilepsy will rollover into the present study.

Has been changed to:

As originally designed, up to 500 subjects (<16 years of age upon entry in their previous pediatric **BRV** study) **might** possibly enroll in this study during the pediatric development plan, based upon the assumption that 90% of subjects having completed a previous pediatric study with BRV as adjunctive treatment in epilepsy **would** rollover into **N01266**.

With Protocol Amendment 3, enrollment is expanded to include up to 100 eligible directly enrolled subjects ≥4 years to <17 years of age with POS, which will allow up to 600 subjects to enroll in N01266 instead of the up to 500 originally planned.

Change #18, Section 5.1.3, Anticipated regions and countries

The original text:

The regions and countries participating in this study will depend on the location of the sites participating in the previous pediatric study/studies, as these sites should have access to this LTFU study. Europe, US, and Mexico are foreseen, with the possibility to extend to other countries and regions if deemed necessary.

Has been changed to:

As originally designed, the regions and countries participating in this study depende**d** on the location of the sites participating in the previous pediatric **BRV** study/studies, as these sites should have **had** access to **the originally planned** LTFU study. Europe, US, and Mexico **were** foreseen, with the possibility to extend to other countries and regions if deemed necessary.

With Protocol Amendment 3, directly enrolled subjects may be enrolled from sites participating in N01263 and possibly other sites, including, but not limited to, those participating in other pediatric BRV studies.

Change #19, Section 5.2, Schedule of study assessments, header text

The original text:

Schedule of study assessments

Has been changed to:

Schedules of study assessments

Change #20, Section 5.2, Schedule of study assessments

The following text has been added immediately below the section header:

Once a directly enrolled subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than the minimum specified dose) for 7±2 days during the Up-Titration Period, the subject will attend the EV, enter the Evaluation Period on that dose, and follow the study assessments in Table 5-1.

Table 5-1 provides a schedule of all study assessments for LTFU subjects and for assessments subsequent to the final TV for directly enrolled subjects. Table 5-2 provides a schedule of study assessments for directly enrolled subjects from the ScrV through the final TV.

Change #21, Section 5.2, Table 5:1

The original title:

Schedule of study assessments

Has been changed to:

Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

The original header:

Period	Evaluation						Down-Titration	Safety (Drug-free)
Visit	Entry Visit	Minimal Evaluation Visit	Full Evaluation Visit	Yearly Evaluation Visit/Final Visit	Unscheduled Visit	Early Discontinuation Visit	Down-Titration Visit	Safety Visit
	(EV)[a]	(MEV)	(FEV)	(YEV/FV[b])	(UV)	(EDV)	(DTV)[c]	(SV)

Has been changed to:

Period	Evaluation							Down-Titration	Safety (Drug-free)
Visit	Entry Visit		Minimal Evaluation Visit	Full Evaluation Visit	Yearly Evaluation Visit/Final Visit	Unscheduled Visit	Early Discontinuation Visit	Down-Titration Visit	Safety Visit
	(EV)		(MEV)	(FEV)	(YEV/FV[b])	(UV)	(EDV)	(DTV)[c]	(SV)
Subjects	LTFU	DE	All						

The following row was deleted:

Demographic data	X							

The following cells have been added:

BRIEF-P/BRIEF[s]				X	X		X		
PedsQL[t]				X	X		X		

The original table has been replaced with the following (with changes in addition to those noted above [title and header] indicated):

Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	**Evaluation**							**Down-Titration**	**Safety (Drug-free)**
Visit	**Entry Visit**		**Minimal Evaluation Visit**	**Full Evaluation Visit**	**Yearly Evaluation Visit/Final Visit**	**Unscheduled Visit**	**Early Discontinuation Visit**	**Down-Titration Visit**	**Safety Visit**
	(EV)		**(MEV)**	**(FEV)**	**(YEV/FV[b])**	**(UV)**	**(EDV)**	**(DTV)[c]**	**(SV)**
Subjects	**LTFU[a]**	**DE**	**All**						
Assessment									
Written informed consent/assent	X								
Subject identification card dispensing	X								
Childbearing potential	X[a]	X	X	X	X		X		
Verification inclusion/exclusion	X								

Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	**Evaluation**							**Down-Titration**	**Safety (Drug-free)**
Visit	**Entry Visit**		**Minimal Evaluation Visit**	**Full Evaluation Visit**	**Yearly Evaluation Visit/Final Visit**	**Unscheduled Visit**	**Early Discontinuation Visit**	**Down-Titration Visit**	**Safety Visit**
	(EV)		**(MEV)**	**(FEV)**	**(YEV/FV[b])**	**(UV)**	**(EDV)**	**(DTV)[c]**	**(SV)**
Subjects	**LTFU[a]**	**DE**	**All**						
Assessment									
criteria									
Physical and neurological examinations	**X[a]**	**X**		X	X		X		X
Psychiatric and mental status	**X[a]**	**X**		X	X		X		X
Vital signs[d]	**X[a]**	**X**	X	X	X		X	X	X
Body weight and height	**X[a]**	**X**	X	X	X		X		X
ECG[e]	**X[a]**	**X**			X		X		X[f]
EEG[g]	**X[a]**		X	X	X		X		
DRC dispensed	X	**X**	X	X	X[h]		X	X	
DRC retrieved		**X**	X	X	X		X	X	X
Seizure count	**X[a]**	**X**	X	X	X		X	X	X
Assessment of seizure				X	X				

Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	**Evaluation**							**Down-Titration**	**Safety (Drug-free)**
Visit	**Entry Visit**		**Minimal Evaluation Visit**	**Full Evaluation Visit**	**Yearly Evaluation Visit/Final Visit**	**Unscheduled Visit**	**Early Discontinuation Visit**	**Down-Titration Visit**	**Safety Visit**
	(EV)		**(MEV)**	**(FEV)**	**(YEV/FV[b])**	**(UV)**	**(EDV)**	**(DTV)[c]**	**(SV)**
Subjects	**LTFU[a]**	**DE**	**All**						
Assessment types[i]									
Recording of medications[j]	X[a]	**X**	X	X	X	X	X	X	X
Recording of procedures	X[a]	**X**	X	X	X	X	X	X	X
Recording of AEs[k]	X[a]	**X**	X	X	X	X	X	X	X
IVRS	X	**X**	X	X	X	X	X	X	X
Study drug dispensed	X	**X**	X	X	X[h]		X		
Study drug returned[l]		**X**	X	X	X		X	X	
Study drug compliance		**X**	X	X	X		X	X	

Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	**Evaluation**							**Down-Titration**	**Safety (Drug-free)**
Visit	**Entry Visit**		**Minimal Evaluation Visit**	**Full Evaluation Visit**	**Yearly Evaluation Visit/Final Visit**	**Unscheduled Visit**	**Early Discontinuation Visit**	**Down-Titration Visit**	**Safety Visit**
	(EV)		**(MEV)**	**(FEV)**	**(YEV/FV[b])**	**(UV)**	**(EDV)**	**(DTV)[c]**	**(SV)**
Subjects	**LTFU[a]**	**DE**	**All**						
Assessment									
Laboratory assessments for safety[m]	**X[a]**	**X**	**X[n]**	X	X		X		X[f]
BRV plasma concentrations[o]				X	X		X		
Phenytoin plasma concentrations, if applicable	**X[a]**			X	X		X		X[f]
C-SSRS[p]	**X[a]**	**X**	X	X	X		X	X	X
Bayley-III scales[q]				X	X		X		
Achenbach CBCL[r]				X	X		X		
BRIEF-P/BRIEF[s]				**X**	**X**		**X**		
PedsQL[t]				**X**	**X**		**X**		

Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	**Evaluation**							**Down-Titration**	**Safety (Drug-free)**
Visit	**Entry Visit**		**Minimal Evaluation Visit**	**Full Evaluation Visit**	**Yearly Evaluation Visit/Final Visit**	**Unscheduled Visit**	**Early Discontinuation Visit**	**Down-Titration Visit**	**Safety Visit**
	(EV)		**(MEV)**	**(FEV)**	**(YEV/FV[b])**	**(UV)**	**(EDV)**	**(DTV)[c]**	**(SV)**
Subjects	**LTFU[a]**	**DE**	**All**						
Assessment									
Health care provider consultations not foreseen by protocol	**X[a]**	**X**	X	X	X	X	X	X	X
Hospital stays[u]	**X[a]**	**X**	X	X	X	X	X	X	X
End of study status					X[v]				X

AE=adverse event; AED=antiepileptic drug; ALP=alkaline phosphatase; ALT=alanine aminotransferase; 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; C-SSRS=Columbia-Suicide Severity Rating Scale; **DE=directly enrolled;** DRC=daily record card; ECG=electrocardiogram; eCRF=electronic case report form; EEG=electroencephalogram; GGT=gamma-glutamyltransferase; IVRS=interactive voice response system; **LTFU=long-term follow-up;** M=Month; **PedsQL=Pediatric Quality of Life Inventory;** SAE=serious adverse event; **TV=Titration Visit;** V=Visit

[a] **For LTFU subjects, t**he following data will be obtained from Baseline of the previous pediatric **BRV** study and should not be recorded on the eCRF for N01266: **demographics,** general medical and procedure history, epilepsy history, AED history, height, Bayley-III scales, the Achenbach CBCL**, BRIEF-P/BRIEF, and PedsQL** scores. The following data will be obtained from the **final** visit of the previous pediatric **BRV** study and should not be recorded **in** the eCRF for N01266: **AEs, childbearing potential, recording of medications, recording of procedures,** seizure count, EEG, ECG, laboratory assessments for safety, including phenytoin plasma concentrations (if applicable), the C-SSRS, vital signs, body weight, physical and neurological examinations, psychiatric and mental status, and data on health care provider consultations not foreseen by the protocol and hospital stays. The EV is also the final evaluation visit of the previous pediatric **BRV** study.

[b] For subjects staying in the study until it ends, the same procedures as for a YEV should be performed at the subject's FV.

[c] Visit should be scheduled at the end of the Down-Titration Period. The duration of the Down-Titration Period will depend on when the **final** dose of the

Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	Evaluation							Down-Titration	Safety (Drug-free)
Visit	Entry Visit		Minimal Evaluation Visit	Full Evaluation Visit	Yearly Evaluation Visit/Final Visit	Unscheduled Visit	Early Discontinuation Visit	Down-Titration Visit	Safety Visit
	(EV)		(MEV)	(FEV)	(YEV/FV[b])	(UV)	(EDV)	(DTV)[c]	(SV)
Subjects	LTFU[a]	DE	All						
Assessment									

study drug was taken during the Evaluation Period, with a maximum duration of 4 weeks.

[d] Vital sign measurements include blood pressure, pulse rate, and body temperature.

[e] An ECG has to be scheduled once a year at the YEV and at the EDV in the case of early discontinuation.

[f] At the SV, ECGs, laboratory assessments for safety, and determination of phenytoin plasma concentration will be performed only if abnormal at the EDV.

[g] EEG **(for LTFU subjects only)**

- For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: every 3 months during the first 6 months (starting at V4), and then yearly thereafter: an EEG of at least 1 hour of recording including hyperventilation and intermittent photic stimulation must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, an EEG of at least 1 hour of recording should also be performed at the EDV.
- For subjects ≥1 month to <2 years of age on the day of the study visit: every 3 months during the first 6 months (starting at V4), then yearly thereafter: an EEG of at least 24 hours of recording including sleeping and awakening periods must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, an EEG of at least 24 hours of recording should also be performed at the EDV.

[h] No DRC or study drug will be dispensed at the FV.

[i] The assessment of seizure types will be done at 6-monthly intervals (at the FEV and the YEV) for subjects <2 years of age.

[j] **For LTFU subjects, a**ny ongoing medications (**including** AEDs and non-AEDs) at the time the subject completed the previous pediatric **BRV** study should not be recorded **in** the eCRF for N01266, unless there is a change regarding the administration of the medication. In this event, the start date corresponding to the date of change in administration should be recorded **in** the eCRF.

[k] **For LTFU subjects, a**ny ongoing AEs at the time the subject completed the previous pediatric **BRV** study should not be recorded on the eCRF for N01266, unless there is a change in intensity or seriousness. In this event, the AE should be recorded **in** the eCRF for N01266**,** with the onset date corresponding to the date of change in condition.

[l] Drug return includes study medication intake recording **and** accountability**.**

[m] Full laboratory assessments for safety include hematology, biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT), and

Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	Evaluation							Down-Titration	Safety (Drug-free)
Visit	Entry Visit		Minimal Evaluation Visit	Full Evaluation Visit	Yearly Evaluation Visit/Final Visit	Unscheduled Visit	Early Discontinuation Visit	Down-Titration Visit	Safety Visit
	(EV)		(MEV)	(FEV)	(YEV/FV[b])	(UV)	(EDV)	(DTV)[c]	(SV)
Subjects	LTFU[a]	DE	All						
Assessment									

endocrinology for all subjects and urinalysis for subjects ≥4 years of age as described in Section 9.5.1. Female subjects with a Tanner stage >1 should have a urine pregnancy test performed at all laboratory assessment visits, except for the EDV and the SV, when a serum pregnancy test will be performed. Endocrinology testing will be performed at the YEV/FV.

[n] **Laboratory assessments are to be done only at the MEV at V4 (M3) and V6 (M9) and are to include only hepatic monitoring (ALE, AST, ALP, total bilirubin, and GGT).**

[o] **In addition to the scheduled assessments, a** pharmacokinetic sample **for determination of BRV plasma concentration** should be taken whenever **a** subject experiences an SAE.

[p] The C-SSRS will be administered to subjects ≥6 years of age. **The "Since Last Visit" version of the C-SSRS will be used, with the following exception: If a subject turns 6 years of age during N01266, the "Already Enrolled" version of the C-SSRS should be completed at the first visit after the sixth birthday, and the "Since Last Visit" version of the C-SSRS should be completed at subsequent visits.**

[q] The cognition scale (Bayley-III) to be used in **N01266** for subjects <18 months of age and enrolled in English-speaking countries will be the same as the one used in the previous pediatric **BRV** study. If the subject reaches 18 months of age in this study, the subject will still be assessed using the Bayley-III to allow for an evaluation of the change from Baseline even if **his/her** age increases to ≥18 months.

[r] The version of the Achenbach CBCL (CBCL/1½-5 or CBCL/6-18) **should be in accordance with the subject's age, with the following exception: If a subject completed the Achenbach CBCL/1½-5 at the Baseline assessment (previous pediatric BRV study for LTFU subjects and ScrV for directly enrolled subjects) 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.**

[s] **The BRIEF-P should be used for subjects ≥2 years to <5 years of age and the BRIEF should be used for subjects ≥5 years of age, with the following exception: For subjects who completed the BRIEF-P at the Baseline assessment (previous pediatric BRV study for LTFU subjects and ScrV for directly enrolled subjects) and turn 6 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.**

[t] **The version of the PedsQL used should be consistent with the subject's age at each visit when it is administered with the following exception: If a subject ages up to the next PedsQL between the Baseline assessment (previous pediatric BRV study for LTFU subjects and ScrV for directly**

Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	Evaluation							Down-Titration	Safety (Drug-free)
Visit	Entry Visit		Minimal Evaluation Visit	Full Evaluation Visit	Yearly Evaluation Visit/Final Visit	Unscheduled Visit	Early Discontinuation Visit	Down-Titration Visit	Safety Visit
	(EV)		(MEV)	(FEV)	(YEV/FV[b])	(UV)	(EDV)	(DTV)[c]	(SV)
Subjects	LTFU[a]	DE	All						
Assessment									

enrolled subjects) and the initial YEV, the PedsQL that was used at the Baseline assessment should be completed through and including the initial YEV, and subsequently the PedsQL consistent with the age at the time of assessment should be completed.

[u] This refers to any hospital stay that occurs during the study. Data recorded in the eCRF include the reason for the hospitalization, the admission ward, transfers, and length of stay.

End of study status only for subjects who continue in the study until it ends and for whom the visit corresponds to the **final** evaluation visit or FV.

Change #22, Section 5.2, Schedule of study assessments

Table 5-2 has been added.

Change #23, Section 5.3, Visit sequence, Table 5:2

The following cells were added:

Directly enrolled subjects		
	Visit	**Type of visit**
	ScrV	**Screening**
W1	**TV1[a]**	**TV**
W2	**TV2[a]**	**TV**
W3	**TV3a**	**TV**
All subjects		

The following cells were deleted:

Subjects coming from any pediatric study providing access to this LTFU		
Month (M)	**Visit (V)**	**Type of visit**

The following have been added to the abbreviations list:

BRV=brivaracetam; M=Month; ScrV=Screening Visit; TV=Titration Visit; V=Visit; W=Week

The original footnotes:

[a] The Entry Visit is the final evaluation visit of the previous pediatric study.
[b] Subsequent years will follow the same visit schedule.
[c] Liver function tests only will be performed as described in Section 9.5.1.

Have been changed to (and referenced in the table in accordance with the updated lettering, as applicable):

[a] All directly enrolled subjects must participate in at least TV1, but may participate in fewer than 3 TVs as described in Section 7.2.1 .
[b] For LTFU subjects, the EV is the final evaluation visit of the previous pediatric **BRV** study. **For directly enrolled 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.
[d] Subsequent years will follow the same visit schedule.

Change #24, Section 5.4, Rationale for study design and selection of dose

The original text:

This present study will allow additional BRV long-term safety and tolerability data to be collected from pediatric subjects with epilepsy who will have participated in previous BRV pediatric studies and now have the opportunity to continue BRV treatment. The safety and efficacy data collected in this LTFU study will support the applications for BRV indications in pediatric patients.

A physiologically-based PK model (N01313) was developed to predict the doses to be tested in N01263. For subjects aged ≥8 years, the approximate doses to be administered are 0.4, 0.8, and 1.6mg/kg bid (0.8, 1.6, and 3.2 mg/kg/day corresponding to 50, 100, and 200mg/day in adults). For subjects aged <8 years, the approximate doses to be administered are 0.5, 1.0, and 2.0mg/kg bid (1.0, 2.0, and 4.0 mg/kg/day, respectively). Daily doses will be adjusted by body weight, but will not exceed maximums of 50mg/day, 100mg/day, and 200mg/day. The dose selection was based on the following observations in adult subjects:

- The PK of BRV is linear and of low variability in adults up to 1 order of magnitude above the therapeutic dose range.
- Efficacious doses in adults are expected to be from 50mg/day up to 200mg/day.
- Drug clearance is expected to be higher in children than in adults because of the physiologically based PK simulations.

In this LTFU study, subjects will start on the individual BRV dose that they had reached at the completion of the previous pediatric study (N01263 or any future pediatric study). Subjects entering this LTFU must be able to tolerate the minimum dose and not exceed the maximum dose from their previous pediatric study. The maximum dose allowed in this study will be 200mg/day.

Has been changed to:

N01266 will allow BRV long-term safety and tolerability data to be collected from pediatric subjects with epilepsy who will have participated in previous pediatric **BRV** studies and now have the opportunity to continue BRV treatment, **and from directly enrolled subjects with POS**. The safety and efficacy data collected in this study will support the applications for BRV indications in pediatric patients.

Each LTFU subject will begin treatment in N01266 at the individualized BRV dose he/she was receiving at the completion of the previous pediatric study. Directly enrolled subjects will participate in up to 3 weeks of an Up-Titration Period. If a subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV for 7±2 days during the Up-Titration Period, the subject will be allowed to enter the Evaluation Period (subject must be able to tolerate the minimum specified dose; see Section 7).

A physiologically-based PK model (N01313) was developed to predict the doses to be tested in N01263. **The same doses that were used for up titration in N01263 will be used for the**

3 consecutive weeks that comprise the Up-Titration Period of N01266. For subjects ≥8 years **of age**, the approximate doses to be administered 0.4, 0.8, and 1.6mg/kg bid (0.8, 1.6, and 3.2mg/kg/day**, respectively,** corresponding to 50, 100, and 200mg/day in adults) **for Weeks 1, 2, and 3 of up titration, respectively**. For subjects <8 years **of age**, the approximate doses to be administered are 0.5, 1.0, and 2.0mg/kg bid (1.0, 2.0, and 4.0mg/kg/day, respectively) **for Weeks 1, 2, and 3 of up titration, respectively**. Daily doses will be adjusted by body weight, but will not exceed maximums of 50mg/day, 100mg/day, and 200mg/day. The dose selection was based on the following observations in adult subjects:

- The PK of BRV is linear and of low variability in adults up to 1 order of magnitude above the therapeutic dose range.
- Efficacious doses in adults are expected to be from 50mg/day up to 200mg/day.
- Drug clearance is expected to be higher in children than in adults because of the physiologically based PK simulations.

Brivaracetam (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 previous BRV study to be eligible for entry into the Evaluation Period of N01266. This minimum tolerated BRV dose for LTFU subjects from N01263 is 0.8mg/kg/day if ≥8 years of age and 1.0mg/kg/day if <8 years of age. The same minimums apply to directly enrolled subjects.

The maximum allowable BRV dose in N01266 is 3.2mg/kg/day for subjects ≥8 years of age and 4.0mg/kg/day for subjects <8 years of age. Younger subjects (<7 years of age) will be administered BRV oral solution. Subjects above 50kg will be dosed as adults, up to a maximum total daily dose not exceeding 200mg/day, and should transition from the oral solution to the equivalent oral tablet dose, if appropriate.

The maximum **BRV** dose allowed in this study will be 200mg/day (**100mg bid), which is the maximum allowed dose for those subjects dosed as adults.**

Change #25, Section 6.1, Inclusion criteria

The original text:

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the parent(s) or legal representative(s). The Consent form or a specific Assent form, where required, will be signed and dated by minors.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.
3. Male or female subjects having participated in a previous pediatric study in epilepsy with BRV, and having access to the present study, and for whom a reasonable benefit from long-term administration of BRV is expected.

4. Female subjects without childbearing potential are eligible.
5. Female subjects with childbearing potential who are not sexually active are eligible. Subjects need to notify the Investigator if there is an anticipated change in status.
6. Female subjects with childbearing potential who are sexually active are eligible if they use a medically accepted contraceptive method. Oral or depot contraceptive treatment with at least ethinylestradiol 30µg per intake or ethinylestradiol 50µg per intake if associated with any strong inducer (eg, carbamazepine, phenobarbital, primidone, phenytoin, oxcarbazepine, St. John's Wort, rifampicin), a monogamous relationship with a vasectomized partner, or double-barrier contraception, are acceptable methods. The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the Investigator of any potential change in status.
7. Female subjects with childbearing potential must have a negative pregnancy test at the EV.

Has been changed to the following, which includes movement of some original criteria under new headers and the addition of new sections:

To be eligible to participate in this study, all of the following criteria must be met **as specified. Criteria that were in place before Protocol Amendment 3 have retained the previous numbering.**

6.1.1 Inclusion criteria for all subjects

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the parent(s) or legal representative(s). The Consent form or a specific Assent form, where required, will be signed and dated by minors.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.
4. Female subjects without childbearing potential are eligible.
5. Female subjects with childbearing potential who are not sexually active are eligible. Subjects need to notify the Investigator if there is an anticipated change in status.
6. Female subjects with childbearing potential who are sexually active are eligible if they use a medically accepted contraceptive method. Oral or depot contraceptive treatment with at least ethinylestradiol 30µg per intake or ethinylestradiol 50µg per intake if associated with any strong inducer (eg, carbamazepine, phenobarbital, primidone, phenytoin, oxcarbazepine, St. John's Wort, rifampicin), a monogamous relationship with a vasectomized partner, or double-barrier contraception, are acceptable methods. The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the Investigator of any potential change in status.
7. Female subjects with childbearing potential must have a negative pregnancy test.

6.1.2 Inclusion criteria for LTFU subjects only

3. Male or female subjects having participated in a previous pediatric study in epilepsy with BRV and for whom a reasonable benefit from long-term administration of BRV is expected.

6.1.3 Inclusion criteria for directly enrolled subjects only

8. Subject is a male or female ≥4 years to <17 years of age.

9. Subject has a clinical diagnosis of POS according to the ILAE classification.

10. Subject has an EEG compatible with the clinical diagnosis of POS.

11. Subject has been observed to have uncontrolled POS after an adequate course of treatment (in the opinion of the Investigator) with at least 1 AED (concurrently or sequentially).

12. Subject had at least 1 seizure (POS) during the 3 weeks before the ScrV.

13. Subject is taking at least 1 AED. All AEDs need to be at a stable dose for at least 7 days before the ScrV. Vagal nerve stimulator-stable for at least 2 weeks before the ScrV is allowed and will be counted as a concomitant AED. Benzodiazepines taken more than once a week (for any indication) will be considered as a concomitant AED.

Change #26, Section 6.2, Exclusion criteria

The original text:

Subjects are not permitted to enroll in the study if any of the following criteria is met:

1. Subject is a pregnant or nursing female.
2. Subject has developed hypersensitivity to any components of the investigational medicinal product (IMP) or comparative drugs as stated in this protocol during the course of the previous study.
3. Subject has severe medical, neurological, or psychiatric disorders or laboratory values, which may have an impact on the safety of the subject.
4. Subject had poor compliance with the visit schedule or medication intake in the previous BRV study.
5. Subject has planned participation in any clinical study of another investigational drug or device.
6. Subject has any medical condition, which in the Investigator's opinion, warrants exclusion.
7. Subject has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at the EV.

Has been changed to the following, with movement of some original criteria under new headers and the addition of new sections:

Subjects are not permitted to enroll in the study if any of the following criteria **are** met **as specified. Criteria that were in place before Protocol Amendment 3 have retained the previous numbering.**

6.2.1 Exclusion criteria for all subjects

1. Subject is a pregnant or nursing female.
3. Subject has severe medical, neurological, or psychiatric disorders or laboratory values, which may have an impact on the safety of the subject.
5. Subject has planned participation in any clinical study of another investigational drug or device.
6. Subject has any medical condition, which in the Investigator's opinion, warrants exclusion.

6.2.2 Exclusion criteria for LTFU subjects only

2. Subject has developed hypersensitivity to any components of the investigational medicinal product (IMP) or comparative drugs as stated in this protocol during the course of the previous **BRV** study.
4. Subject had poor compliance with the visit schedule or medication intake in the previous BRV study.
7. Subject has a lifetime history of suicide attempt (including an **actual** attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at the EV.

6.2.3 Exclusion criteria for directly enrolled subjects only

8. Subject has previously received BRV.

9. Subject had concomitant use of LEV at the ScrV. In addition, the use of LEV is prohibited for at least 4 weeks prior to the ScrV.

10. Subject has epilepsy secondary to a progressive cerebral disease or tumor, or any other progressively neurodegenerative disease. Stable arteriovenous malformations, meningiomas or other benign tumors may be acceptable according to Investigator's opinion.

11. Subject has a history of primary generalized epilepsy.

12. Subject has a history of status epilepticus in the month immediately prior to the ScrV or during the Up-Titration Period.

13. Subject has a history or presence of pseudoseizures.

14. Subject is suffering only from febrile seizures.

15. **Subject is on felbamate with less than 18 months continuous exposure. Subject who has taken felbamate for a combined duration of treatment and wash out of <18 months before the ScrV.**
16. **Subjects treated with vigabatrin who have visual field defects.**
17. **Subject has an allergy to pyrrolidone derivatives or investigational product excipients or a history of multiple drug allergies.**
18. **Subject has any clinically significant acute or chronic illness as determined during the physical examination or from other information available to the Investigator (eg, bone marrow depression, chronic hepatic disease, severe renal impairment, psychiatric disorder).**
19. **Subject has an underlying disease or is receiving a treatment that may interfere with the absorption, distribution, metabolism, and elimination of the study drug.**
20. **Subject has any medical condition that might interfere with his/her study participation (eg, serious infection or scheduled elective surgery).**
21. **Subject has a terminal illness.**
22. **Subject has any clinically significant deviations from reference range values for laboratory parameters as determined by the Investigator.**
23. **Subject has a clinically relevant ECG abnormality according to the Investigator.**
24. **Subject had major surgery within 6 months prior to the ScrV.**
25. **Subject received any investigational drug or device within the 30 days prior to the ScrV. The use of AEDs marketed for adults but not approved for pediatric use is not considered to be "investigational" for the purposes of this study.**
26. **Investigators' and co-Investigators' children may not be included as subjects in the study.**
27. **Subject has impaired hepatic function:**
    - **Alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alkaline phosphatase of more than 2x the upper limit of normal (ULN), or total bilirubin of more than 2xULN.**
    - **Gamma-glutamyltransferase (GGT) values of more than 3xULN. A result of GGT exceeding 3xULN can be accepted only if attributable to hepatic enzyme induction caused by concomitant antiepileptic treatment and if other hepatic enzymes are below 2xULN.**
28. **Subject has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the C-SSRS-Baseline/Screening at the ScrV.**

Change #27, Section 6.3, Withdrawal criteria, criterion 9, 10, and 11

The original text:

9. Subject has the following findings based on liver function tests (LFT):
    - If the subject has LFT results of transaminases (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]) ≥3x the upper limit of normal (ULN) to <5xULN or total bilirubin ≥2xULN, the measurements will be repeated within a few days. If the repeat testing confirms the abnormality (eg, transaminases are ≥3xULN to <5xULN), then monitoring of LFTs should continue at subsequent study visits until resolved (eg, <3xULN or stable condition). The Investigator is to decide whether or not to stop the study medication.
    - If the subject has LFT results of transaminases (AST and/or ALT) ≥5xULN, study medication should be tapered off immediately and the subject must be withdrawn from the study.
10. Criteria for subjects who completed a C-SSRS assessment at the EV:
    - Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.
11. Criteria for already enrolled subjects who did not complete a C-SSRS assessment at the EV:
    - Subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt) of the "Already Enrolled Subjects" version of the C-SSRS. The Investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional.
    - Subject had active suicidal ideation prior to study entry or since study start as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Already Enrolled Subjects" version of the C-SSRS. The Investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the subject from the study.
    - Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Has been changed to:

9. Subject has the following findings based on liver function tests (LFT):
    - If the subject has LFT results of transaminases (AST and/or ALT) ≥3x the upper limit of normal (ULN) to <5xULN or total bilirubin ≥2xULN, the measurements will be repeated within a few days. If the repeat testing confirms the abnormality (eg, transaminases are ≥3xULN to <5xULN), then monitoring of LFTs should continue at subsequent study visits until resolved (eg, <3xULN or stable condition). The Investigator is to decide whether or not to stop the study medication.
    - If the subject has LFT results of transaminases (AST and/or ALT) ≥5xULN, study medication should be tapered off immediately and the subject must be withdrawn from the study.
10. Criteria for subjects who completed a C-SSRS assessment at the **final visit of the previous BRV study (LTFU subjects) or at the ScrV (directly enrolled subjects)**:
    - Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.
11. Criteria for subjects who **become 6 years of age during N01266 and for whom the "Already Enrolled Subjects" version of the C-SSRS was completed at the first visit after the sixth birthday**:
    - Subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an **actual** attempt, interrupted attempt, or aborted attempt) of the "Already Enrolled Subjects" version of the C-SSRS. The Investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional.
    - Subject had active suicidal ideation prior to study entry or since study start as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Already Enrolled Subjects" version of the C-SSRS. The Investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the subject from the study.
    - Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Change #28, Section 7.2, Treatments to be administered, paragraphs 1 through 4

The original text:

At study entry (EV), subjects will ordinarily start on the individualized BRV dose that they had reached at the completion of the previous study.

Subjects entering this study from N01263 must be able to tolerate at least 0.4mg/kg of BRV bid if ≥8 years of age or at least 0.5mg/kg if <8 years of age. The maximum BRV dose for subjects ≥8 years of age is 3.2mg/kg/day and 4.0mg/kg/day for subjects <8 years of age. Subjects above 50kg will be dosed as adults, up to a maximum total daily dose not exceeding 200mg/day, and should transition from the oral solution to the equivalent oral tablet dose, unless the subject's condition prevents him/her from swallowing oral tablets. Subjects <7 years of age should not transition to oral tablet treatment. Oral solution should not be mixed with other liquids prior to administration.

The maximum dose allowed in this study is 200mg/day, given bid in 2 equally divided doses.

The mg dosage for the oral tablet treatment should be calculated to match as closely as possible the mg/kg oral solution treatment and should be a combination of the BRV 10mg, 25mg, and 50mg tablets (given bid in 2 equally divided doses). Only the following exact dosages are allowed for the oral tablet administration: BRV 20, 40, 50, 70, 100, 150, and 200mg/day. Subjects should be dosed with either oral tablets or oral solution and not a combination of both.

Has been changed to:

The LTFU subjects will ordinarily start **dosing** on the individualized BRV dose **they were receiving** at the completion of the previous **pediatric BRV** study. **The directly enrolled subjects will participate in an Up-Titration Period as described in Section 7.2.1 before entry into the Evaluation Period.**

The LTFU subjects must be able to tolerate the minimum BRV dose specified in their previous study to be eligible for entry into the Evaluation Period of N01266. For subjects entering **N01266** from N01263**, the minimum BRV dose is** 0.**8mg**/kg/**day** if ≥8 years of age or at least **1.0**mg/kg/**day** if <8 years of age; **directly enrolled subjects must also tolerate at least these dosages for 7±2 days during the Up-Titration Period before entry into the Evaluation Period.**

The maximum BRV dose for subjects ≥8 years of age is 3.2mg/kg/day and 4.0mg/kg/day for subjects <8 years of age. Subjects above 50kg will be dosed as adults, up to a maximum total daily dose not exceeding 200mg/day, and should transition from the oral solution to the equivalent oral tablet dose, unless the subject's condition prevents him/her from swallowing oral tablets. Subjects <7 years of age should not transition to oral tablet treatment. Oral solution should not be mixed with other liquids prior to administration.

The maximum dose allowed in this study is 200mg/day (**100mg bid**).

Brivaracetam should be given bid approximately 12 hours apart in 2 equally divided doses. The mg dosage for the oral tablet treatment should be calculated to match as closely as possible the mg/kg**-based dosage** and should be a combination of the BRV 10mg, 25mg, and 50mg tablets. Only the following exact dosages are allowed for the oral tablet administration: BRV 20, 40, 50, 70, 100, 150, and 200mg/day. Subjects should be dosed with either oral tablets or oral solution and not a combination of both.

Change #29, Section 7.2, Treatments to be administered, paragraph 6

The original text:

All subjects who prematurely discontinue the study, should complete an EDV and have their BRV dose down titrated by a maximum of half the dose every week until a dose of 1.0mg/kg/day is reached.

Has been changed to:

All subjects who prematurely discontinue the study should complete an EDV and have their BRV dose down titrated by a maximum of half the dose every week until a dose of 1.0mg/kg/day is reached **for subjects <8 years of age or until a dose of 0.8mg/kg/day is reached for subjects ≥8 years of age**.

Change #30, Section 7.2, Treatments to be administered

The following section has been added:

7.2.1 Up-Titration Period for directly enrolled subjects

Beginning with Protocol Amendment 3, at TV1, eligible directly enrolled subjects will initiate treatment with BRV (oral solution or tablet, as chosen by the Investigator and subject/caregiver).

The BRV dose will be titrated to optimize tolerability and seizure control. Table 7-1 provides the recommended titration steps for the oral solution and tablet formulations. Subjects must be on the same daily dose for 7±2 days before the dose is titrated to the next dosing level. 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. Fewer than 3 TVs may be needed before entry into the Evaluation Period, depending on the BRV dose at which acceptable tolerability and seizure control is demonstrated.

Based on tolerability and seizure control, a subject's BRV dose may be reduced to no lower than the age-designated minimum dose indicated in Table 7-1. If a subject had previously received the reduced BRV dose for 7±2 days with acceptable tolerability and seizure control, then the subject may enter directly into the Evaluation Period.

Table 7-1: Recommended BRV dosing schedule for directly enrolled subjects during the Up-Titration Period

Visit (Week)	BRV dose per dosing occasion (mg/kg)		BRV dose per day (mg/kg/day)	
	≥8 years	<8 years	≥8 years	<8 years
TV1 (1)	~0.4	~0.5	~0.8	~1.0
TV2 (2)	~0.8	~1.0	~1.6	~2.0
TV3 (3)	~1.6	~2.0	~3.2	~4.0

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

Change #31, Section 7.7, Procedures for monitoring subject compliance, paragraph 1

The original text:

The IMP (oral solution or oral tablets) will be supplied to the subject/parent(s)/legal representative(s) at the EV, MEV, FEV, YEV, and at the EDV in the case of early discontinuation.

Has been changed to:

The IMP (oral solution or oral tablets) will be supplied to the subject/parent(s)/legal representative(s) at the **TV(s) (directly enrolled subjects only),** EV, MEV, FEV, YEV, and at the EDV in the case of early discontinuation.

Change #32, Section 7.7, Procedures for monitoring subject compliance, paragraph 5

The original text:

Study drug compliance will be assessed at the MEV, FEV, YEV, FV, and at the EDV and the Down-Titration Visit (DTV) in the case of early discontinuation.

Has been changed to:

Study drug compliance will be assessed at the **TV(s) and EV (directly enrolled subjects only),** MEV, FEV, YEV, FV, and at the EDV and the Down-Titration Visit (DTV) in the case of early discontinuation.

Change #33, Section 7.8, Concomitant medications/treatments, paragraphs 1 through 3

The original text:

For any treatment other than the IMP, including over-the-counter products, an accurate record, must be kept in the clinic chart (source documentation) and in the eCRF.

Ongoing medications at the time the subject completed the previous pediatric study, should not be recorded on the eCRF at the EV, unless there is a change regarding the administration of the medication. In this event, the start date corresponding to the date of change in administration should be recorded on the eCRF.

All changes in concomitant AEDs and nonAEDs will be recorded on the AED or nonAED concomitant medication page in the eCRF, respectively. This record should include the name of the drug (preferably the brand name), the dose, the date(s) of administration, and the indication for use.

Has been changed to:

For any treatment other than the IMP, including over-the-counter products, an accurate record must be kept in the clinic chart (source documentation) and in the eCRF.

For LTFU subjects, ongoing medications at the time the subject completed the previous pediatric **BRV** study should not be recorded **in** the eCRF at the EV**, or any subsequent visit**,

unless there is a change regarding the administration of the medication. **For directly enrolled subjects, all concomitant medications should be recorded in the eCRF at the ScrV and subsequently be recorded only if there is a change regarding the administration of the medication. For all subjects, new medications should be recorded in the eCRF at only the first visit at which they are reported and subsequently only if there is a change. For any change**, the start date corresponding to the date of change in administration should be recorded **in** the eCRF.

For all subjects, all changes in concomitant AEDs and non-AEDs will be recorded on the AED or non-AED concomitant medication page**, respectively,** in the eCRF This record should include the name of the drug (preferably the brand name), the dose, the date(s) of administration, and the indication for use.

Change #34, Section 7.8.1.1, Permitted concomitant medications

The following text has been added:

Levetiracetam is allowed after the EV.

Felbamate is allowed as follows:

- **LTFU subjects:**
  - **At the established dose if a stable dose was maintained during the previous pediatric BRV study**
- **Directly enrolled subjects:**
  - **At a stable dose during the Screening and Up-Titration Periods**
  - **At the established dose from the EV onwards if a stable dose was maintained during the Screening and Up-Titration Periods**

Change #35, Section 7.8.2, Prohibited concomitant medications

The original text:

The following concomitant AED medication is prohibited during the study:

- Felbamate (except if on a stable dose during the previous study)

Has been changed to:

The following concomitant AED medication is prohibited during the study:

- **LTFU subjects:**
  - Felbamate (except if on a stable dose during the previous pediatric BRV study)
- **Directly enrolled subjects:**
  - **Felbamate (except if on a stable dose during the Screening and Up-Titration Periods)**
  - **LEV (from the ScrV until the EV)**

Change #36, Section 7.9, Blinding

The original text:

This is an open-label LTFU study and therefore, no blinding is required.

Has been changed to:

This is an open-label study and therefore, no blinding is required.

Change #37, Section 7.10, Randomization and numbering of subjects

The original text:

Subjects will not be randomized in this study, as each subject will start on the individualized BRV dose that they had reached at the completion of the previous study.

To enroll a subject (EV, V1), the Investigator will call the IVRS and provide brief details about the subject to be enrolled. Subjects will continue with the 5-digit subject number assigned by the IVRS in the previous pediatric study. The subject number will be required in all communication between the Investigator (or designee) and the IVRS regarding a particular subject. Subjects' status and the dispensing of IMP (bottle numbers) will be tracked via the IVRS.

Has been changed to:

Subjects will not be randomized in this study, as each **LTFU** subject will start on the individualized BRV dose that **he/she was receiving** at the completion of the previous study**, and directly enrolled subjects will start the Evaluation Period on the dose established during the Up-Titration Period**.

To enroll a **LTFU** subject (EV, V1), the Investigator will call the IVRS and provide brief details about the subject to be enrolled. Subjects will continue with the 5-digit subject number assigned by the IVRS in the previous pediatric **BRV** study.

Directly enrolled subjects will be assigned unique numbers for the purpose of study and subject identification, as well as for subject confidentiality. To enroll these subjects, at the ScrV, the Investigator will call the IVRS and provide information about the subject to be enrolled. Subjects will then be assigned a 5-digit subject number by the IVRS.

For all subjects, the subject number will be required in all communication between the Investigator (or designee) and the IVRS regarding a particular subject. Subjects' status and the dispensing of IMP (bottle numbers) will be tracked via the IVRS.

Change #38, Section 8, STUDY PROCEDURES BY VISIT, paragraph 1, final sentence

The original text:

Additionally, if applicable (according to subject's age and local requirements), the subject will sign an IRB/IEC Assent form.

Has been changed to:

Additionally, if applicable (according to subject's age and local requirements), the subject will sign an IRB/IEC**-approved** Assent form.

Change #39, Section 8, STUDY PROCEDURES BY VISIT

The following sections were added and the subsequent numbering of headers in this section increased accordingly:

8.1 Screening Visit for directly enrolled subjects only

The ScrV is applicable only to directly enrolled subjects (ie, subjects ≥4 years to <17 years of age with POS who have not previously participated in a pediatric BRV study). Beginning with Protocol Amendment 3, up to 100 directly enrolled subjects will be allowed to participate in N01266. The Screening Period will serve as the Baseline Period for directly enrolled subjects.

The ScrV is not applicable for LTFU subjects; the first N01266 visit for LTFU subjects is the Entry Visit (Section 8.3.1).

The ScrV assessments will be conducted 7±2 days prior to the first administration of BRV. It is acceptable for the ScrV assessments to be conducted on more than 1 day.

The ScrV assessments are as follows:

- **Signing and dating of written Informed Consent by parent(s)/legal representative(s)**
- **Signing and dating of Assent form by the subject (if applicable, according to age and local requirements)**
- **Subject identification card dispensing**
- **Demographic data**
- **Childbearing potential**
- **Verification of inclusion/exclusion criteria**
- **Physical (including Tanner Scale, as applicable) and neurological (including measurement of head size) examinations**
- **Psychiatric and mental status**
- **General medical and procedures history**
- **Epilepsy and AED history**
- **Vital signs (blood pressure, pulse rate, and body temperature)**
- **Body weight and height**
- **ECG**
- **EEG (A previous EEG documenting the POS diagnosis must be available at the ScrV for directly enrolled subjects. If an EEG is not available at the ScrV, it must be scheduled during the Screening Period.)**

- **Neuro-imaging procedure (brain magnetic resonance imaging/brain computerized tomography scan [except in Germany]/ultrasounds or any other imaging test) should be performed if no report is available within the previous 2 years**
- **DRC dispensed**
- **Recording of medications**
- **Recording of procedures**
- **Recording of AEs**
- **IVRS call**
- **Laboratory assessments for safety including:**
  - **Hematology**
  - **Biochemistry including hepatic monitoring**
  - **Urinalysis**
  - **Endocrinology**
  - **Serum pregnancy test (if applicable)**
- **Phenytoin plasma concentrations (if applicable)**
- **Suicidality assessment (C-SSRS-Baseline/Screening) (for subjects ≥6 years of age)**
- **Achenbach CBCL (version consistent with age at the visit)**
- **BRIEF-P (<5 years of age)/BRIEF (≥5 years of age) (version consistent with age at the visit)**
- **PedsQL (version consistent with age at the visit)**
- **Appointment for the next visit (TV1) 7±2 days later**

8.2 Titration Visit(s) (TV1, TV2, and TV3) for directly enrolled subjects only

Directly enrolled subjects will initiate treatment with BRV at TV1 (see Section 7.2.1 for dosing information). The TVs are not applicable for LTFU subjects; the first visit in N01266 for these subjects is the EV (Section 8.3.1).

The first dose of BRV at each titration level will be administered at the clinic during the TV. Subjects will remain on the BRV dose administered at the clinic for 7±2 days before titrating up to the next dose. The BRV up-titration schedule is provided in Section 7.2.1.

A total of up to 3 TVs may be required; however, based on tolerability and seizure control, a subject's BRV dose may be titrated to a lower dose level and 3 TVs would not be needed.

The following assessments are required at each TV:

- **Verification of inclusion/exclusion criteria (TV1 only)**

- **Vital signs (blood pressure, pulse rate, and body temperature)**
- **Body weight**
- **ECG**
- **DRC dispensed**
- **DRC retrieved**
- **Seizure count**
- **Recording of medications**
- **Recording of procedures**
- **Recording of AEs**
- **IVRS call**
- **Hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT (TV3 only unless the Investigator anticipates that TV2 will be the final TV, in which case hepatic monitoring assessments are to be done at TV2)**
- **Study drug dispensed**
- **Study drug returned (TV2 and TV3 only)**
- **Study drug compliance (TV2 and TV3 only)**
- **Suicidality assessment (C-SSRS) (for subjects ≥6 years of age)**
- **Healthcare provider consultation not foreseen by the protocol**
- **Hospital stays**
- **Appointment for the next visit 7±2 days later**

Change #40, Section 8.1, Entry Visit

The original section:

8.1 Entry Visit

- Signing and dating of written Informed Consent by parent(s)/legal representative(s)
- Signing and dating of Assent form by the subject (if applicable, according to age and local requirements)
- Subject identification card dispensing
- Demographic data
- Childbearing potential
- Verification of inclusion/exclusion criteria
- DRC dispensed
- Recording of medications

Any ongoing medications (AEDs and nonAEDs) at the time the subject completed the previous pediatric study should not be recorded on the eCRF for N01266, unless there is a change regarding the administration of the medication. In this event, the start date corresponding to the date of change in administration should be recorded on the eCRF.

- Recording of procedures
- Recording of AEs

Any ongoing AEs at the time the subject completed the previous pediatric study should not be recorded on the eCRF for N01266, unless there is a change in intensity or seriousness. In this event, the AE should be recorded on the eCRF for N01266, with the onset date corresponding to the date of change in condition.

- IVRS call
- Study drug dispensed
- Appointment for the next visit according to the schedule described in Section 5.3

The EV is also the final evaluation visit of the previous pediatric study. The following data will be obtained from Baseline of the previous pediatric study and should not be recorded on the eCRF for N01266:

- General medical and procedures history
- Epilepsy history
- AED history
- Height
- Bayley-III scales for subjects <18 months of age at Baseline of N01263 or other pediatric studies and only for subjects enrolled in English-speaking countries
- Achenbach CBCL score for subjects ≥18 months of age at Baseline of N01263

The following data will be obtained from the last visit of the previous pediatric study and should not be recorded on the eCRF for N01266:

- Seizure count
- EEG
  - For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: an EEG of at least 1 hour of recording (including hyperventilation and intermittent photic stimulation) must be performed
  - For subjects ≥1 month to <2 years of age on the day of the study visit: an EEG of at least 24 hours of recording (including sleeping and awakening periods) must be performed
- ECG
- Laboratory assessments for safety (including hepatic monitoring)

- Suicidality assessment (C-SSRS) for subjects ≥6 years of age
- Phenytoin plasma concentrations (if applicable)
- Vital signs
- Body weight
- Physical examination
- Neurological examination
- Psychiatric and mental status
- Health care provider consultations not foreseen by the protocol
- Hospital stays

Has been changed to (with addition of third-level section headers and reorganization of the EV for LTFU subjects):

8.3 Entry Visit

At the EV, the progress of directly enrolled subjects will become aligned with LTFU subjects; for all subjects, the EV is the time of entry into the Evaluation Period. For LTFU subjects, the EV is the first visit in N01266. For directly enrolled subjects, the EV will occur after subjects have attended the ScrV and at least 1 TV and achieved, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than the minimum specified dose) for 7±2 days.

8.3.1 LTFU subjects

- Signing and dating of written Informed Consent by parent(s)/legal representative(s)
- Signing and dating of Assent form by the subject (if applicable, according to age and local requirements)
- Subject identification card dispensing
- **DRC dispensed**
- **Verification of inclusion/exclusion criteria**
- **IVRS call**
- **Study drug dispensed**
- **Recording of medications (Any ongoing medications [including AEDs and non-AEDs] at the time the subject completed the previous pediatric BRV study should not be recorded in the eCRF for N01266, unless there is a change regarding the administration of the medication. In this event, the start date corresponding to the date of change in administration should be recorded in the eCRF.)**
- **Recording of AEs (Any ongoing AEs at the time the subject completed the previous pediatric BRV study should not be recorded in the eCRF for N01266, unless there is a change in intensity or seriousness. In this event, the AE should be recorded in the**

eCRF for N01266, with the onset date corresponding to the date of change in condition.)

- **Appointment for the next visit according to the schedule described in Section 5.3**

The following data will be obtained from Baseline of the previous pediatric BRV study and should not be recorded in the eCRF for N01266:

- **Demographic data**
- **General medical and procedures history**
- **Epilepsy history**
- **AED history**
- **Height**
- **Bayley-III scales (for LFTU subjects <18 months of age at Baseline of N01263 or other pediatric BRV studies and only for subjects enrolled in English-speaking countries)**
- **Achenbach CBCL score (see Section 10.3.3)**
- **Laboratory assessments**
  - **Endocrinology**

The following data will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266:

- **Childbearing potential**
- **Recording of medications**
- **Recording of procedures**
- **Seizure count**
- **EEG**
  - **For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: an EEG of at least 1 hour of recording (including hyperventilation and intermittent photic stimulation) must be performed**
  - **For subjects ≥1 month to <2 years of age on the day of the study visit: an EEG of at least 24 hours of recording (including sleeping and awakening periods) must be performed**
- **ECG**
- **Laboratory assessments for safety**
  - **Hematology**
  - **Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)**

  - **Urinalysis (for subjects ≥4 years of age)**
  - **Urine pregnancy test (if applicable)**
- **Phenytoin plasma concentrations (if applicable)**
- **Suicidality assessment (C-SSRS) (for subjects ≥6 years of age)**
- **Vital signs**
- **Body weight**
- **Physical examination**
- **Neurological examination**
- **Psychiatric and mental status**
- **Health care provider consultations not foreseen by the protocol**
- **Hospital stays**

8.3.2 Directly enrolled subjects

Directly enrolled subjects will finish the Up-Titration Period and attend the EV when the same BRV dose (no lower than the minimum specified dose) has been maintained for 7±2 days at a level that, in the opinion of the Investigator, achieves acceptable tolerability and seizure control.

- **Childbearing potential**
- **Physical examination**
- **Neurological examination**
- **Psychiatric and mental status**
- **Vital signs (blood pressure, pulse rate, and body temperature)**
- **Body weight and height**
- **DRC dispensed**
- **DRC retrieved**
- **Recording of medications**
- **Recording of procedures**
- **Recording of AEs**
- **ECG**
- **Seizure count**
- **IVRS call**
- **Study drug dispensed**
- **Study drug returned**

- **Study drug compliance**
- **Laboratory assessments for safety**
  - **Hematology**
  - **Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)**
  - **Urinalysis**
  - **Urine pregnancy test (if applicable)**
- **Suicidality assessment (C-SSRS) (for subjects ≥6 years of age)**
- **Health care provider consultations not foreseen by the protocol**
- **Hospital stays**
- **Appointment for the next visit according to the schedule described in Section 5.3**

Change #41, Section 8.2, Minimal Evaluation Visit

The following original bullets:

- Liver function tests will be performed at V4 (M3) and V6 (M9) as described in Section 9.5.1
- EEG
- Suicidality assessment (C-SSRS) for subjects ≥6 years of age

Have been changed to:

- **Hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT** (performed **only** at V4 **[**M3**]** and V6 **[**M9**]**)
- EEG **(LTFU subjects only)**
- Suicidality assessment (C-SSRS) **(**for subjects ≥6 years of age**)**

Change #42, Section 8.3, Full Evaluation Visit

The following original bullets:

- Suicidality assessment (C-SSRS) for subjects ≥6 years of age
- Laboratory assessments for safety (hematology and biochemistry including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT for all subjects, and urinalysis for subjects ≥4 years of age)
- Bayley-III scales for subjects <18 months of age at Baseline of N01263 or other pediatric studies and only for subjects enrolled in English-speaking countries
- Achenbach CBCL (the version used in this study, CBCL/1½-5 or CBCL/6-18, should be the same as the one used in the previous study)

Have been changed to:

- Suicidality assessment (C-SSRS) **(**for subjects ≥6 years of age**)**
- Laboratory assessments for safety
  - **Hematology**
  - **Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)**
  - **Urinalysis (for subjects ≥4 years of age)**
  - **Urine pregnancy test (if applicable)**
- Bayley-III scales **(**for **LTFU** subjects <18 months of age at Baseline of N01263 or other pediatric **BRV** studies and only for subjects enrolled in English-speaking countries**)**
- **Achenbach CBCL (see Section 10.3.3)**

The following bullets have been added:

- **BRIEF-P (<5 years of age)/BRIEF (≥5 years of age) (see Section 9.6.8)**
- **PedsQL (see Section 10.3.5)**

Change #43, Section 8.4, Yearly Evaluation Visit

The following original bullets:

- Suicidality assessment (C-SSRS) for subjects ≥6 years of age
- Laboratory assessments for safety (hematology, biochemistry including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT, and endocrinology for all subjects, and urinalysis for subjects ≥4 years of age)
- Bayley-III scales for subjects <18 months of age at Baseline of N01263 or other pediatric studies and only for subjects enrolled in English-speaking countries
- Achenbach CBCL (the version used in this study, CBCL/1½-5 or CBCL/6-18, should be the same as the one used in the previous study, if age appropriate)

Have been changed to (and now appear in Section 8.6, Yearly Evaluation Visit):

- Suicidality assessment (C-SSRS) **(**for subjects ≥6 years of age)
- Laboratory assessments for safety
  - **Hematology**
  - **Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)**
  - **Urinalysis (for subjects ≥4 years of age)**
  - **Urine pregnancy test (if applicable)**
  - **Endocrinology**

- Bayley-III scales **(**for **LTFU** subjects <18 months of age at Baseline of N01263 or other pediatric **BRV** studies and only for subjects enrolled in English-speaking countries**)**
- Achenbach CBCL **(see Section 10.3.3)**

The following bullets have been added (and now appear in Section 8.6, Yearly Evaluation Visit):

- **BRIEF-P (<5 years of age)/BRIEF (≥5 years of age) (see Section 9.6.8)**
- **PedsQL (see Section 10.3.5)**

Change #44, Section 8.6, Early Discontinuation Visit

The following original bullets:

- Suicidality assessment (C-SSRS) for subjects ≥6 years of age
- Laboratory assessments for safety (hematology, biochemistry including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT, and endocrinology for all subjects, and urinalysis for subjects ≥4 years of age)
- Bayley-III scales for subjects <18 months of age at Baseline of N01263 or other pediatric studies and only for subjects enrolled in English-speaking countries
- Achenbach CBCL (the version used in this study, CBCL/1½-5 or CBCL/6-18, should be the same as the one used in the previous study, if age appropriate)

Have been changed to (and now appear in Section 8.8, Early Discontinuation Visit)

- Suicidality assessment (C-SSRS) **(**for subjects ≥6 years of age**)**
- Laboratory assessments for safety
  - **Hematology**
  - **Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)**
  - **Urinalysis (for subjects ≥4 years of age)**
  - **Serum pregnancy test (if applicable)**
- Bayley-III scales **(**for **LTFU** subjects <18 months of age at Baseline of N01263 or other pediatric **BRV** studies and only for subjects enrolled in English-speaking countries**)**
- Achenbach CBCL (**see Section 10.3.3**)

The following bullets have been added (and now appear in Section 8.8, Early Discontinuation Visit):

- **BRIEF-P (<5 years of age)/BRIEF (≥5 years of age) (see Section 9.6.8)**
- **PedsQL (see Section 10.3.5)**

Change #45, Section 8.7, Down-Titration Visit

The following original bullet:

- Suicidality assessment (C-SSRS) for subjects ≥6 years of age

Has been changed to:

- Suicidality assessment (C-SSRS) **(**for subjects ≥6 years of age**)**

Change #46, Section 8.8, Safety Visit

The following original bullets:

- Suicidality assessment (C-SSRS) for subjects ≥6 years of age
- Laboratory assessments for safety (hematology, biochemistry including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT, and endocrinology for all subjects, and urinalysis for subjects ≥4 years of age) performed only if abnormal at the EDV

Have been changed to (and now appear in Section 8.10, Safety Visit):

- Suicidality assessment (C-SSRS) **(**for subjects ≥6 years of age**)**
- Laboratory assessments for safety **(to be performed only if abnormal at the EDV)**
  - **Hematology**
  - **Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)**
  - **Urinalysis (for subjects ≥4 years of age)**
  - **Serum pregnancy test (if applicable)**

Change #47, Section 8.9, Final Visit

The following text and original bullets:

Subjects, who continue in the study until it ends, should complete a FV.

- Suicidality assessment (C-SSRS) for subjects ≥6 years of age
- Laboratory assessments for safety (hematology, biochemistry including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT, and endocrinology for all subjects, and urinalysis for subjects ≥4 years of age).
- Bayley-III scales for subjects <18 months of age at Baseline of N01263 or other pediatric studies and only for subjects enrolled in English-speaking countries
- Achenbach CBCL (the version used in this study, CBCL/1½-5 or CBCL/6-18, should be the same as the one used in the previous study, if age appropriate)

Have been changed to (and now appear in Section 8.11, Final Visit):

Subjects who continue in the study until it ends should complete a FV.

- Suicidality assessment (C-SSRS) **(**for subjects ≥6 years of age**)**
- Laboratory assessments for safety
  - **Hematology**
  - **Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)**
  - **Urinalysis (for subjects ≥4 years of age)**
  - **Urine pregnancy test (if applicable)**
  - **Endocrinology**
- Bayley-III scales **(**for **LTFU** subjects <18 months of age at Baseline of N01263 or other pediatric **BRV** studies and only for subjects enrolled in English-speaking countries**)**
- Achenbach CBCL (**see Section 10.3.3**)

The following bullets have been added (and now appear in Section 8.11, Final Visit):

- **BRIEF-P (<5 years of age)/BRIEF (≥5 years of age) score (see Section 9.6.8)**
- **PedsQL (see Section 10.3.5)**

Change #48, Section 9, ASSESSMENT OF SAFETY, first sentence

The original text:

The safety variables will be evaluated during the Evaluation Period.

Has been changed to:

The safety variables will be evaluated during the **Up-Titration Period (directly enrolled subjects only) and the** Evaluation Period.

Change #49, Section 9.1.2, Procedures for reporting and recording adverse events

The following paragraph has been added to the end of the section:

For LTFU subjects, AEs ongoing at the time the subject completed the previous pediatric BRV study should not be recorded in the eCRF at the EV, or any subsequent visit, unless there is a change in intensity or seriousness. For all subjects, new AEs should be recorded in the eCRF at only the first visit at which they are reported and subsequently only if there is a change.

Change #50, Section 9.1.6, Pregnancy, first sentence

The original text:

Should a subject become pregnant after the first intake of any IMP, UCB's Global Clinical Safety and Pharmacovigilance (GCSP) department should be informed immediately.

Has been changed to:

Should a subject become pregnant after the first intake of any IMP, UCB's **Drug Safety** department should be informed immediately.

Change #51, Section 9.1.8, Safety signal detection, paragraph 2

The original text:

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the GCSP representative.

Has been changed to:

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the **Drug Safety** representative.

Change #52, Section 9.2, Serious adverse events

The following text was added immediately under the header:

A blood sample for determination of BRV plasma concentration should be obtained for any subject who has an SAE.

Change #53, Section 9.2.3, Follow-up of serious adverse events, paragraph 2

The original text:

Information on SAEs obtained after clinical database lock will be captured through the GCSP database without limitation of time.

Has been changed to:

Information on SAEs obtained after clinical database lock will be captured through the **Drug Safety** database without limitation of time.

Change #54, Section 9.5.1, Laboratory assessments for safety

The following have been added to the list of abbreviations under the table:

ScrV=Screening Visit; TV=Titration Visit

The original footnotes:

[a] Urinalysis will be performed in subjects ≥4 years of age.
[b] In addition, liver function tests will be assessed at the MEVs at V4 (M3) and V6 (M9), as described in Section 9.5..1.
[c] Includes bacteria, cells, casts, and crystals for all samples.

[d] Female subjects with a Tanner stage >1 should have a urine pregnancy test at all laboratory assessment visits, except the EDV and the SV, when a serum pregnancy test will be performed.
[e] Endocrinology testing will be performed once a year at the YEV.

Have been changed to:

[a] Urinalysis will be performed in subjects ≥4 years of age.
[b] **This assessment is used for hepatic monitoring.**
[c] Includes bacteria, cells, casts, and crystals for all samples.
[d] Female subjects with a Tanner stage >1 should have urine pregnancy test**s at the EV (directly enrolled subjects only), YEVs/FV, and FEVs and serum pregnancy tests at the ScrV (directly enrolled subjects only), EDV, and SV.**
[e] Endocrinology testing will be performed **at the ScrV (directly enrolled subjects only) and** at the YEV/**FV**.

Change #55, Section 9.5.1, Laboratory assessments for safety, paragraphs 5 and 6

The original text:

Laboratory safety assessments at the EV will be obtained from the last visit of the previous pediatric study and should not be recorded on the eCRF for N01266. Laboratory safety assessments will be performed at the FEV, YEV, FV, and at the EDV in the case of early discontinuation. Laboratory assessments will also be mandatory at the SV if the laboratory results at the EDV are abnormal. In addition, liver function tests will be performed at the MEVs at V4 (M3) and V6 (M9) during the first year. Endocrinology testing will be performed once a year at the YEV.

Female subjects who have a Tanner stage >1 should have a urine pregnancy test at all laboratory assessment visits, except the EDV and the SV, when a serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) will be performed. A serum pregnancy test will be performed as backup if a urine sample is not available. A urine pregnancy test should be performed at any time during the study if a pregnancy is suspected.

Has been changed to:

For LTFU subjects, laboratory safety assessments at the EV will be obtained from the **final** visit of the previous pediatric **BRV** study and should not be recorded **in** the eCRF for N01266. Laboratory safety assessment**s (hematology, biochemistry [including hepatic monitoring: total bilirubin, ALP, AST, ALT, and GGT], urinalysis [for subjects ≥4 years of age, and pregnancy testing [as applicable])** will be performed at the **ScrV and EV (directly enrolled subjects only),** FEV, YEV, FV, and at the EDV in the case of early discontinuation. Laboratory assessments will also be mandatory at the SV if the laboratory results at the EDV are abnormal. **Only hepatic monitoring assessments will be performed at the final TV (directly enrolled subjects only), and** the MEVs at V4 (M3) and V6 (M9) **during the first year; no laboratory safety assessments will be performed at other MEVs.** Endocrinology testing will be performed a**t the ScrV (directly enrolled subjects only) and** once a year at the YEV. **For LTFU subjects, the Baseline endocrinology data will be taken from Baseline of the previous pediatric BRV study.**

Female subjects who have a Tanner stage >1 should have urine pregnancy test**s** at **the EV (directly enrolled subjects only), YEVs/FV, and FEVs,** and serum pregnancy test**s** at the **ScrV (directly enrolled subjects only),** EDV, and the SV. A serum pregnancy test will be

performed as backup if a urine sample is not available. A urine pregnancy test should be performed at any time during the study if a pregnancy is suspected.

Change #56, Section 9.5.2.1, BRV plasma concentrations, paragraph 2

The original text:

A PK blood sample should be taken whenever the subject experiences an SAE.

Has been changed to:

A blood sample **for determination of BRV plasma concentration** should be taken whenever the subject experiences an SAE.

Change #57, Section 9.5.2.2, Phenytoin plasma concentrations (if applicable), sentence 1

The original text:

Subjects receiving phenytoin as a concomitant AED during the study will have blood samples collected at the FEV, YEV, FV, and at the EDV in the case of early discontinuation to monitor phenytoin plasma concentrations.

Has been changed to:

Subjects receiving phenytoin as a concomitant AED during the study will have blood samples collected at the **ScrV (directly enrolled subjects only),** FEV, YEV, FV, and at the EDV in the case of early discontinuation to monitor phenytoin plasma concentrations.

Change #58, Section 9.6.1, ECG, paragraph 1

The original text:

A standard 12-lead ECG will be performed at the YEV, FV, and at the EDV in the case of early discontinuation. An ECG will be performed at the SV only if the ECG results at the EDV are abnormal. At the EV, ECG data will be obtained from the last visit of the previous pediatric study and should not be recorded in the eCRF for N01266. The Investigator will determine whether the results of the ECG are normal or abnormal and assess the clinical significance of any abnormalities.

Has been changed to:

A standard 12-lead ECG will be performed at the **ScrV, TV(s), and EV (directly enrolled subjects only),** YEV, FV, and at the EDV in the case of early discontinuation. An ECG will be 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 previous pediatric **BRV** study and should not be recorded in the eCRF for N01266. The Investigator will determine whether the results of the ECG are normal or abnormal and assess the clinical significance of any abnormalities.

Change #59, Section 9.6.2, Vital signs, paragraph 1

The original text:

Vital signs, including measurements of blood pressure, supine or sitting pulse rate, and body temperature, will be performed after 5 minutes of rest at the MEV, FEV, YEV, FV, and at the EDV, DTV, and the SV in the case of early discontinuation. At the EV, vital sign data will be obtained from the last visit of the previous pediatric study and should not be recorded in the eCRF for N01266.

Has been changed to:

Vital signs, including measurements of blood pressure, supine or sitting pulse rate, and body temperature, will be performed after 5 minutes of rest at the **ScrV, TV(s), and EV (directly enrolled subjects only),** MEV, FEV, YEV, FV, and at the EDV, 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 previous pediatric **BRV** study and should not be recorded in the eCRF for N01266.

Change #60, Section 9.6.3, Body weight and height

The original text:

Body weight (subject wearing light clothing without shoes) will be measured at the MEV, FEV, YEV, FV, and at the EDV and the SV in the case of early discontinuation. At the EV, body weight will be obtained from the last visit and height data will be obtained from Baseline of the previous pediatric study and should not be recorded in the eCRF for N01266.

Has been changed to:

Body weight (subject wearing light clothing without shoes) will be measured at the **ScrV, TV(s), and EV (directly enrolled subjects only),** MEV, FEV, YEV, FV, and at the EDV and the SV in the case of early discontinuation. **For LTFU subjects, a**t the EV, body weight will be obtained from the **final** visit and height data will be obtained from Baseline of the previous pediatric **BRV** study and should not be recorded in the eCRF for N01266.

Body height will be recorded at the ScrV (directly enrolled subjects only), MEV, FEV, YEV, FV, and at the EDV and the SV in the case of early discontinuation.

Change #61, Section 9.6.4, Physical examination, paragraphs 1 and 2

The original text:

A standard physical examination will be performed at the FEV, YEV, FV, and at the EDV and the SV in the case of early discontinuation.

At the EV, physical examination data will be obtained from the last visit of the previous pediatric study and should not be recorded in the eCRF for N01266. Clinically significant new or worsened abnormalities must be reported as AEs.

Has been changed to:

A standard physical examination will be performed at the **ScrV and EV (directly enrolled subjects only),** FEV, YEV, FV, and at the EDV and the SV in the case of early

discontinuation. **For LTFU subjects, at** the EV, physical examination data will be obtained from the **final** visit of the previous pediatric **BRV** study and should not be recorded in the eCRF for N01266.

Clinically significant new or worsened abnormalities **discovered at the physical examination** must be reported as AEs.

Change #62, Section 9.6.5, Neurological examination

The original text:

A standard neurological examination will be performed at the FEV, YEV, FV, and at the EDV and the SV in the case of early discontinuation. At the EV, neurological examination data will be obtained from the last visit of the previous pediatric study and should not be recorded in the eCRF for N01266.The neurological examination will include a measurement of the head size (occipital-frontal circumference). Clinically significant new or worsened abnormalities must be reported as AEs.

Has been changed to:

A standard neurological examination will be performed at **the ScrV and EV (directly enrolled subjects only),** FEV, YEV, FV, and at the EDV and the SV in the case of early discontinuation. **For LTFU subjects, a**t the EV, neurological examination data will be obtained from the **final** visit of the previous pediatric **BRV** study and should not be recorded in the eCRF for N01266. The neurological examination will include a measurement of the head size (occipital-frontal circumference). Clinically significant new or worsened abnormalities must be reported as AEs.

Change #63, Section 9.6.6, Psychiatric and mental status

The original text:

Psychiatric and mental status will be reported by recording the presence or absence of psychiatric symptoms, mental impairment, and behavioral problems at FEV, YEV, FV, and at the EDV and the SV in the case of early discontinuation. At the EV, psychiatric and mental status data will be obtained from the last visit of the previous pediatric study and should not be recorded in the eCRF for N01266. Clinically significant new or worsened abnormalities must be reported as AEs.

Has been changed to:

Psychiatric and mental status will be reported by recording the presence or absence of psychiatric symptoms, mental impairment, and behavioral problems at **the ScrV and EV (directly enrolled 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 will be obtained from the **final** visit of the previous pediatric **BRV** study and should not be recorded in the eCRF for N01266. Clinically significant new or worsened abnormalities must be reported as AEs.

Change #64, Section 9.6.7, Assessment of suicidality, sentence 3

The original text:

The C-SSRS will be completed according to the tabular schedule of study procedures, Section 5.2.

Has been changed to:

The C-SSRS will be completed according to the tabular schedules of study procedures, Section 5.2.

Change #65, Section 9.6.7, Assessment of suicidality

The following text was added:

The "Since Last Visit" version of the C-SSRS will be used, with the following exceptions:

- **For directly enrolled subjects, the "Baseline/Screening" version of the C-SSRS should be completed at the ScrV.**
- **If a subject turns 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be completed at the first visit after the sixth birthday.**

Change #66, Section 9, ASSESSMENT OF SAFETY

The following section has been added:

9.6.8 BRIEF-P and BRIEF

The BRIEF-P and the BRIEF are validated tools that will be used for the evaluation of subjects ≥2 years to <5 years of age and ≥5 years of age, respectively. The BRIEF-P and BRIEF include rating forms used by parents 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-P rating form consists of items that measure various aspects of executive functioning: Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize. The clinical scales form 3 broad indexes (Inhibitory Self-Control, Flexibility, and Emergent Metacognition) and 1 composite score (Global Executive Composite).

The BRIEF rating form contains items in nonoverlapping clinical scales. These theoretically and statistically derived scales form 2 broader Indexes: Behavioral Regulation (3 scales) and Metacognition (5 scales), as well as a Global Executive Composite score.

Both the BRIEF-P and the BRIEF include validity scales to measure negativity and inconsistency of responses.

The BRIEF-P/BRIEF will be completed at the ScrV (directly enrolled subjects only), FEV, YEV, FV, and the EDV in the case of early discontinuation. For LTFU subjects, at the EV, the BRIEF-P/BRIEF score will be obtained from Baseline of the previous

pediatric BRV study and should not be recorded in the eCRF for N01266. For directly enrolled subjects, the Baseline BRIEF-P/BRIEF should be completed at the ScrV.

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 6 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.

Change #67, Section 10, ASSESSMENT OF EFFICACY

The original text:

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). The EEG data will be reviewed by 3-month periods for the first 6 months and then yearly, thereafter.

Has been changed to:

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 directly enrolled subjects, seizure count information collected during the Up-Titration Period will be summarized separately.** The EEG data will be reviewed by 3-month periods for the first 6 months and yearly thereafter.

Change #68, Section 10.2, Efficacy assessments for seizure data based on EEG, paragraph 1

The original text:

At the EV, seizure data based on an EEG of at least 24 hours of recording (including sleeping and awakening periods) for subjects <2 years of age and data on absence seizure count (based on an EEG of at least 1 hour of recording for subjects ≥2 years of age suffering from absences) will be obtained from the last visit of the previous pediatric study and should not be recorded in the eCRF for N01266.

All EEGs specific to this study will be recorded in the eCRF modules specifically designed for this purpose.

Has been changed to:

At the EV, seizure data based on an EEG of at least 24 hours of recording (including sleeping and awakening periods) for subjects <2 years of age and data on absence seizure count (based on an EEG of at least 1 hour of recording for subjects ≥2 years of age suffering from absences) will be obtained from the **final** visit of the previous pediatric **BRV** study and should not be recorded in the eCRF for N01266. All EEGs specific to this study will be recorded in the eCRF modules specifically designed for this purpose.

Change #69, Section 10.3.1.1, Concomitant medications/treatments, paragraphs 1 and 2

The original text:

Concomitant medications will be collected and recorded in the eCRF at the following visits: MEV, FEV, YEV, UV, FV, and at the EDV, DTV, and the SV in the case of early discontinuation. Any ongoing medications (AEDs and nonAEDs) at the time the subject completed the previous pediatric study should not be recorded on the eCRF for N01266 at the EV, unless there is a change regarding the administration of the medication. In this event, the medication should be recorded on the eCRF for N01266 with the start date corresponding to the date of change in administration.

Has been changed to:

Concomitant **medication information** will be collected and recorded in the eCRF at the following visits: **ScrV and TV(s) (directly enrolled subjects only), EV**, MEV, FEV, YEV, UV, FV, and at the EDV, DTV, and the SV in the case of early discontinuation.

For LTFU subjects, any ongoing medications (**including** AEDs and non**-**AEDs) at the time the subject completed the previous pediatric **BRV** study should not be recorded **in** the eCRF for N01266, unless there is a change regarding the administration of the medication. In this event, the medication should be recorded **in** the eCRF for N01266 with the start date corresponding to the date of change in administration.

Change #70, Section 10.3.1.2, Medical procedures, paragraph 2

The original text:

Medical procedures will be recorded at the following visits: EV, MEV, FEV, YEV, UV, FV, and at the EDV, DTV, and the SV in the case of early discontinuation.

Has been changed to:

Medical procedures will be recorded at the following visits: **ScrV and TV(s) (directly enrolled subjects only),** EV, MEV, FEV, YEV, UV, FV, and at the EDV, DTV, and the SV in the case of early discontinuation.

Change #71, Section 10.3.1.3, Health care provider consultations not foreseen by the protocol

The original text:

At the MEV, FEV, YEV, UV, FV, and at the EDV, DTV, and the SV in the case of early discontinuation, health care provider consultations not foreseen by the protocol will be recorded in the eCRF. It will include the type of provider (general practitioner, specialist physician, nurse), the site of care (office-private, office-hospital, home, emergency room), and the reason leading to the consultation. At the EV, information on the health care provider consultations not foreseen by the protocol will be obtained from the final visit of the previous pediatric study and should not be recorded in the eCRF for N01266.

Has been changed to:

At the **TV(s) and EV (directly enrolled subjects only),** MEV, FEV, YEV, UV, FV, and at the EDV, DTV, and the SV in the case of early discontinuation, health care provider consultations not foreseen by the protocol will be recorded in the eCRF. It will include the type of provider (general practitioner, specialist physician, nurse), the site of care (office-private, office-hospital, home, emergency room), and the reason leading to the consultation. **For LTFU subjects, at the EV,** information on the health care provider consultations not foreseen by the protocol will be obtained from the **final** visit of the previous pediatric **BRV** study and should not be recorded in the eCRF for N01266.

Change #72, Section 10.3.1.4, Hospital stays

The original text:

At the MEV, FEV, YEV, UV, FV, and at the EDV, DTV, and the SV in the case of early discontinuation, data on hospital stays will be collected in the eCRF. It will include the reason leading to the hospitalization, the admission ward, transfers, and length of stay. At the EV, information on hospital stays will be obtained from the last visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266.

Has been changed to:

During the TV(s) and EV (directly enrolled subjects only), MEV, FEV, YEV, UV, FV, and at the EDV, DTV, and the SV in the case of early discontinuation, data on hospital stays will be collected in the eCRF. It will include the reason leading to the hospitalization, the admission ward, transfers, and length of stay. **For LTFU subjects, a**t the EV, information on hospital stays will be obtained from the **final** visit of the previous pediatric **BRV** study and should not be recorded in the eCRF for N01266.

Change #73, Section 10.3.2, Bayley Scales of Infant and Toddler Development, Third Edition, paragraph 2

The original text:

This scale is validated as a tool for assessment of neurological development in young children and is therefore considered appropriate for N01266. The same scale has been completed by the Investigator or designee at Baseline (V1) of N01263 for children from 1 month to <18 months of age at Baseline enrolled in English-speaking countries. Children started on the Bayley-III scales at Baseline of N01263 will also be assessed using the Bayley-III scales in N01266 even if their age increases to ≥18 months.

Has been changed to:

This scale is validated as a tool for assessment of neurological development in young children and is therefore considered appropriate for N01266. The same scale has been completed by the Investigator or designee at Baseline (V1) of N01263 for children from 1 month to <18 months of age at Baseline enrolled in English-speaking countries. Children started on the Bayley-III scales at Baseline of N01263 will also be assessed using the Bayley-III scales in N01266 even if their age increases to ≥18 months. **Bayley-III scale assessments are not applicable to directly enrolled subjects due to age-based considerations.**

Change #74, Section 10.3.2, Bayley Scales of Infant and Toddler Development, Third Edition, paragraph 5

The original text:

At the EV, the Bayley-III scales will be obtained from Baseline of the previous pediatric study if the subject was enrolled in an English-speaking country, and data should not be recorded in the eCRF in N01266. The Bayley-III scales will be completed at the FEV, YEV, FV, and at the EDV in the case of early discontinuation. The Bayley-III scales should be completed by the same person who completed the Bayley-III scales in the previous pediatric study.

Has been changed to:

At the EV, the Bayley-III scales will be obtained from Baseline of the previous pediatric **BRV** study if the subject was enrolled in an English-speaking country, and data should not be recorded in the eCRF in N01266. The Bayley-III scales will be completed at the FEV, YEV, FV, and at the EDV in the case of early discontinuation. The Bayley-III scales should be completed by the same person who completed the Bayley-III scales in the previous pediatric **BRV** study.

Change #75, Section 10.3.3, Achenbach Child Behavior Checklist, paragraph 2 through end of section

The original text:

The version of the Achenbach CBCL (CBCL/1½-5 or CBCL/6-18) used should be the same as the one used in the previous pediatric study. However, if the subject reaches 6 years of age in this LTFU study, the version of the Achenbach CLCB should not be changed until at least after the first assessment in N01266.

The Achenbach CBCL should be completed by the same parent(s)/legal representative(s) who completed the CBCL in the previous pediatric study. The completion of the Achenbach CBCL will require approximately 45 minutes.

In both questionnaires, the occurrence of certain problems and behaviors in the past 6 months will be scored on the following scale:

0=not true (as far as known)

1=somewhat or sometimes true

2=very true or often true

Eight syndrome scores will be calculated from these questions, which will in turn be summarized by 2 composite scores. Additionally, for each score on the question, syndrome, and total level, categorizations based on a normative sample will be used to evaluate normal, borderline, or clinically relevant behavior.

In addition, the Achenbach CBCL/6-18 includes ratings related to performance in school, activities in leisure time, and special interests.

At the EV, the Achenbach CBCL score will be obtained from Baseline of the previous pediatric study and should not be recorded in the eCRF in N01266. The Achenbach CBCL will be completed at the FEV, YEV, FV, and at the EDV in the case of early discontinuation.

Has been changed to the following:

The Achenbach CBCL should be completed by the same parent(s)/legal representative(s) who completed the CBCL in the previous pediatric **BRV** study. The completion of the Achenbach CBCL will require approximately 45 minutes.

In both questionnaires, the occurrence of certain problems and behaviors in the past 6 months will be scored on the following scale:

0=not true (as far as known)

1=somewhat or sometimes true

2=very true or often true

Eight syndrome scores will be calculated from these questions, which will in turn be summarized by 2 composite scores. Additionally, for each score on the question, syndrome, and total level, categorizations based on a normative sample will be used to evaluate normal, borderline, or clinically relevant behavior.

In addition, the Achenbach CBCL/6-18 includes ratings related to performance in school, activities in leisure time, and special interests.

The Achenbach CBCL will be completed at the **ScrV (directly enrolled subjects only),** FEV, YEV, FV and the EDV in the case of early discontinuation. **For LTFU subjects, a**t the EV, the Achenbach score will be obtained from Baseline of the previous pediatric **BRV** study and should not be recorded in the eCRF **for** N01266. **For directly enrolled subjects, the Achenbach CBCL will be completed at the ScrV will be the Baseline assessment.**

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.

Change #76, Section 10, ASSESSMENT OF EFFICACY

The following section has been added:

10.3.5 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 1 month to 24 months, ≥2 years to ≤4 years, ≥5 years to ≤7 years, ≥8 years to ≤12 years, and ≥13 years to ≤18 years of age. Self-report is measured for pediatric subjects ≥5 years to ≤18 years of age, and parent proxy report of child HRQoL is measured for pediatric subjects ≥2 years to ≤18 years of age.

The multidimensional PedsQL generic core scales encompass the essential core domains for pediatric HRQoL measurement: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. The PedsQL assessment is retrospective to the prior 4 weeks, and individual items are scored using a 5-point Likert scale (never, almost never, sometimes, often, or always). A total health summary score ranging between 0 and 100 is calculated from the sum of the raw scores, with higher scores indicating higher HRQoL.

The PedsQL will be completed at the ScrV (directly enrolled subjects only), FEV, YEV, FV, and the EDV in the case of early discontinuation. For LTFU subjects, at the EV, the PedsQL score will be obtained from Baseline of the previous pediatric BRV study and will not be recorded in the eCRF in N01266. For directly enrolled subjects, the Baseline PedsQL will be completed at the ScrV.

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 #77, Section 11.2.1, Definition of source data, paragraph 5

The following text:

Electronic data records, such as holter monitor records or EEG records must be saved and stored as instructed by UCB (or designee).

Has been changed to:

Electronic data records, such as **H**olter monitor records or EEG records must be saved and stored as instructed by UCB (or designee).

Change #78, Section 12.1, Definition of analysis sets

The following bullet:

- The Safety Set (SS) will consist of all enrolled subjects who took at least 1 dose of study medication in the LTFU study. All safety analyses will be performed on the SS.

Has been changed to:

- The Safety Set (SS) will consist of all enrolled subjects who took at least 1 dose of study medication in **this long-term** study. All safety analyses will be performed on the SS.

Change #79, Section 12.2, General statistical considerations

The following sentence has been added to the end of the section:

Data collected during the Up-Titration Period for directly enrolled subjects will be summarized separately.

Change #80, Section 12.5, Other analyses

The original text:

The Achenbach CBCL, the Bayley-III scores, and change from previous study Baseline scores will be analyzed in a descriptive manner.

Has been changed to:

The Achenbach CBCL, the Bayley-III scores **(LTFU subjects only), BRIEF-P/BRIEF, PedsQL,** and change from Baseline scores **(previous BRV study for LTFU subjects and ScrV for directly enrolled subjects)** will be analyzed in a descriptive manner.

Change #81, Section 12.9, Determination of sample size

The original text:

No formal sample size calculation was performed for this study. Up to 500 subjects may possibly enroll in this study, based upon the assumption that 90% of the subjects having completed a previous pediatric study with BRV as adjunctive treatment in epilepsy will rollover into the present study.

Has been changed to:

No formal sample size calculation was performed for this study. **Originally,** up to 500 subjects **might have** possibly enroll**ed** in this study. **The original number was** based upon the assumption that 90% of the subjects having completed a previous pediatric study with BRV as adjunctive treatment in epilepsy will rollover into the present study. **With Protocol Amendment 3, enrollment is expanded to include up to 100 directly enrolled subjects (≥4 years to <17 years of age) with POS, thus increasing possible enrollment to up to 600 subjects.**

Change #82, Section 13.1, Informed consent, paragraph 3, final sentence

The original text:

Any subject who is over 16 years of age during the LTFU study must sign and date the Informed Consent form according to local regulations.

Has been changed to:

Any subject who is over 16 years of age during **N01266** must sign and date the Informed Consent form according to local regulations.

Change #83, Section 15, REFERENCES

The following reference has been added

Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care. 1999;37:126-39.

16.4 Protocol Amendment 4

Rationale for the amendment

As a result of the PK analyses performed on the plasma samples collected at N01263 completion, the plasma concentrations approximating the concentrations for adults receiving BRV 200mg/day were not achieved by the dosing scheme initially included in N01266. Thus, N01266 was amended to allow a maximum BRV dose of 5.0mg/kg/day (not to exceed a total dose of BRV 200mg/day).

The number of directly enrolled subjects has been increased from "up to" to "at least" 100 subjects with the planned total enrollment of approximately 600 subjects to allow flexibility in the number of patients reaching 1 year of exposure.

Demographics and childbearing potential will be captured at the EV for LTFU subjects, instead of using the data recorded from either the Baseline or the final visit of the previous study.

The handling of protocol deviations has been made consistent with the updated statistical analysis process.

In addition, it was clarified that although no formal interim analysis will be performed, the data may be reported prior to the completion of this study to support the ongoing data cleaning, annual reports, regulatory submissions, and publications.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- For all subjects, the titration dosage for pediatric subjects has been aligned without age limitations.
- The maximum allowable BRV dose has been changed from 3.2mg/kg/day for subjects ≥8 years of age and 4.0mg/kg/day for subjects <8 years of age to 5.0mg/kg/day (2.5mg/kg bid) for all subjects (not to exceed a total dose of BRV 200mg/day).
- For administrative purposes and to ensure consistency with other documents, demographics and childbearing potential will be assessed at the EV for LTFU subjects, instead of using the data captured from either the Baseline or the final visit of the previous study. In addition, for the same reason, the age that triggers the switch from BRIEF-P to BRIEF between the Baseline and the initial YEV has been changed from 6 to 5 years of age.
- Visit windows have been added for clarity.
- Minor administrative and editorial changes.

Specific changes

Change #1, SPONSOR DECLARATION

The original text:

Study Physician

[redacted]

_____
Date/Signature

Clinical Program Director

[redacted]

_____
Date/Signature

Exploratory Development Director

[redacted]

_____
Date/Signature

Has been changed to:

Study Physician

[redacted]

_____
Date/Signature

Clinical Program Director

[redacted]

_____
Date/Signature

Clinical Pharmacology Director

[redacted]

_____
Date/Signature

Change #2, STUDY CONTACT INFORMATION

The original text:

Sponsor Study Physician

Name:	[redacted]
Address:	8010 Arco Corporate Drive, [redacted] Raleigh, NC 27617 United States
Phone:	[redacted]
Fax:	[redacted]

Clinical Monitoring Contract Research Organization

Name:	Pharma-Research Associates (UK) Ltd.
Address:	Imperial Way Reading, Berkshire RG2 OTD United Kingdom
Phone:	+44 118 918 1000
Fax:	+44 118 918 1001

Has been changed to:

Sponsor Study Physician

Name:	[redacted]
Address:	8010 Arco Corporate Drive, [redacted] Raleigh, NC 27617 United States
Phone:	[redacted]
Fax:	[redacted]

Clinical Monitoring Contract Research Organization

Name:	Pharma-Research Associates (UK) Ltd.
Address:	**Green Park** **500 South Oak Way** **Reading, RG2 6AD** United Kingdom
Phone:	+44 118 918 1000
Fax:	+44 118 918 1001

Change #3, SERIOUS ADVERSE EVENT REPORTING

The original text:

Serious adverse event reporting (24h) and safety related issues	
Fax	**Europe and Rest of the World (except Japan):** +32 2 386 2421 **US:** +1 800 880 6949 **Canada:** +1 877 582 8842
Email	**Europe, US, and Rest of the World (except Japan):** DS_ICT@ucb.com

Has been changed to:

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h) and safety related issues	
Fax	**Europe and Rest of the World (except Japan):** +32 2 386 2421 **US:** +1 800 880 6949 **Canada:** +1 877 582 8842
Email	**Europe, US, and Rest of the World (except Japan): DS-ICT@ucb.com**

Change #4, LIST OF ABBREVIATIONS

The following abbreviation has been deleted:

DRM	data review meeting

The following abbreviation has been added:

UV	Unscheduled Visit

Change #5, Section 1, SUMMARY, paragraph 1

The original text:

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 was initially designed for pediatric subjects who had completed N01263 or would complete other future pediatric BRV studies (herein referred to as "long-term follow-up" [LTFU] subjects). With Protocol Amendment 3, enrollment was expanded to include up to 100 subjects ≥4 years to <17 years of age with POS who had not previously enrolled in a pediatric BRV study (herein referred to as "directly enrolled subjects").

Has been changed to:

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 was initially designed for pediatric subjects who had completed N01263 or would complete other future

pediatric BRV studies (herein referred to as "long-term follow-up" [LTFU] subjects). With Protocol Amendment 3, enrollment was expanded to include up to 100 subjects ≥4 years to <17 years of age with POS who had not previously enrolled in a pediatric BRV study (herein referred to as "directly enrolled subjects"). **With Protocol Amendment 4, the number of directly enrolled subjects is increased to at least 100 subjects with the planned total enrollment of approximately 600 subjects. In addition, the dosing scheme was aligned so that it is no longer age-dependent; previously, subjects ≥8 or <8 years of age were dosed under different dosing schemes.**

Change #6, Section 1, SUMMARY, paragraphs 3 to 5

The original text:

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 previous pediatric BRV 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 directly enrolled subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than the minimum specified dose) for 7±2 days during the Up-Titration Period, the subject will attend the EV and enter the Evaluation Period on that dose.

Brivaracetam (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 previous BRV study to be eligible for entry into the Evaluation Period. This minimum tolerated dose for LTFU subjects from N01263 is 0.8mg/kg/day if ≥8 years of age and 1.0mg/kg/day if <8 years of age. The same minimums apply to directly enrolled subjects as indicated in Section 7.2.

The maximum allowable BRV dose is 3.2mg/kg/day for subjects ≥8 years of age and 4.0mg/kg/day for subjects <8 years of age. Younger subjects (<7 years of age) will be administered BRV oral solution. Subjects above 50kg will be dosed as adults, up to a maximum total daily dose not exceeding 200mg/day, and should transition from the oral solution to the equivalent oral tablet dose, if 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.

Has been changed to:

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 previous pediatric BRV 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 directly enrolled subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than **1.0mg/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.

Brivaracetam (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 previous BRV study to be eligible for entry into the Evaluation Period **of N01266. All directly enrolled subjects must be able to tolerate at least 1.0mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266,** as indicated in Section 7.2.

The maximum allowable BRV dose is **5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg. Subjects <7 years of age will receive oral solution. Subjects ≥7 years of age will receive 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.

Change #7, Section 2.5, Rationale for the study, paragraphs 3 and 4

The original text:

N01263 is the first study of BRV in pediatric subjects. This is an open-label, fixed 3-step up-titration, PK, safety and efficacy study to evaluate BRV as adjunctive therapy in children (aged ≥1 month to <16 years) with epilepsy using an oral solution. The safety and PK data from this study will be used for BRV dose adaptation in pediatric subjects with epilepsy.

N01266 was originally designed to give subjects who complete N01263 or other future pediatric BRV studies (ie, LTFU subjects) an opportunity to continue BRV treatment for approximately 3 years, until approval of BRV is granted for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor. With Protocol Amendment 3, enrollment is expanded to include up to 100 eligible subjects ≥4 years to <17 years of age with POS who have not participated in another pediatric BRV study (ie, directly enrolled subjects). Thus, N01266 will gather additional long-term safety and tolerability data on BRV in pediatric subjects with epilepsy while providing access to BRV for subjects who may benefit from long-term treatment.

Has been changed to:

N01263 is the first study of BRV in pediatric subjects. This **was** an open-label, fixed 3-step up-titration, PK, safety and efficacy study to evaluate BRV as adjunctive therapy in children (aged ≥1 month to <16 years) with epilepsy using an oral solution. The safety and PK data

from this study will be used for BRV dose adaptation in pediatric subjects with epilepsy. **A total of 100 subjects were enrolled into this study.**

N01266 was originally designed to give subjects who complete N01263 or other future pediatric BRV studies (ie, LTFU subjects) an opportunity to continue BRV treatment for approximately 3 years, until approval of BRV is granted for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor. With Protocol Amendment 3, enrollment **was** expanded to include up to 100 eligible subjects ≥4 years to <17 years of age with POS who have not participated in another pediatric BRV study (ie, directly enrolled subjects). Thus, N01266 will gather additional long-term safety and tolerability data on BRV in pediatric subjects with epilepsy while providing access to BRV for subjects who may benefit from long-term treatment. **With Protocol Amendment 4, the number of directly enrolled subjects is increased to at least 100 subjects with the planned total enrollment of approximately 600 subjects. In addition, based on the PK analyses performed on the plasma samples collected in N01263, the dosing scheme for Protocol Amendment 4 was aligned so that it is no longer age-dependent; previously, subjects ≥8 or <8 years of age were dosed under different dosing schemes.**

Change #8, Section 5.1, Study description, paragraphs 3 to 4

The original text:

Brivaracetam (tablet and oral solution) should be administered bid in 2 equally divided doses. All LTFU subjects must be able to tolerate the minimum BRV dose specified in the previous study to be eligible for entry into the Evaluation Period of N01266. For LTFU subjects from N01263, this minimum tolerated BRV dose is 0.8mg/kg/day if ≥8 years of age and 1.0mg/kg/day if <8 years of age. The same minimums apply to directly enrolled subjects.

For all subjects enrolled in N01266, the maximum BRV dose is 3.2mg/kg/day for subjects ≥8 years of age and 4.0mg/kg/day for subjects <8 years of age. Younger subjects (<7 years of age) will be administered BRV oral solution. Subjects above 50kg will be dosed as adults, up to a maximum total daily dose not exceeding 200mg/day, and should transition from the oral solution to the equivalent oral tablet dose. Dose adjustments of BRV and/or concomitant AEDs are allowed at any time based on clinical judgment; however, during the Up-Titration Period, dose adjustments for BRV should be made only as specified in Section 7.2.1. Additional information on BRV administration is presented in Section 7.2. Subjects will continue to receive BRV treatment in this study for approximately 3 years, until approval for BRV has been obtained for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor.

Has been changed to:

Brivaracetam (tablet and oral solution) should be administered bid in 2 equally divided doses. All LTFU subjects must be able to tolerate the minimum BRV dose specified in the previous study to be eligible for entry into the Evaluation Period of N01266. **All directly enrolled subjects must be able to tolerate at least 1.0mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266, as indicated in Section 7.2.**

For all subjects enrolled in N01266, the maximum BRV dose is **5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg. Subjects**

<7 years of age will receive oral solution. Subjects ≥7 years of age will receive tablets, as appropriate. Dose adjustments of BRV and/or concomitant AEDs are allowed at any time based on clinical judgment; however, during the Up-Titration Period, dose adjustments for BRV should be made only as specified in Section 7.2.1. Additional information on BRV administration is presented in Section 7.2. Subjects will continue to receive BRV treatment in this study for approximately 3 years, until approval for BRV has been obtained for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor.

Change #9, Section 5.1, Study description, paragraph 7

The original text:

No formal interim analysis is planned (see Section 12.8).

Has been changed to:

No formal interim analysis is planned**; however, data may be reported prior to the completion of this study** (see Section 12.8).

Change #10, Section 5.1.2, Planned number of subjects and sites, paragraph 2

The original text:

With Protocol Amendment 3, enrollment is expanded to include up to 100 eligible directly enrolled subjects ≥4 years to <17 years of age with POS, which will allow up to 600 subjects to enroll in N01266 instead of the up to 500 originally planned.

Has been changed to:

With Protocol Amendment 3, enrollment **was** expanded to include up to 100 eligible directly enrolled subjects ≥4 years to <17 years of age with POS, which **allowed** up to 600 subjects to enroll in N01266 instead of the up to 500 originally planned. **With Protocol Amendment 4, the number of directly enrolled subjects is increased to at least 100 subjects with the planned total enrollment of approximately 600 subjects.**

Change #11, Section 5.2, Schedules of study assessments

Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Footnote a appended to childbearing potential at EV for LTFU subjects has been deleted and the following assessment has been added:

Period	Evaluation							Down-Titration	Safety (Drug-free)
Visit	Entry Visit		Minimal Evaluation Visit	Full Evaluation Visit	Yearly Evaluation Visit/Final Visit	Unscheduled Visit	Early Discontinuation Visit	Down-Titration Visit	Safety Visit
	(EV)		(MEV)	(FEV)	(YEV/FV[b])	(UV)	(EDV)	(DTV)[c]	(SV)
Subjects	LTFU[a]	DE	All						
Assessment									
Demographic data	X								

Change #12, Section 5.2, Schedules of study assessments, abbreviations

The original text:

AE=adverse event; AED=antiepileptic drug; ALP=alkaline phosphatase; ALT=alanine aminotransferase; 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; C-SSRS=Columbia-Suicide Severity Rating Scale; DE=directly enrolled; DRC=daily record card; ECG=electrocardiogram; eCRF=electronic case report form; EEG=electroencephalogram; GGT=gamma-glutamyltransferase;

IVRS=interactive voice response system; LTFU=long-term follow-up; M=Month; PedsQL=Pediatric Quality of Life Inventory; SAE=serious adverse event; TV=Titration Visit; V=Visit

Has been changed to:

AE=adverse event; AED=antiepileptic drug; ALP=alkaline phosphatase; ALT=alanine aminotransferase; 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; C-SSRS=Columbia-Suicide Severity Rating Scale; DE=directly enrolled; DRC=daily record card; **DTV=Down-Titration Visit;** ECG=electrocardiogram; eCRF=electronic case report form; **EDV=Early Discontinuation Visit;** EEG=electroencephalogram; **EV=Entry Visit; FEV=Full Evaluation Visit; FV=Final Visit;** GGT=gamma-glutamyltransferase; IVRS=interactive voice response system; LTFU=long-term follow-up; M=Month; **MEV=Minimal Evaluation Visit;** PedsQL=Pediatric Quality of Life Inventory; SAE=serious adverse event; **SV=Safety Visit;** TV=Titration Visit; **UV=Unscheduled Visit;** V=Visit**; YEV=Yearly Evaluation Visit**

Change #13, Section 5.2, Schedules of study assessments, footnote a

The original text:

a For LTFU subjects, the following data will be obtained from Baseline of the previous pediatric BRV study and should not be recorded on the eCRF for N01266: demographics, general medical and procedure history, epilepsy history, AED history, height, Bayley-III scales, the Achenbach CBCL, BRIEF-P/BRIEF, and PedsQL scores. The following data will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266: AEs, childbearing potential, recording of medications, recording of procedures, seizure count, EEG, ECG, laboratory assessments for safety, including phenytoin plasma concentrations (if applicable), the C-SSRS, vital signs, body weight, physical and neurological examinations, psychiatric and mental status, and data on health care provider consultations not foreseen by the protocol and hospital stays. The EV is also the final evaluation visit of the previous pediatric BRV study.

Has been changed to:

a For LTFU subjects, the following data will be obtained from Baseline of the previous pediatric BRV study and should not be recorded on the eCRF for N01266: **general medical and procedure history, epilepsy history, AED history, height, Bayley-III scales, the Achenbach CBCL, BRIEF-P/BRIEF, and PedsQL scores**. The following data will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266: **AEs, recording of medications, recording of procedures, seizure count, EEG, ECG, laboratory assessments for safety, including phenytoin plasma concentrations (if**

applicable), the C-SSRS, vital signs, body weight, physical and neurological examinations, psychiatric and mental status, and data on health care provider consultations not foreseen by the protocol and hospital stays. The EV is also the final evaluation visit of the previous pediatric BRV study.

Change #14, Section 5.2, Schedules of study assessments, footnote q

The original text:

q The cognition scale (Bayley-III) to be used in N01266 for subjects <18 months of age and enrolled in English-speaking countries will be the same as the one used in the previous pediatric BRV study. If the subject reaches 18 months of age in this study, the subject will still be assessed using the Bayley-III to allow for an evaluation of the change from Baseline even if his/her age increases to ≥18 months.

Has been changed to:

q The cognition scale (Bayley-III) to be used in N01266 for subjects **<18 months to 42** months of age and enrolled in English-speaking countries will be the same as the one used in the previous pediatric BRV study. If the subject reaches 18 months of age in this study, the subject will still be assessed using the Bayley-III to allow for an evaluation of the change from Baseline even if his/her age increases to ≥18 months.

Change #15, Section 5.2, Schedules of study assessments, footnote s

The original text:

s The BRIEF-P should be used for subjects ≥2 years to <5 years of age and the BRIEF should be used for subjects ≥5 years of age, with the following exception: For subjects who completed the BRIEF-P at the Baseline assessment (previous pediatric BRV study for LTFU subjects and ScrV for directly enrolled subjects) and turn 6 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.

Has been changed to:

s The BRIEF-P should be used for subjects ≥2 years to <5 years of age and the BRIEF should be used for subjects ≥5 years of age, with the following exception: For subjects who completed the BRIEF-P at the Baseline assessment (previous pediatric BRV study for LTFU subjects and ScrV for directly enrolled subjects) 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.

Change #16, Section 5.3, Visit sequence, Table 5-3: Visit sequence

The original table:

Directly enrolled 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	V11, V12, etc	YEV, MEV, etc

Has been changed to:

Table 5-3: Visit sequence

Directly enrolled 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

Change #17, Section 5.3, Visit sequence, Table 5-3: Visit sequence, note

The original text:

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

Has been changed to:

Note: **Visits at W1, W2, W3, and M0 will occur 7±2 days after the previous visit; visits at 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.

Change #18, Section 5.4, Rationale for study design and selection of dose, paragraphs 2 through 5

The original text:

Each LTFU subject will begin treatment in N01266 at the individualized BRV dose he/she was receiving at the completion of the previous pediatric study. Directly enrolled subjects will participate in up to 3 weeks of an Up-Titration Period. If a subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV for 7±2 days during the Up-Titration Period, the subject will be allowed to enter the Evaluation Period (subject must be able to tolerate the minimum specified dose; see Section 7).

A physiologically-based PK model (N01313) was developed to predict the doses to be tested in N01263. The same doses that were used for up titration in N01263 will be used for the 3 consecutive weeks that comprise the Up-Titration Period of N01266. For subjects ≥8 years of age, the approximate doses to be administered are 0.4, 0.8, and 1.6mg/kg bid (0.8, 1.6, and 3.2mg/kg/day, respectively, corresponding to 50, 100, and 200mg/day in adults) for Weeks 1, 2, and 3 of up titration, respectively. For subjects <8 years of age, the approximate doses to be administered are 0.5, 1.0, and 2.0mg/kg bid (1.0, 2.0, and 4.0mg/kg/day, respectively) for Weeks 1, 2, and 3 of up titration, respectively. Daily doses will be adjusted by body weight, but will not exceed maximums of 50mg/day, 100mg/day, and 200mg/day. The dose selection was based on the following observations in adult subjects:

- The PK of BRV is linear and of low variability in adults up to 1 order of magnitude above the therapeutic dose range.
- Efficacious doses in adults are expected to be from 50mg/day up to 200mg/day.
- Drug clearance is expected to be higher in children than in adults because of the physiologically based PK simulations.

Brivaracetam (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 previous BRV study to be eligible for entry into the Evaluation Period of N01266. This minimum tolerated BRV dose for LTFU subjects from N01263 is 0.8mg/kg/day if ≥8 years of age and 1.0mg/kg/day if <8 years of age. The same minimums apply to directly enrolled subjects.

The maximum allowable BRV dose in N01266 is 3.2mg/kg/day for subjects ≥8 years of age and 4.0mg/kg/day for subjects <8 years of age. Younger subjects (<7 years of age) will be administered BRV oral solution. Subjects above 50kg will be dosed as adults, up to a maximum total daily dose not exceeding 200mg/day, and should transition from the oral solution to the equivalent oral tablet dose, if appropriate.

Has been changed to:

Each LTFU subject will begin treatment in N01266 at the individualized BRV dose he/she was receiving at the completion of the previous pediatric study. Directly enrolled subjects will participate in up to 3 weeks of an Up-Titration Period. If a subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV for 7±2 days during the Up-Titration Period, the subject will be allowed to enter the Evaluation Period (subject must be able to tolerate the minimum dose **of 1.0mg/kg/day**; see Section **7.2**).

A physiologically-based PK model (N01313) was developed to predict the doses to be tested in N01263. The same doses that were used for **up-titration** in N01263 will be used for the 3 consecutive weeks that comprise the Up-Titration Period of N01266. **Based on the PK analyses performed on the plasma samples collected in N01263, the plasma concentrations approximating the concentrations for adults receiving BRV 200mg/day were not achieved by the dosing scheme initially included in N01266; as a result, it was recommended that the same doses are to be administered in all pediatric subgroups, ≥1 month to ≤16 years of age.** For **all** subjects, the approximate doses to be administered are 0.5, 1.0, and 2.0mg/kg bid (1.0, 2.0, and 4.0mg/kg/day, respectively)**, with the daily doses not exceeding the maximums of 50mg/day, 100mg/day, and 200mg/day** for Weeks 1, 2, and 3 of **up-titration**, respectively. The dose selection was based on the following observations:

- The PK of BRV is linear and of low variability in adults up to 1 order of magnitude above the therapeutic dose range.
- Efficacious doses in adults are expected to be from 50mg/day up to 200mg/day.
- **In the recently completed N01263, BRV was eliminated more rapidly in pediatric subjects than in adult subjects, resulting in a lower plasma concentration. Therefore, clearance of BRV was shown to be higher in pediatric subjects than in adult subjects.**

Brivaracetam (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 previous BRV study to be eligible for entry into the Evaluation Period of N01266. **All directly enrolled subjects must be able to tolerate at least 1.0mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266, as indicated in Section 7.2.**

The maximum allowable BRV dose in N01266 is **5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg. Subjects <7 years of**

age will receive oral solution. Subjects ≥7 years of age will receive tablets, as appropriate.

Change #19, Section 7.2, Treatments to be administered

The original text:

The LTFU subjects will ordinarily start dosing on the individualized BRV dose they were receiving at the completion of the previous pediatric BRV study. The directly enrolled subjects will participate in an Up-Titration Period as described in Section 7.2.1 before entry into the Evaluation Period.

The LTFU subjects must be able to tolerate the minimum BRV dose specified in their previous study to be eligible for entry into the Evaluation Period of N01266. For subjects entering N01266 from N01263, the minimum BRV dose is 0.8mg/kg/day if ≥8 years of age or at least 1.0mg/kg/day if <8 years of age; directly enrolled subjects must also tolerate at least these dosages for 7±2 days during the Up-Titration Period before entry into the Evaluation Period.

The maximum BRV dose for subjects ≥8 years of age is 3.2mg/kg/day and 4.0mg/kg/day for subjects <8 years of age. Subjects above 50kg will be dosed as adults, up to a maximum total daily dose not exceeding 200mg/day, and should transition from the oral solution to the equivalent oral tablet dose, unless the subject's condition prevents him/her from swallowing oral tablets. Subjects <7 years of age should not transition to oral tablet treatment. Oral solution should not be mixed with other liquids prior to administration.

The maximum dose allowed in this study is 200mg/day (100mg bid).

Brivaracetam should be given bid approximately 12 hours apart in 2 equally divided doses. The mg dosage for the oral tablet treatment should be calculated to match as closely as possible the mg/kg-based dosage and should be a combination of the BRV 10mg, 25mg, and 50mg tablets. Only the following exact dosages are allowed for the oral tablet administration:

BRV 20, 40, 50, 70, 100, 150, and 200mg/day. Subjects should be dosed with either oral tablets or oral solution and not a combination of both.

The dose of oral solution will be measured using the appropriate syringes (1mL, 3mL, and/or 10mL) with an adaptor able to fit both bottle sizes. Dose adjustments of IMP and/or concomitant AEDs are allowed at any time based on clinical judgment.

All subjects who prematurely discontinue the study should complete an EDV and have their BRV dose down titrated by a maximum of half the dose every week until a dose of 1.0mg/kg/day is reached for subjects <8 years of age or until a dose of 0.8mg/kg/day is reached for subjects ≥8 years of age.

Subjects should take their BRV treatment according to instructions provided by the Investigator.

Dispensation of IMP will be done by an interactive voice response system (IVRS).

Has been changed to:

Brivaracetam **(tablet and oral solution)** should be **administered** bid approximately 12 hours apart in 2 equally divided doses. **Subjects should be dosed with either oral tablets or oral solution and not a combination of both.** The mg dosage for the oral tablet treatment should be calculated to match as closely as possible the mg/kg based dosage and should be a combination of the BRV 10mg, 25mg, and 50mg tablets. Only the following exact dosages are allowed for the oral tablet administration: BRV 20, 40, 50, 70, 100, 150, and 200mg/day.

The dose of oral solution will be measured using the appropriate syringes (1mL, 3mL, and/or 10mL) with an adaptor able to fit both bottle sizes. **Oral solution should not be mixed with other liquids prior to administration.**

All subjects who prematurely discontinue the study should complete an EDV and have their BRV dose down titrated by a maximum of half the dose every week until a dose of **1.0mg/kg/day is reached**.

Subjects should take their BRV treatment according to instructions provided by the Investigator. **Dose adjustments for concomitant AEDs are allowed at any time based on clinical judgment.**

Dispensation of IMP will be done by an interactive voice response system (IVRS).

Change #20, Section 7.2.1, Up-Titration Period for directly enrolled subjects, paragraph 3 and Table 7-1

The original text:

Based on tolerability and seizure control, a subject's BRV dose may be reduced to no lower than the age-designated minimum dose indicated in Table 7–1. If a subject had previously received the reduced BRV dose for 7±2 days with acceptable tolerability and seizure control, then the subject may enter directly into the Evaluation Period.

Table 7–1: Recommended BRV dosing schedule for directly enrolled subjects during the Up-Titration Period

Visit (Week)	BRV dose per dosing occasion (mg/kg)		BRV dose per day (mg/kg/day)	
	≥8 years	<8 years	≥8 years	<8 years
TV1 (1)	~0.4	~0.5	~0.8	~1.0
TV2 (2)	~0.8	~1.0	~1.6	~2.0
TV3 (3)	~1.6	~2.0	~3.2	~4.0

Has been changed to:

Based on tolerability and seizure control, a subject's BRV dose may be reduced to no lower than the **designated** minimum dose indicated in Table 7–1. If a subject had previously received the reduced BRV dose for 7±2 days with acceptable tolerability and seizure control, then the subject may enter directly into the Evaluation Period.

Table 7–1: Recommended BRV dosing schedule for directly enrolled subjects during the Up-Titration Period

Visit (Week)	BRV 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

Change #21, Section 7.2.1, Up-Titration Period for directly enrolled subjects

The following paragraph has been added:

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.

Change #22, Section 7.2.2, Evaluation Period for all subjects

The following section has been added:

7.2.2 Evaluation Period for all subjects

The maximum BRV dose will be 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg. Subjects <7 years of age will receive oral solution. Subjects ≥7 years of age will receive tablets, as appropriate.

The LTFU subjects will ordinarily start dosing on the individualized BRV dose they were receiving at the completion of the previous pediatric BRV study. They must be able to tolerate the minimum BRV dose specified in their previous study to be eligible for entry into the Evaluation Period of N01266.

Dose can be adjusted at any time as considered necessary by the Investigator and required by the subject's medical condition. The newly adjusted dose must not exceed the maximum allowed dose (5mg/kg/day [2.5mg/kg bid], not to exceed a dose of 200mg/day).

Change #23, Section 8.1, Screening Visit for directly enrolled subjects only, paragraph 1

The original text:

The ScrV is applicable only to directly enrolled subjects (ie, subjects ≥4 years to <17 years of age with POS who have not previously participated in a pediatric BRV study). Beginning with Protocol Amendment 3, up to 100 directly enrolled subjects will be allowed to participate in N01266. The Screening Period will serve as the Baseline Period for directly enrolled subjects.

Has been changed to:

The ScrV is applicable only to directly enrolled subjects (ie, subjects ≥4 years to <17 years of age with POS who have not previously participated in a pediatric BRV study). Beginning

with Protocol Amendment 3, up to 100 directly enrolled subjects **were** allowed to participate in N01266. The Screening Period will serve as the Baseline Period for directly enrolled subjects. **With Protocol Amendment 4, the number of directly enrolled subjects is increased to at least 100 subjects with the planned total enrollment of approximately 600 subjects.**

Change #24, Section 8.1, Screening Visit for directly enrolled subjects only, bullet point 21

The original text:

- Laboratory assessments for safety including:
  - Hematology
  - Biochemistry including hepatic monitoring
  - Urinalysis
  - Endocrinology
  - Serum pregnancy test (if applicable)

Has been changed to:

- Laboratory assessments for safety including:
  - Hematology
  - Biochemistry including hepatic monitoring
  - Urinalysis
  - Endocrinology
  - Serum pregnancy test (**see Section 9.5.1**)

Change #25, Section 8.3.1, LTFU subjects

The original text:

- Signing and dating of written Informed Consent by parent(s)/legal representative(s)
- Signing and dating of Assent form by the subject (if applicable, according to age and local requirements)
- Subject identification card dispensing
- DRC dispensed
- Verification of inclusion/exclusion criteria
- IVRS call
- Study drug dispensed
- Recording of medications (Any ongoing medications [including AEDs and non-AEDs] at the time the subject completed the previous pediatric BRV study should not be recorded

in the eCRF for N01266, unless there is a change regarding the administration of the medication. In this event, the start date corresponding to the date of change in administration should be recorded in the eCRF.)

- Recording of AEs (Any ongoing AEs at the time the subject completed the previous pediatric BRV study should not be recorded in the eCRF for N01266, unless there is a change in intensity or seriousness. In this event, the AE should be recorded in the eCRF for N01266, with the onset date corresponding to the date of change in condition.)
- Appointment for the next visit according to the schedule described in Section 5.3

The following data will be obtained from Baseline of the previous pediatric BRV study and should not be recorded in the eCRF for N01266:

- Demographic data
- General medical and procedures history
- Epilepsy history
- AED history
- Height
- Bayley-III scales (for LTFU subjects <18 months of age at Baseline of N01263 or other pediatric BRV studies and only for subjects enrolled in English-speaking countries)
- Achenbach CBCL score (see Section 10.3.3)
- Laboratory assessments
  - Endocrinology

The following data will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266:

- Childbearing potential Recording of medications
- Recording of procedures
- Seizure count
- EEG
  - For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: an EEG of at least 1 hour of recording (including hyperventilation and intermittent photic stimulation) must be performed
  - For subjects ≥1 month to <2 years of age on the day of the study visit: an EEG of at least 24 hours of recording (including sleeping and awakening periods) must be performed
- ECG
- Laboratory assessments for safety
  - Hematology

  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects ≥4 years of age)
  - Urine pregnancy test (if applicable)
- Phenytoin plasma concentrations (if applicable)
- Suicidality assessment (C-SSRS) (for subjects ≥6 years of age)
- Vital signs
- Body weight
- Physical examination
- Neurological examination
- Psychiatric and mental status
- Health care provider consultations not foreseen by the protocol
- Hospital stays

Has been changed to:

- Signing and dating of written Informed Consent by parent(s)/legal representative(s)
- Signing and dating of Assent form by the subject (if applicable, according to age and local requirements)
- Subject identification card dispensing
- DRC dispensed
- Verification of inclusion/exclusion criteria
- **Demographic data**
- **Childbearing potential**
- IVRS call
- Study drug dispensed
- Recording of medications (Any ongoing medications [including AEDs and non-AEDs] at the time the subject completed the previous pediatric BRV study should not be recorded in the eCRF for N01266, unless there is a change regarding the administration of the medication. In this event, the start date corresponding to the date of change in administration should be recorded in the eCRF.)
- Recording of AEs (Any ongoing AEs at the time the subject completed the previous pediatric BRV study should not be recorded in the eCRF for N01266, unless there is a change in intensity or seriousness. In this event, the AE should be recorded in the eCRF for N01266, with the onset date corresponding to the date of change in condition.)
- Appointment for the next visit according to the schedule described in Section 5.3

The following data will be obtained from Baseline of the previous pediatric BRV study and should not be recorded in the eCRF for N01266:

- General medical and procedures history
- Epilepsy history
- AED history
- Height
- Bayley-III scales (for LTFU subjects <18 months of age at Baseline of N01263 or other pediatric BRV studies and only for subjects enrolled in English-speaking countries)
- Achenbach CBCL score (see Section 10.3.3)
- Laboratory assessments
  - Endocrinology

The following data will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266:

- Recording of medications
- Recording of procedures
- Seizure count
- EEG
  - For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: an EEG of at least 1 hour of recording (including hyperventilation and intermittent photic stimulation) must be performed
  - For subjects ≥1 month to <2 years of age on the day of the study visit: an EEG of at least 24 hours of recording (including sleeping and awakening periods) must be performed
- ECG
- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects ≥4 years of age)
  - Urine pregnancy test (**see Section 9.5.1**)
- Phenytoin plasma concentrations (if applicable)
- Suicidality assessment (C-SSRS) (for subjects ≥6 years of age)
- Vital signs

- Body weight
- Physical examination
- Neurological examination
- Psychiatric and mental status
- Health care provider consultations not foreseen by the protocol
- Hospital stays

Change #26, Section 8.3.2, Directly enrolled subjects, bullet point 18

The original text:

- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis
  - Urine pregnancy test (if applicable)

Has been changed to:

- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis
  - Urine pregnancy test (**see Section 9.5.1**)

Change #27, Section 8.4, Minimal Evaluation Visit, header

The original text:

8.4 Minimal Evaluation Visit

Has been changed to:

8.4 Minimal Evaluation Visit **(all subjects)**

Change #28, Section 8.5, Full Evaluation Visit, header

The original text:

8.5 Full Evaluation Visit

Has been changed to:

8.5 Full Evaluation Visit **(all subjects)**

Change #29, Section 8.5, Full Evaluation Visit, bullet point 20

The original text:

- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects ≥4 years of age)
  - Urine pregnancy test (if applicable)

Has been changed to:

- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects ≥4 years of age)
  - Urine pregnancy test (**see Section 9.5.1**)

Change #30, Section 8.6, Yearly Evaluation Visit, header

The original text:

8.6 Yearly Evaluation Visit

Has been changed to:

8.6 Yearly Evaluation Visit **(all subjects)**

Change #31, Section 8.6, Yearly Evaluation Visit, bullet point 21

The original text:

- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects ≥4 years of age)
  - Urine pregnancy test (if applicable)
  - Endocrinology

Has been changed to:

- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects ≥4 years of age)
  - Urine pregnancy test (**see Section 9.5.1**)
  - Endocrinology

Change #32, Section 8.7, Unscheduled Visit, header

The original text:

8.7 Unscheduled Visit

Has been changed to:

8.7 Unscheduled Visit **(all subjects)**

Change #33, Section 8.8, Early Discontinuation Visit, header

The original text:

8.8 Early Discontinuation Visit

Has been changed to:

8.8 Early Discontinuation Visit **(all subjects)**

Change #34, Section 8.8, Early Discontinuation Visit, bullet point 20

The original text:

- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects ≥4 years of age)
  - Serum pregnancy test (if applicable)

Has been changed to:

- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects ≥4 years of age)

- Serum pregnancy test (**see Section 9.5.1**)

Change #35, Section 8.9, Down-Titration Visit, header

The original text:

8.9 Down-Titration Visit

Has been changed to:

8.9 Down-Titration Visit **(all subjects)**

Change #36, Section 8.10, Safety Visit, header

The original text:

8.10 Safety Visit

Has been changed to:

8.10 Safety Visit **(all subjects)**

Change #37, Section 8.10, Safety Visit, bullet point 14

- Laboratory assessments for safety (to be performed only if abnormal at the EDV)
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects ≥4 years of age)
  - Serum pregnancy test (if applicable)

Has been changed to:

- Laboratory assessments for safety (to be performed only if abnormal at the EDV)
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects ≥4 years of age)
  - Serum pregnancy test (**see Section 9.5.1**)

Change #38, Section 8.11, Final Visit, header

The original text:

8.11 Final Visit

Has been changed to:

8.11 Final Visit **(all subjects)**

Change #39, Section 8.11, Final Visit, bullet point 18

The original text:

- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects ≥4 years of age)
  - Urine pregnancy test (if applicable)
  - Endocrinology

Has been changed to:

- Laboratory assessments for safety
  - Hematology
  - Biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT)
  - Urinalysis (for subjects ≥4 years of age)
  - Urine pregnancy test (**see Section 9.5.1**)
  - Endocrinology

Change #40, Section 9.5.1, Laboratory assessments for safety, table footnote d

The original text:

[d] Female subjects with a Tanner stage >1 should have urine pregnancy tests at the EV (directly enrolled subjects only), YEVs/FV, and FEVs and serum pregnancy tests at the ScrV (directly enrolled subjects only), EDV, and SV.

Has been changed to:

[d] **All female** subjects with a Tanner stage >1 should have urine pregnancy tests at the **EV**, YEVs/FV, and FEVs and serum pregnancy tests at the ScrV (directly enrolled subjects only), EDV, and SV.

Change #41, Section 9.5.1, Laboratory assessments for safety, paragraphs 5 and 6

The original text:

For LTFU subjects, laboratory safety assessments at the EV will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266. Laboratory safety assessments (hematology, biochemistry [including hepatic monitoring: total bilirubin, ALP, AST, ALT, and GGT], urinalysis [for subjects ≥4 years of age, and pregnancy testing [as applicable]) will be performed at the ScrV and EV (directly

enrolled subjects only), FEV, YEV, FV, and at the EDV in the case of early discontinuation. Laboratory assessments will also be mandatory at the SV if the laboratory results at the EDV are abnormal. Only hepatic monitoring assessments will be performed at the final TV (directly enrolled subjects only), and the MEVs at V4 (M3) and V6 (M9) during the first year; no laboratory safety assessments will be performed at other MEVs. Endocrinology testing will be performed at the ScrV (directly enrolled subjects only) and once a year at the YEV. For LTFU subjects, the Baseline endocrinology values will be taken from Baseline of the previous pediatric BRV study.

Female subjects who have a Tanner stage >1 should have urine pregnancy tests at the EV (directly enrolled subjects only), YEVs/FV, and FEVs and serum pregnancy tests at the ScrV (directly enrolled subjects only), EDV, and the SV. A serum pregnancy test will be performed as backup if a urine sample is not available. A urine pregnancy test should be performed at any time during the study if a pregnancy is suspected.

Has been changed to:

For LTFU subjects, **pregnancy testing (if applicable) will be performed at the EV and other** laboratory safety assessments at the EV will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266. Laboratory safety assessments (hematology, biochemistry [including hepatic monitoring: total bilirubin, ALP, AST, ALT, and GGT], urinalysis [for subjects ≥4 years of age, and pregnancy testing [as applicable]) will be performed at the ScrV and EV (directly enrolled subjects only), FEV, YEV, FV, and at the EDV in the case of early discontinuation. Laboratory assessments will also be mandatory at the SV if the laboratory results at the EDV are abnormal. Only hepatic monitoring assessments will be performed at the final TV (directly enrolled subjects only), and the MEVs at V4 (M3) and V6 (M9) during the first year; no laboratory safety assessments will be performed at other MEVs. Endocrinology testing will be performed at the ScrV (directly enrolled subjects only) and once a year at the YEV. For LTFU subjects, the Baseline endocrinology values will be taken from Baseline of the previous pediatric BRV study.

All female subjects who have a Tanner stage >1 should have urine pregnancy tests at the **EV**, YEVs/FV, and FEVs and serum pregnancy tests at the ScrV (directly enrolled subjects only), EDV, and the SV. A serum pregnancy test will be performed as backup if a urine sample is not available. A urine pregnancy test should be performed at any time during the study if a pregnancy is suspected.

Change #42, Section 9.6.8, BRIEF-P and BRIEF, paragraph 6

The original text:

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 6 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.

Has been changed to:

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.

Change #43, Section 12.6, Handling of protocol deviations

The original text:

After all eCRFs have been entered and queries addressed, and prior to locking the clinical database, a data review meeting (DRM) will be held. The purpose of this DRM will be to assess the quality of the data for subsequent database lock, identify protocol deviations, and finalize analysis sets.

Has been changed to:

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. To the extent feasible, the rules for identifying protocol deviations will be defined without review of the data and without the 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 database lock to confirm exclusion from analysis sets.

Change #44, Section 12.8, Planned interim analysis and data monitoring

The original text:

Due to the single-arm open-label design of this study, no formal interim analysis as such will be performed. However, interim database locks will be performed to allow safety and efficacy analyses in support of submission activities and to allow optimization of the development program.

Has been changed to:

No formal interim analysis is planned; however, data may be reported prior to the completion of this study to support ongoing data cleaning, annual reports, regulatory submissions, and publications.

Change #45, Section 12.9, Determination of sample size

The original text:

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 previous pediatric study with BRV as adjunctive treatment in epilepsy will rollover into the present study. With Protocol Amendment 3, enrollment is expanded to include up to 100 directly enrolled subjects (≥4 years to <17 years of age) with POS, thus increasing possible enrollment up to 600 subjects.

Has been changed to:

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 previous pediatric study with BRV as adjunctive treatment in epilepsy will rollover into the present study. With Protocol Amendment 3, enrollment **was** expanded to include up to 100 directly enrolled subjects (≥4 years to <17 years of age) with POS, thus increasing possible enrollment up to 600 subjects. **With Protocol Amendment 4, the number of directly enrolled subjects is increased to at least 100 subjects with the planned total enrollment of approximately 600 subjects.**

16.5 Protocol Amendment 5

Rationale for the amendment

The main purposes of this amendment are to:

- Add an updated list of Anticipated SAEs.
- Add a section on AEs of special interest in accordance with the Sponsor template requirement.
- Update of the schema for down-titration to align with N01263 and provide uniformity across the BRV pediatric development program.
- Removal of requirement that subjects <7 years of age receive oral solution and, as appropriate, subjects ≥7 years of age receive tablets in recognition of individual subject preferences to allow subjects additional flexibility in treatment options.
- Provide Entry Visit information specific to subjects who enroll from core studies under development.
- Provide additional clarity regarding enrolled subjects who participate in EP0065 and then resume participation in N01266. Protocol Amendment 3 had allowed for subjects to participate in what was called a "substudy."
- Clarified requirement that subjects ≥2 years of age with typical absence seizures have at least a 24-hour EEG, instead of a 1-hour EEG.
- Eliminate the EEG at the 3-month visit (V4) and the requirement for subjects to have EEGs after they reach 2 years of age (exception: subjects with typical absence seizures) and allow the EDV EEGs to be done at the Investigator's discretion. This change was made due to the limited clinical utility of these assessments and to unburden the Investigator, subject, and subject's caregiver/family.

- Replace serum pregnancy tests with urine pregnancy tests and inclusion of urine pregnancy tests at all MEVs.
- Update according to the current Sponsor protocol template. This includes:
  - The addition of text regarding PDILI; these changes were strictly template-driven. They do not reflect a change in the liver safety signal for BRV and are included only for alignment with updated standard Sponsor text across programs.
  - The streamlining of Introduction with reference to the availability of additional information in the Investigator's Brochure.
- Update of Introduction text to include more current literature references and to include information about the marketing authorization of BRV.
- Revision of the duration of the study for an individual subject from approximately 3 years to at least 3 years, with the addition of the possibility of subjects entering a managed access program, if available.
- Removal of the BRV 1.0mg/mL oral solution from the description of the IMP as the BRV 10mg/mL oral solution is adequate for dosing.

Modifications and changes

Global changes

These following changes are considered administrative in nature and are not included as separate listings in the table of specific changes below:

- BRV 1.0mg/kg/day, 2.0mg/kg/day, and 4.0mg/kg/day have been changed to 1mg/kg/day, 2mg/kg/day, and 4mg/kg/day, respectively, for consistency across the BRV pediatric development program.
- "Drug Safety" has been replaced with "Patient Safety" as an administrative change to a departmental name.
- Stylistic changes and minor editorial changes have been made and are of no consequence to the meaning of content.

Specific changes

The following table provides a list of specific changes to the protocol. Specific changes to the tables in Section 5.2 (Table 5-1, Table 5-2, Table 5-3, and Table 5-4) are provided immediately after the table and are not included in the table itself.

Section Impacted	Key components of previous text		Key components of amended text	Rationale
Sponsor Declaration	Sponsor Declaration I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice. Clinical Project Manager [redacted] Clinical Trial Biostatistician [redacted] Study Physician [redacted] Clinical Program Director [redacted] Clinical Pharmacology Director [redacted]	_____ Date/Signature _____ Date/Signature _____ Date/Signature _____ Date/Signature _____ Date/Signature	Removed text and signatures/dates (not shown).	Update per template. Required signatures are now provided as the final page of the protocol.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Study Contact Information	Sponsor Study Physician: Name: [redacted] Address: 8010 Arco Corporate Drive, [redacted] Raleigh, NC 27617 United States Phone: [redacted] Fax: [redacted] Clinical Project Manager: Name: [redacted] Address: UCB Center Bruxelles Phone: [redacted]	Sponsor Study Physician: Name: [redacted] Address: UCB Biosciences GmbH Alfred Nobel Strabe 10 40789 Monheim Germany Phone: [redacted] Fax: [redacted] Clinical Project Manager: Name: [redacted] Address:UCB BioPharma sprl Phone: [redacted]	Update with administrative changes.
Serious Adverse Event Reporting	Serious adverse event reporting (24h) and safety related issues **Fax:** Europe and Rest of the World (except Japan): +32 2 386 2421 US: +1 800 880 6949 Canada: +1 877 582 8842 **Email:** Europe, US, and Rest of the World (except Japan): DS-ICT@ucb.com	Serious adverse event reporting (24h) **Fax:** Europe and Rest of the World: +32 2 386 2421 US and Canada: +1 800 880 6949 or +1 866 890 3175 **Email**: Global: DS_ICT@ucb.com	Update to Sponsor template.
List of Abbreviations	ICH: International Conference on Harmonisation PND: postnatal day ULD: Unverricht-Lundborg disease	ICH: International Council for Harmonization iv: intravenous PDILI: potential drug-induced liver injury PS: Patient Safety SV2A: synaptic vesicle protein 2A	Revise abbreviation. Provide intradocument consistency.

Section 1

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 1	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 was initially designed for pediatric subjects who had completed N01263 or would complete other future pediatric BRV studies (herein referred to as "long-term follow-up" [LTFU] subjects). With Protocol Amendment 3, enrollment was expanded to include up to 100 subjects ≥4 years to <17 years of age with POS who had not previously enrolled in a pediatric BRV study (herein referred to as "directly enrolled subjects"). With Protocol Amendment 4, the number of directly enrolled subjects is increased to at least 100 subjects with the planned total enrollment of approximately 600 subjects. In addition, the dosing scheme was aligned so that it is no longer age-dependent; previously, subjects ≥8 or <8 years of age were dosed under different dosing schemes. 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 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 the previous BRV study and	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 POS who had not previously enrolled in a pediatric BRV study (herein referred to as "directly enrolled 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 directly enrolled 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 ≥1 month of age at the Baseline of the core study and for all directly	Update to Sponsor template to provide focus on current study design. Update to provide clarification/ additional information for subjects entering N01266 from core studies (previously referred to as previous BRV studies) and for enrolled subjects who participate in EP0065 then resume participation in N01266. Removal of age-based requirements for use of oral solution and tablets in recognition of individual subject preferences. Revise duration of individual subject participation to at least 3 years. Add managed access

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	for all directly enrolled subjects. With Protocol Amendment 3, the effect of BRV on cognition will also be assessed using the Behavior Rating Inventory of Executive Function® (BRIEF®)/BRIEF®-Preschool Version (BRIEF®-P) and the effect of BRV on quality of life will be assessed using the Pediatric Quality of Life Inventory™ (PedsQL™) for LTFU subjects ≥1 month of age at the Baseline of the previous BRV study and for all directly enrolled 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 <18 months of age at Baseline of the previous pediatric BRV study; the Bayley-III will not be used to access directly enrolled 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 previous pediatric BRV 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 directly enrolled subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than 1.0mg/kg/day) for 7±2 days during the Up-Titration Period, the subject will attend the EV and enter the Evaluation Period on that	enrolled 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 <18 months of age at Baseline of the core study; the Bayley-III will not be used to assess directly enrolled 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 directly enrolled 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. Brivaracetam (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 directly enrolled subjects must be able to tolerate at least 1mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266, as indicated in	as a factor for determining length of participation. Change urinalysis from age-based requirement to feasibility requirement in recognition individual subject capabilities. Clarify that head circumference is included as a safety variable (previously included with neurological examination variable).

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	dose. Brivaracetam (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 previous BRV study to be eligible for entry into the Evaluation Period of N01266. All directly enrolled subjects must be able to tolerate at least 1.0mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266, as indicated in Section 7.2. The maximum allowable BRV dose is 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg. Subjects <7 years of age will receive oral solution. Subjects ≥7 years of age will receive 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 approximately 3 years, until approval of BRV has been obtained for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor. For LTFU subjects, the EV is the first study	Section 7.2. The maximum allowable BRV dose is 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg. 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, 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 directly enrolled 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	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	visit. For directly enrolled 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 study drug-free Safety Period, and a final Safety Visit (SV). At selected sites, subjects may be able to participate in a substudy without withdrawing from N01266. 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-glutamyltransferase [GGT], and endocrinology for all subjects and urinalysis for subjects ≥4 years of age), plasma concentrations of BRV and phenytoin (if applicable), electrocardiograms (ECGs), vital signs, physical and neurological examinations, psychiatric and mental status, body weight, and height.	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. 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-glutamyltransferase [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. 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	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	Up to 600 subjects may possibly enroll in this study. The number and location of sites will depend on those participating in N01263 and other future pediatric BRV 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 N01263 and other pediatric BRV studies.	enrollment will include, but not be limited to, sites participating in core studies.	

Section 2

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 2.1	Header: Background and epidemiology of targeted disease. Epilepsy is one of the most common and challenging neurological disorders. It has been estimated that over 50 million people are affected worldwide (Engel and Pedley, 1998; Sander and Shorvon, 1996; Hauser et al, 1993; Loiseau et al, 1990). The prevalence of epilepsy is around 1%. The annual incidence in developed countries is approximately 50 to 70 cases per 100,000. In developing countries, the figure is higher due to more limited obstetric services and the greater likelihood of cerebral infection and trauma. The incidence varies greatly with age, with high rates occurring in childhood, falling to low levels in early adult life, but with a second peak in those aged over 65 years. In many people, particularly children, the condition may remit, although a significant	Header: Background regarding targeted disease. Epilepsy is the second most prevalent neurological disorder in the world. It is estimated that almost 70 million people suffer from epilepsy (Ngugi et al, 2011). Epilepsy affects about 4 to 6 out of 1,000 children aged less than 20 years old, and the overall annual incidence rates of epilepsy for all seizure types for all children aged less than 19 years range between 45 and 86 out of 100,000 children. Long-term prognosis of epilepsy varies across several factors such as types of syndromes, etiology, and presence of co-morbidities. The existing treatment options for epilepsy in childhood generally follow the treatment options for adults, and clinical experience demonstrates that children may benefit from the administration of conventional AEDs for the treatment of partial-onset seizures (POS) with comparable	Update header to Sponsor template. Update to provide more current and concise background information.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	proportion will have epilepsy lifelong. The disease duration is often determined by the underlying cause. Sudden unexpected death, a complication of great concern, occurs in 1 to 5 per 1000 patient years, particularly if the seizure disorder remains uncontrolled. The treatment for epilepsy remains difficult, and there is an ongoing medical need for new AEDs. For a considerable proportion (up to 30%) of patients, seizure freedom can still not be reached with currently available AEDs (Nasreddine et al, 2010; Kwan and Brodie, 2001). Seizures encountered in adulthood may also be experienced in childhood, including simple and complex partial seizures (Dulac, 1994). The existing treatment options for partial epilepsy in childhood generally follow the treatment options for adults, and clinical experience demonstrates that children may benefit from the administration of conventional AEDs for the treatment of partial-onset seizures (POS) with comparable results to adults.	results to adults. Despite the availability of new AEDs, more than 25% of pediatric patients have inadequate seizure control on currently available AEDs, or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007). Thus, there remains a need for potent AEDs with a positive benefit-risk profile in this population.	
Section 2.2	Brivaracetam is a chemical relative of the AED levetiracetam (LEV, Keppra®). Like LEV, BRV displays a high and selective interaction with a novel brain-specific binding site, synaptic vesicle protein 2A (SV2A). However, the binding affinity of BRV for SV2A is approximately 10-fold higher. This binding site appears to be the major target for its pharmacological activity. Unlike LEV, BRV also reduces voltage-dependent sodium currents. Brivaracetam also reverses the inhibitory effects	Brivaracetam ((2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1*H*-pyrrol-1-yl]butanamide) displays a high and selective affinity for the synaptic vesicle protein 2A (SV2A) in the brain. Binding to SV2A is believed to be the primary mechanism for BRV anticonvulsant activity. In 2016, marketing authorization for the use of oral and iv BRV as adjunctive treatment of partial-onset seizures (POS) in patients 16 years of age and older with epilepsy was granted in the EU, US, Australia, and Switzerland, and in	Update to provide marketing approval status and to remove information available in the Investigator's Brochure.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	of negative allosteric modulators on gamma-aminobutyric acid- and glycine-induced currents. Brivaracetam is extensively metabolized, but seizure protection appears to be associated with the parent compound. The effects of long-term oral administration of BRV were evaluated in juvenile rats (9-week study; up to 600mg/kg/day) and in juvenile dogs (9-month study; up to 100mg/kg/day). In juvenile rats and dogs, and consistent with adult animals, the target organ was the liver with different sensitivity across species. In the rat, the highest dose tested (600mg/kg/day) was considered to induce developmental adverse effects (mortality, clinical signs, and decreased body weights, mainly in preweaning pups). In the younger age category (postnatal day [PND] 4 in a rat and PND 4 in a dog corresponds to a preterm human neonate), exposure at the no-observed-adverse-effect level was 17- to 38-fold higher in rats and 3- to 7-fold higher in dogs than the anticipated exposure in the equivalent pediatric population (29µg.h/mL or 63µg.h/mL, which are the area under the curve [AUC_{0-24h}] in adults at the doses of 100 or 200mg/day, respectively). At later periods, the exposure multiples were similar to those seen in adult toxicity studies (at least 3-fold in rats and 1.2-fold in dogs). Brivaracetam is rapidly and completely absorbed throughout the gastrointestinal tract. The extent of BRV absorption is not affected by food. The pharmacokinetics (PK) are dose-proportional (at least from 10mg to	Canada for patients 18 years and older with epilepsy. More detailed information regarding the nonclinical and clinical development programs for BRV, including all completed and ongoing studies, is provided in the Investigator's Brochure.	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	600mg). Brivaracetam is weakly bound to plasma proteins (≤20%). The volume of distribution is 0.5L/kg, a value that is close to that of total body water. The plasma half-life of BRV is approximately 8 hours in young healthy male adults. The main metabolic pathway of BRV is by hydrolysis of the acetamide group to the corresponding carboxylic acid, ucb-42145, while a minor pathway is the ω1-hydroxylation into ucb-100406-1 mediated by cytochrome P450 (CYP)2C19. The combination of these 2 pathways results in the hydroxyacid terminal metabolite ucb-107092-1. These metabolites are not pharmacologically active. There is no evidence of chiral inversion of BRV. Brivaracetam is eliminated primarily by metabolism and by excretion in the urine. More than 95% of the dose, with less than 9% as unchanged BRV, is excreted in urine within 72 hours after dosing. Pharmacokinetic studies in elderly and in subjects with renal impairment showed a similar PK profile of BRV compared to that in healthy subjects while the elimination of the metabolites was markedly slowed down. A PK study in subjects with hepatic impairment showed a 50% increase in exposure to BRV associated with decreased hydroxylation. Brivaracetam does not impair the efficacy of oral contraceptives containing ethinylestradiol 30µg and levonorgestrel 150µg. Brivaracetam does not induce CYP3A4 using midazolam as a marker probe. Brivaracetam has no interaction on lamotrigine and topiramate.		

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	Brivaracetam plasma concentration is not increased by gemfibrozil, a selective CYP2C8/9 inhibitor, but is increased in a nonclinically relevant manner in subjects possessing defective CYP2C19 mutations. Brivaracetam clearance is doubled by rifampicin, a potent CYP inducer. Trough levels of concomitant AEDs were monitored in all efficacy studies. No significant change from Baseline or dose-related trend was observed for the plasma concentrations of: carbamazepine, lamotrigine, LEV, oxcarbazepine metabolite, phenobarbital, phenytoin, topiramate, valproate, or zonisamide. Carbamazepine epoxide was increased by 50% to 60% at BRV doses of 100 and 150mg/day due to inhibition of epoxide hydrolase. There is no need for BRV dose adjustment in the presence of carbamazepine.		
No longer applicable (Section 2.3 of Amendment 4)	Section 2.3 Efficacy with BRV (adult studies) Following completion of the Phase 2 studies (N01114 and N01193), clinical results supported further development of BRV for the adjunctive treatment of POS. Two adequate and well-controlled fixed-dose studies (N01252 and N01253) were conducted to assess BRV across a dose range of 5 to 100mg/day. N01253 assessed BRV doses of 5, 20, and 50mg/day and provided statistically significant and clinically relevant evidence of the efficacy of BRV 50mg/day. N01252 assessed BRV doses of 20, 50, and 100mg/day. Although N01252 was not positive, it provided supporting evidence for the efficacy of BRV 100mg/day in	Deleted.	Update to remove information now available in the prescribing information and the Investigator's Brochure.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	subjects with epilepsy. Two Phase 3 studies (N01187 and N01236) were conducted to evaluate the efficacy and safety of BRV at doses of 5, 50, and 150mg/day used as adjunctive treatment in adult subjects with genetically ascertained Unverricht-Lundborg disease (ULD). In both studies, primary efficacy endpoints failed to reach statistical significance. Clinical photoparoxysmal response data (PPR, N01069) suggested efficacy of BRV in subjects with photosensitive epilepsy. In addition, a subset of subjects (N=49) with generalized epilepsy in the well-controlled, flexible-dose, safety study (N01254) provides further evidence of efficacy of BRV against generalized seizures.		
No longer applicable (Section 2.4 of Amendment 4)	Section 2.4: Safety with BRV (adult studies) In Phase 2/3 studies, a favorable safety and tolerability profile has been demonstrated for BRV. The discontinuation rate and the discontinuation rate due to treatment-emergent adverse events (TEAEs) were low and similar to placebo for all studies. The most frequently reported TEAEs were headache, somnolence, dizziness, and fatigue. The overall incidence of serious adverse events (SAEs) was low and similar to placebo. There were no clinically relevant changes in laboratory values, vital signs, or ECG abnormalities. Safety results in ULD subjects indicate that BRV was well tolerated. The most frequently	Deleted.	Update to remove information now available in prescribing information and in the Investigator's Brochure.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	reported TEAEs were headache, somnolence, and dizziness in N01187 and headache, myoclonus, and somnolence in N01236. In addition, there are 3 ongoing open-label LTFU studies (N01125, N01199, and N01315) that include subjects with POS, primary generalized seizures, or ULD who completed 1 of the Phase 2/3 well-controlled studies. As of 08 Sep 2011, 1629 subjects have been enrolled in these studies and 1624 subjects have received study medication. The median duration of BRV exposure in LTFU studies was 119 weeks. The most common TEAEs, based on interim safety monitoring review, include headache, dizziness, nasopharyngitis, convulsion, somnolence, and fatigue. Overall, 272 subjects reported SAEs. The only SAE occurring at a frequency >1% was convulsion (2.5%). Overall, 142 subjects discontinued due to TEAEs. The most common TEAEs leading to premature discontinuation were convulsion and depression. For additional details on the safety and efficacy of BRV, please refer to the Investigator's Brochure.		
Section 2.3 (Section 2.5 of Amendment 4)	Epilepsy affects about 4 to 6 out of 1,000 children aged less than 20 years old, and the overall annual incidence rates of epilepsy for all seizure types for all children aged less than 19 years range between 45 and 86 out of 100,000 children. Long-term prognosis of epilepsy varies across several factors such as types of syndromes, etiology, and presence of co-morbidities. Despite the availability of new	N01266 is designed for pediatric subjects ≥1 month to <17 years of age who have completed core studies (LTFU subjects) and for at least 100 subjects ≥4 years to <17 years of age with POS who have not participated in a core study (directly enrolled subjects). The total enrollment planned for N01266 is approximately 600 subjects. N01266 will provide long-term safety and	Eliminate repeated informational content from Section 2.1. Update in accordance with current study design.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	AEDs, more than 25% of pediatric patients have inadequate seizure control on currently available AEDs, or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007). There remains a need for potent AEDs with a positive benefit:risk profile in this population. Generally, new treatments should be made available to children through clinical studies as soon as efficacy in adults is established. Studies using BRV as adjunctive therapy in adults with POS have shown promising results in terms of both efficacy (Section 2.3) and safety (Section 2.4). In addition, BRV has demonstrated efficacy in a PPR study (N01069) as well as in a subset of subjects with generalized epilepsy in N01254. N01263 is the first study of BRV in pediatric subjects. This was an open-label, fixed 3-step up-titration, PK, safety and efficacy study to evaluate BRV as adjunctive therapy in children (aged ≥1 month to <16 years) with epilepsy using an oral solution. The safety and PK data from this study will be used for BRV dose adaptation in pediatric subjects with epilepsy. A total of 100 subjects were enrolled into this study. N01266 was originally designed to give subjects who complete N01263 or other future pediatric BRV studies (ie, LTFU subjects) an opportunity to continue BRV treatment for approximately 3 years, until approval of BRV is granted for pediatric subjects in their age range, or until the investigational product development is stopped	tolerability data on BRV in pediatric subjects with epilepsy, while providing access to BRV for subjects who may benefit from long-term treatment. The enrollment of directly enrolled subjects is intended to provide both long-term safety and tolerably data and efficacy data for subjects 4 years to <17 years of age with POS to supplement data collected for subjects with POS in N01263. 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, or until the investigational product development in the related age range of the pediatric population is stopped by the Sponsor, whichever comes first. Subjects already enrolled in N01266 may participate in EP0065, if eligible, and then resume participation in N01266.	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	by the Sponsor. With Protocol Amendment 3, enrollment was expanded to include up to 100 eligible subjects ≥4 years to <17 years of age with POS who have not participated in another pediatric BRV study (ie, directly enrolled subjects). Thus, N01266 will gather additional long-term safety and tolerability data on BRV in pediatric subjects with epilepsy while providing access to BRV for subjects who may benefit from long-term treatment. With Protocol Amendment 4, the number of directly enrolled subjects is increased to at least 100 subjects with the planned total enrollment of approximately 600 subjects. In addition, based on the PK analyses performed on the plasma samples collected in N01263, the dosing scheme for Protocol Amendment 4 was aligned so that it is no longer age-dependent; previously, subjects ≥8 or <8 years of age were dosed under different dosing schemes.		

Section 3

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 3.3	• To assess the effect of BRV on cognition using the Bayley-III scales in subjects <18 months of age (applicable only to LTFU subjects enrolled in English-speaking countries)	• To assess the effect of BRV on cognition using the Bayley-III scales in subjects <18 months of age (applicable only to LTFU subjects enrolled in English-speaking countries)	Clarification regarding age.

Section 4

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 4.1	• Safety laboratory tests (hematology, biochemistry including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT, and endocrinology for all subjects and urinalysis for subjects ≥4 years of age) • Body weight and height	• Safety laboratory tests (hematology, biochemistry including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT, and endocrinology for all subjects and urinalysis for subjects for whom sample collection is feasible) (see Section 9.2.1) • Body weight, height, and head circumference	Change of urinalysis sampling criteria as described above. Clarify that head circumference is included as described above.
Section 4.2	• Responder rate for total POS defined as the percentage of subjects with a ≥50% reduction in ADF (average daily frequency) of POS recorded on EEG • Absolute and percent reduction in ADF of POS	• Responder rate for total POS defined as the percentage of subjects with a ≥50% reduction in ADF (average daily frequency) of POS recorded on EEG (subjects with POS only) • Absolute and percent reduction in ADF of POS (subjects with POS only)	Clarity that variables apply to subjects with POS only.
Section 4.3	• Change 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 • Change from Baseline in the BRIEF-P/BRIEF score for subjects ≥2 years of age • Change from previous BRV study Baseline in the Bayley-III scales for children <18 months of age (applicable only to LTFU subjects enrolled in English-speaking	• Change 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 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 the Baseline in the Bayley-III scales for children <18 months of age at	Provide clarification regarding ages. Revise for intradocument consistency in terminology regarding core studies.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	countries) • Change from Baseline in PedsQL for subjects ≥1 month of age	baseline of the core study (applicable only to LTFU subjects enrolled in English-speaking countries) • Change from Baseline in PedsQL for subjects ≥1 month of age (age at initiation of study drug in N01266 or core study)	

Section 5

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1	This is a Phase 3, open-label, single-arm, multicenter, long-term study to evaluate the safety and efficacy of BRV in up to 600 subjects with epilepsy. Subjects who enroll in N01266 from N01263 or another pediatric BRV study (ie, LTFU subjects) must have been <16 years of age upon entry in their previous study; eligible subjects who have POS and enroll in N01266 without having participated in a previous pediatric BRV study (ie, directly enrolled subjects) must be ≥4 years to <17 years of age. Upon enrollment, eligible LTFU subjects will enter the Evaluation Period and continue their BRV treatment in accordance with their individualized dose at the completion of their previous pediatric BRV study. Brivaracetam (tablet and oral solution) should be administered bid in 2 equally divided doses. All LTFU subjects must be able to tolerate the minimum BRV dose specified in the previous	This is a Phase 3, open-label, single-arm, multicenter, long-term study to evaluate the safety and efficacy of BRV in up to 600 subjects with epilepsy. Subjects who enroll in N01266 from a core study (ie, LTFU subjects) must have been <16 years of age upon entry in the core study; eligible subjects who have POS and enroll in N01266 without having participated in a core study (ie, directly enrolled subjects) must be ≥4 years to <17 years of age. Upon enrollment, eligible LTFU subjects will enter the Evaluation Period and continue their BRV treatment in accordance with their individualized dose at the completion of the core study. The subjects already enrolled in N01266 who then participate in EP0065 will resume dosing in N01266 in accordance with the individualized dose they received at the completion of EP0065. Brivaracetam (tablet and oral solution) should be administered bid in 2 equally divided doses. All	Revise for intradocument consistency in terminology regarding core studies. Update in accordance with current study design.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	study to be eligible for entry into the Evaluation Period of N01266. All directly enrolled subjects must be able to tolerate at least 1.0mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266, as indicated in Section 7.2. For all subjects enrolled in N01266, the maximum BRV dose is 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg. Subjects <7 years of age will receive oral solution. Subjects ≥7 years of age will receive tablets, as appropriate. Subjects will continue to receive BRV treatment in this study for approximately 3 years, until approval for BRV has been obtained for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor. Following the EDV, subjects will have their dose of BRV down titrated over a maximum of 4 weeks (Down-Titration Period). After 2 weeks free of study drug (Safety Period), subjects will complete the SV.	LTFU subjects must be able to tolerate the minimum BRV dose specified in the core study to be eligible for entry into the Evaluation Period of N01266. All directly enrolled subjects must be able to tolerate at least 1mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266, as indicated in Section 7.2. For all subjects enrolled in N01266, the maximum BRV dose is 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg. Subjects will receive oral solution or oral tablets, as appropriate. Following the EDV, subjects will have their BRV dose reduced by a maximum of half the dose every week for a maximum of 4 weeks until a dose of 1mg/kg/day (50mg/day for subjects with body weights >50kg) is reached. Enrolled subjects who participate in EP0065 and then resume participation N01266 will maintain the visit schedule established for them in N01266 before participation in EP0065.	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1.1	Subject participation will extend from study entry for approximately 3 years, until approval of BRV has been obtained for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor.	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, or until the investigational product development in the related age range of the pediatric population is stopped by the Sponsor, whichever comes first.	Revise duration of individual subject participation to at least 3 years. Addition of managed access as a factor for determining length of participation.
Section 5.1.2	As originally designed, up to 500 subjects (<16 years of age upon entry in their previous pediatric BRV study) might possibly enroll in this study during the pediatric development plan, based upon the assumption that 90% of subjects having completed a previous pediatric study with BRV as adjunctive treatment in epilepsy would rollover into N01266. With Protocol Amendment 3, enrollment was expanded to include up to 100 eligible directly enrolled subjects ≥4 years to <17 years of age with POS, which allowed up to 600 subjects to enroll in N01266 instead of the up to 500 originally planned. With Protocol Amendment 4, the number of directly enrolled subjects is increased to at least 100 subjects with the planned total enrollment of approximately 600 subjects.	N01266 is planned for a total enrollment of approximately 600 subjects, including at least 100 eligible directly enrolled subjects ≥4 years to <17 years of age with POS.	Simplify text to reflect current design only and eliminate repetition of sample size estimates from the study rationale section.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1.3	As originally designed, the regions and countries participating in this study depended on the location of the sites participating in the previous pediatric BRV study/studies, as these sites should have had access to the originally planned LTFU study. Europe, US, and Mexico were foreseen, with the possibility to extend to other countries and regions if deemed necessary. With Protocol Amendment 3, directly enrolled subjects may be enrolled from sites participating in N01263 and possibly other sites, including, but not limited to, those participating in other pediatric BRV studies.	The LTFU subjects will be enrolled in regions and countries participating in the core studies. Enrollment is planned for Europe, US, and Mexico, with the possibility to extend to other countries and regions if deemed necessary. Directly enrolled subjects may be enrolled from sites participating in core studies and possibly other sites.	Simplify text to reflect current design only.
Section 5.2	Once a directly enrolled subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than the minimum specified dose) for 7±2 days during the Up-Titration Period, the subject will attend the EV, enter the Evaluation Period on that dose, and follow the study assessments in Table 5-1. Table 5-1 provides a schedule of all study assessments for LTFU subjects and for assessments subsequent to the final TV for directly enrolled subjects. Table 5-2 provides a schedule of study assessments for directly enrolled subjects from the ScrV through the final TV.	Table 5-1 provides a schedule of assessments for the EV (all subjects). Table 5-2 provides a schedule of assessments for the Evaluation, Down-Titration, and Safety (Drug-Free) Periods (all subjects). Table 5-3 provides a schedule of study assessments from the ScrV through the final TV (directly enrolled subjects only).	Update text to reflect addition of new table and update of existing tables.
Section 5.4	N01266 will allow BRV long-term safety and tolerability data to be collected from pediatric subjects with epilepsy who will have participated in previous pediatric BRV studies	N01266 will allow BRV long-term safety and tolerability data to be collected from pediatric subjects with epilepsy who will have participated in core studies and now have the opportunity to	Update for intradocument consistency in terminology

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	and now have the opportunity to continue BRV treatment, and from directly enrolled subjects with POS. The safety and efficacy data collected in this study will support the applications for BRV indications in pediatric patients. Each LTFU subject will begin treatment in N01266 at the individualized BRV dose he/she was receiving at the completion of the previous pediatric study. Directly enrolled subjects will participate in up to 3 weeks of an Up-Titration Period. If a subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV for 7±2 days during the Up-Titration Period, the subject will be allowed to enter the Evaluation Period (subject must be able to tolerate the minimum dose of 1.0mg/kg/day; see Section 7.2). For all subjects, the approximate doses to be administered are 0.5, 1.0, and 2.0mg/kg bid (1.0, 2.0, and 4.0mg/kg/day, respectively), with the daily doses not exceeding the maximums of 50mg/day, 100mg/day, and 200mg/day for Weeks 1, 2, and 3 of up-titration, respectively. In the recently completed N01263, BRV was eliminated more rapidly in pediatric subjects than in adult subjects, resulting in a lower plasma concentration. Therefore, clearance of BRV was shown to be higher in pediatric subjects than in adult subjects. All directly enrolled subjects must be able to	continue BRV treatment, and from directly enrolled subjects with POS. The safety and efficacy data collected in this study will support the applications for BRV indications in pediatric patients. Each LTFU subject will begin treatment in N01266 at the individualized BRV dose he/she was receiving at the completion of the core study. Enrolled subjects who volunteer to participate in EP0065 will resume dosing in N01266 in accordance with the individualized dose they received at the completion of EP0065. Directly enrolled subjects will participate in up to 3 weeks of an Up-Titration Period. If a subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV for 7±2 days during the Up-Titration Period, the subject will be allowed to enter the Evaluation Period (subject must be able to tolerate the minimum dose of 1mg/kg/day; see Section 7.2). For all subjects, the approximate doses to be administered are 0.5, 1, and 2mg/kg bid (1, 2, and 4mg/kg/day, respectively), with the daily doses not exceeding the maximums of 50mg/day, 100mg/day, and 200mg/day for Weeks 1, 2, and 3 of up-titration, respectively. In N01263, BRV was eliminated more rapidly in pediatric subjects than in adult subjects, resulting in a lower plasma concentration. Therefore, clearance of BRV was shown to be higher in pediatric subjects than in adult subjects. All directly enrolled subjects must be able to	regarding core studies. Provide dosing information for subjects who resume dosing in N01266 after participation in EP0065. Remove age-based requirement for oral solution and tablet dosing as described above.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	tolerate at least 1.0mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266, as indicated in Section 7.2. Subjects <7 years of age will receive oral solution. Subjects ≥7 years of age will receive tablets, as appropriate.	tolerate at least 1mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266, as indicated in Section 7.2. Subjects will receive oral solution or tablets, as appropriate.	

Section 6

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 6	Not applicable.	The nonconsecutive numbering and application of letters to some numbers in this section reflect changes that have occurred with protocol amendments.	Provide explanation of renumbering required by Sponsor template.
Section 6.1	Criteria that were in place before Protocol Amendment 3 have retained the previous numbering.	Deleted.	Remove explanation no longer needed.
Section 6.1.1	2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator. 4. Female subjects without childbearing potential are eligible. 5. Female subjects with childbearing potential who are not sexually active are eligible.	2a. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake (including BRV oral solution or tablets) according to the judgment of the Investigator. 14. For female subjects, the subject is • Not of childbearing potential -OR-	Clarify (2a). Update to BRV pediatric development program standards (14).

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	Subjects need to notify the Investigator if there is an anticipated change in status. 6. Female subjects with childbearing potential who are sexually active are eligible if they use a medically accepted contraceptive method. Oral or depot contraceptive treatment with at least ethinylestradiol 30µg per intake or ethinylestradiol 50µg per intake if associated with any strong inducer (eg, carbamazepine, phenobarbital, primidone, phenytoin, oxcarbazepine, St. John's Wort, rifampicin), a monogamous relationship with a vasectomized partner, or double-barrier contraception, are acceptable methods. The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the Investigator of any potential change in status. 7. Female subjects with childbearing potential must have a negative pregnancy test.	• Of childbearing potential, and – Is not sexually active – Has a negative pregnancy test -OR- • Of childbearing potential, and – Is sexually active – Has a negative pregnancy test – Understands the consequences and potential risks of inadequately protected sexual activity, understands and properly uses contraceptive methods, and is willing to inform the Investigator of any contraception changes. Medically acceptable contraceptive methods for the study include, but are not limited to: – Oral or depot contraceptive treatment with at least ethinylestradiol 30µg per intake or ethinylestradiol 50µg per intake if also taking one of the following: carbamazepine, phenobarbital, primidone, phenytoin, oxcarbazepine, St. John's Wort, or rifampicin – Barrier contraception: intrauterine device, diaphragm	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		with spermicide, male or female condom with spermicide – Abstinence from sexual intercourse	
Section 6.1.2	3. Male or female subjects having participated in a previous pediatric study in epilepsy with BRV and for whom a reasonable benefit from long-term administration of BRV is expected.	3a. Male or female subjects having participated in a core study and for whom a reasonable benefit from long-term administration of BRV is expected.	Provide intra-document consistency with "core study" terminology. Revise to allow enrollment of subjects from N01349 (a study in neonates with electroencephalo-grahic neonatal seizures).
Section 6.2.1	Not applicable.	29. Subject has >1.5x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >1.0xULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%). N01349 subjects with a total bilirubin > ULN may be considered for the study if benign unconjugated hyperbilirubinemia is suspected	Update to Sponsor template.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		in the context of prolonged neonatal jaundice, after discussion with the medical monitor. For randomized subjects with a baseline result >ULN for ALT, AST, ALP, or total bilirubin, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the eCRF. If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at the baseline referenced in Table 5-1 for LTFU subjects and the Screening Visit for directly enrolled subjects, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor. Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes re-screening. 30. Subject has chronic liver disease.	
Section 6.2.2	2. Subject has developed hypersensitivity to any components of the investigational medicinal product (IMP) or comparative drugs as stated in this protocol during the course of the previous BRV study. 4. Subject had poor compliance with the visit schedule or medication intake in the previous BRV study.	2a. Subject had hypersensitivity to BRV or excipients or comparative drugs as stated in this protocol during the course of the core study. 4a. Subject had poor compliance with the visit schedule or medication intake in the core study. 7a. Subject ≥ 6 years of age has a lifetime history of suicide attempt (including actual attempt,	Revise to provide consistency with the BRV Investigator's Brochure and across BRV pediatric program. Provide intra-document consistency with "core study"

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	7. Subject has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at the EV.	interrupted attempt, or aborted attempt), has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at the EV. If a subject has active suicidal ideation without a specific plan as indicated by a positive response ("Yes") to Question 4 of Columbia-Suicide Severity Rating Scale (C-SSRS) at the EV, the subject should be referred immediately to a Mental Healthcare Professional and may be excluded from the study based upon the Investigator's judgment of benefit/risk of continuing the subject in the study/on study medication.	terminology.
Section 6.2.3	27. Subject has impaired hepatic function: • Alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alkaline phosphatase of more than 2x the upper limit of normal (ULN), or total bilirubin of more than 2xULN. • Gamma-glutamyltransferase (GGT) values of more than 3xULN. A result of GGT exceeding 3xULN can be accepted only if attributable to hepatic	Deleted.	Replacement by template text for all subjects (see Section 6.2.3)

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	enzyme induction caused by concomitant antiepileptic treatment and if other hepatic enzymes are below 2xULN.		
Section 6.3	Subjects are free to withdraw from the study at any time, without prejudice to their continued care. Subjects should be withdrawn from the study if any of the following events occurs: 1. Subject develops an illness that, in the opinion of the Investigator, would interfere with his/her continued participation or would potentially be detrimental to his/her physical/mental health. 2. Subject presents with current depressive symptoms, current suicidal ideation, and/or behavior. 3. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator. 4. Subject takes prohibited concomitant medications as defined in the protocol. 5. Subject/parent(s)/legal representative(s) withdraws his/her/their consent. 6. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test. 7. The Sponsor or a regulatory agency requests withdrawal of the subject.	Subjects are free to withdraw from the study at any time, without prejudice to their continued care. Withdrawal criteria are provided as follows, with criteria for potential drug-induced liver injury provided in Section 6.3.1. Subjects must be withdrawn from the study if any of the following events occurs: 1. Subject develops an illness that, in the opinion of the Investigator, would interfere with his/her continued participation or would potentially be detrimental to his/her physical/mental health. 4. Subject takes prohibited concomitant medications as defined in the protocol. 5. Subject/parent(s)/legal representative(s) withdraws his/her/their consent. 6. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test. 7. The Sponsor or a regulatory agency requests withdrawal of the subject. 8a. Subject has an episode of convulsive status epilepticus, a prolongation of seizure duration, a worsening of seizure frequency, or emergence of a new type, that is considered by the Investigator to require intervention.	Update to Sponsor template including movement of PDILI criteria to dedicated section (Section 6.3.1). Add information specific to enrolled subjects who volunteer to participate in EP0065.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	8. Subject has an episode of status epilepticus, a prolongation of seizure duration, a worsening of seizure frequency, or emergence of a new type, that is considered by the Investigator to require intervention. 9. Subject has the following findings based on liver function tests (LFT): • If the subject has LFT results of transaminases (AST and/or ALT) ≥3x the upper limit of normal (ULN) to <5xULN or total bilirubin ≥2xULN, the measurements will be repeated within a few days. If the repeat testing confirms the abnormality (eg, transaminases are ≥3xULN to <5xULN), then monitoring of LFTs should continue at subsequent study visits until resolved (eg, <3xULN or stable condition). The Investigator is to decide whether or not to stop the study medication. • If the subject has LFT results of transaminases (AST and/or ALT) ≥5xULN, study medication should be tapered off immediately and the subject must be withdrawn from the study. 10. Criteria for subjects who completed a C-SSRS assessment at the final visit of the previous BRV study (LTFU subjects) or at the ScrV (directly enrolled subjects): • Subject has active suicidal ideation as	12. Investigator decides that withdrawal from further participation would be in the subject's best interest. 13. Subject is unwilling or unable to continue, or the parent/legal guardian is unwilling or unable to allow the subject to continue in this study. 14. If subject is ≥6 years of age, subject has active suicidal ideation with a specific plan as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" or "Already Enrolled Subjects" (as applicable) version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and **must** be withdrawn from the study. Subjects may be withdrawn from the study if any of the following events occurs: 15. If subject is ≥6 years of age, subject has active suicidal ideation without a specific plan as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" or "Already Enrolled Subjects" version of C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and *may* be withdrawn from the study based on the Investigator's judgment of benefit/risk of continuing with the subject in the study/on study medication. If a subject from N01266 enrolls in EP0065 and either withdraws consent solely due to route of BRV administration (iv) or if the subject requires more than 10 iv doses of BRV, the subject may be allowed to return to N01266 after discussion with	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study. 11. Criteria for subjects who become 6 years of age during N01266 and for whom the "Already Enrolled Subjects" version of the C-SSRS was completed at the first visit after the sixth birthday: • Subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt) of the "Already Enrolled Subjects" version of the C-SSRS. The Investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional. • Subject had active suicidal ideation prior to study entry or since study start as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Already Enrolled Subjects" version of the C-SSRS. The Investigator must immediately refer the subject to a Mental Healthcare	and agreement from the Medical Monitor. If a subject from N01266 is advised to withdraw from N01266 after participation in EP0065, the subject will be required to return to the N01266 to complete the required EDV, DTV, and SV assessments. Refer to Table 5-2 for procedures to be performed at the time of withdrawal.	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	Professional and use clinical judgment as to whether to withdraw the subject from the study. • Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study. Refer to Table 5-1 for procedures to be performed at the time of withdrawal.		
Section 6.3.1 (No parallel section in Amendment 4)	Not applicable.	Header: Potential drug-induced injury investigational medicinal product discontinuation criteria Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if the investigational medicinal product (IMP) must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The PDILI criteria below require immediate and permanent discontinuation of IMP: • Subjects with either of the following: – ALT or AST ≥5xULN – ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN	Update to Sponsor template.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		The PDILI criterion below requires immediate discontinuation of IMP: • Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%). The PDILI criterion below allows for subjects to continue on IMP at the discretion of the Investigator. • Subjects with ALT or AST ≥3xULN (and ≥2x baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness). Evaluation of PDILI must be initiated as described in Section 9.2.2. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately. Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.	

Section 7

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 7.1	Brivaracetam oral solution, at concentrations of 1.0mg/mL and 10mg/mL, will be supplied in 150mL and 300mL glass bottles, respectively.	Brivaracetam oral solution at a concentration of 10mg/mL will be supplied in 300mL glass bottles.	Removal of the BRV 1.0mg/mL oral solution as the BRV 10mg/mL oral solution is adequate for dosing.
Section 7.2	All subjects who prematurely discontinue the study should complete an EDV and have their BRV dose down titrated by a maximum of half the dose every week until a dose of 1.0mg/kg/day is reached.	Deleted.	Align down titration across BRV pediatric program. Information now provided in Section 7.2.3.
Section 7.2.1	Beginning with Protocol Amendment 3, at TV1, eligible directly enrolled subjects will initiate treatment with BRV (oral solution or tablet, as chosen by the Investigator and subject/caregiver).	Beginning with Protocol Amendment 3, at TV1, eligible directly enrolled subjects will initiate treatment with BRV (oral solution or tablet, as appropriate).	Provide intradocument consistency.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 7.2.2	The maximum BRV dose will be 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg. Subjects <7 years of age will receive oral solution. Subjects ≥7 years of age will receive tablets, as appropriate. The LTFU subjects will ordinarily start dosing on the individualized BRV dose they were receiving at the completion of the previous pediatric BRV study. They must be able to tolerate the minimum BRV dose specified in their previous study to be eligible for entry into the Evaluation Period of N01266.	The maximum BRV dose will be 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg. Subjects may receive oral solution or oral tablets, as appropriate. The LTFU subjects will ordinarily start dosing in N01266 on the individualized BRV dose they were receiving at the completion of the core study; enrolled subjects who volunteer to participate in EP0065 should resume dosing in N01266 on the individualized BRV dose they were receiving at the completion of EP0065. Subjects must be able to tolerate the minimum BRV dose specified in the core study to be eligible for entry into the Evaluation Period of N01266.	Remove age-based formulation requirement. Provide information specific to enrolled subjects who participate in EP0065 and return to N01266.
Section 7.2.3 (No parallel section in Amendment 4)	Not applicable.	Header: Down-Titration Period All subjects who prematurely discontinue the study should complete an EDV and have their BRV dose down titrated by a maximum of half the dose every week for a maximum of 4 weeks until a dose of 1mg/kg/day (50mg/day for subjects with body weights >50kg) is reached.	Provide dedicated section for the Down-Titration Period for ease of document navigation.
Section 7.3	Oral solution will be packaged in 150mL (1.0mg/mL) and 300mL (10mg/mL) type III amber glass bottles with child-resistant tamper evident polypropylene (PP) screw closures.	Oral solution (10mg/mL) will be packaged in 300mL type III amber glass bottles with child resistant tamper evident polypropylene (PP) screw closures.	Removal of bottles for the BRV 1.0mg/mL oral solution (no longer supplied).

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 7.4	Clinical drug supplies will be labeled in accordance with the current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements	Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements	Revise abbreviation.
Section 7.5	The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access. Storage conditions will be specified on the labels. Appropriate storage conditions must be ensured either by controlled room temperature, or by completing a temperature log in accordance with local requirements on a regular basis (eg, once a week), showing minimum and maximum temperatures reached over the time interval. In case an out-of-range temperature is noted, it must be communicated immediately to the Clinical Project Manager (CPM or designee) before further use of the IMP. The CPM (or designee) will transmit the out-of-range temperature (copy of the temperature log, duration of the out-of-range temperature, if available) to the Drug Supply Coordinator. Based on discussion with Quality Assurance, the Drug Supply Coordinator will then provide the CPM (or designee) with instructions for the site regarding use of the IMP.	The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access, according to the storage conditions mentioned in the label. Appropriate storage conditions must be ensured either by the temperature (eg, room, refrigeration unit) or by completion of a temperature log in accordance with local requirements on a regular basis (eg, once a week), showing actual and minimum/maximum temperatures reached over the time interval. In case an out-of-range temperature is noted, it must be reported as per instructions contained in the IMP Handling Manual.	Update to Sponsor template.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 7.6	A Drug Accountability form will be provided and kept-up-to-date to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. The study medication disposition records, such as shipping, dispensing, and return records, and inventory logs, must be kept at the site, preferably in the pharmacy. Details of any IMP lost (due to breakage or wastage), not used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. Periodically, and/or after completion of the clinical phase of the study, all used (including empty bottles) and unused IMP bottles must be reconciled and returned to UCB (or designee), preferably in their original package.	A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB SOPs or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.	Update to Sponsor template.
Section 7.8	For LTFU subjects, ongoing medications at the time the subject completed the previous pediatric BRV study should not be recorded in the eCRF at the EV, or any subsequent visit, unless there is a change regarding the administration of the medication.	For LTFU subjects, ongoing medications at the time the subject completed the core study should not be recorded in the eCRF at the EV, or any subsequent visit. Changes in ongoing concomitant medications should be recorded in the N01266 eCRF.	Provide intradocument consistency for “core study” terminology.
Section 7.8.1.1	– At the established dose if a stable dose was maintained during the previous pediatric BRV study	– At the established dose if a stable dose was maintained during the core study	Provide intradocument consistency for “core study” terminology.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 7.8.2	– Felbamate (except if on a stable dose during the previous pediatric BRV study)	– Felbamate (except if on a stable dose during the core study)	Provide intradocument consistency for "core study" terminology.
Section 7.10	Subjects will not be randomized in this study, as each LTFU subject will start on the individualized BRV dose that he/she was receiving at the completion of the previous study, and directly enrolled subjects will start the Evaluation Period on the dose established during the Up-Titration Period. Subjects will continue with the 5-digit subject number assigned by the IVRS in the previous pediatric BRV study.	Subjects will not be randomized in this study, as each LTFU subject will start on the individualized BRV dose that he/she was receiving at the completion of the core study, and directly enrolled subjects will start the Evaluation Period on the dose established during the Up-Titration Period. Subjects will continue with the 5-digit subject number assigned by the IVRS in the core study.	Provide intradocument consistency for "core study" terminology.

Section 8

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 8.1	The ScrV is applicable only to directly enrolled subjects (ie, subjects ≥4 years to <17 years of age with POS who have not previously participated in a pediatric BRV study). Beginning with Protocol Amendment 3, up to 100 directly enrolled subjects were allowed to participate in N01266. The Screening Period will serve as the Baseline Period for directly enrolled subjects. With Protocol Amendment 4, the number of directly enrolled subjects is increased to at least 100 subjects with the planned total enrollment of approximately 600 subjects. • Physical (including Tanner Scale, as applicable) and neurological (including measurement of head size) examinations • Body weight and height – Urinalysis (for subjects ≥4 years of age) – Serum pregnancy test (see Section 9.5.1)	The ScrV is applicable only to directly enrolled subjects (ie, subjects ≥4 years to <17 years of age with POS who have not participated in a core study). The Screening Period will serve as the Baseline Period for directly enrolled subjects. • Physical (including Tanner Scale, as applicable) and neurological examinations • Body weight, height, and head circumference – Urinalysis (for subjects for whom sample collection is feasible) – Urine pregnancy test (see Section 9.2.1)	Provide intradocument consistency for "core study" terminology. Remove information regarding numbers of subjects enrolled as non-applicable to this section. Provide clarity regarding head circumference and movement to measurement bullet. Replace urinalysis for subjects ≥4 years of age, to urinalysis for all subjects for whom sample collection is feasible. Replace serum pregnancy test with urine pregnancy test and update section number.
Section 8.3.1.1	Not applicable.	Header: Core study: N01349 The following assessments will be performed at this visit: • Signing and dating of written Informed	Add EV for subjects with N01349 as the core study.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		Consent by parent(s)/legal representative(s) • Subject identification card dispensing • Verification of inclusion/exclusion criteria • Demographic data • Procedure history • AED history • Psychiatric and mental status examination • Vital signs • Body weight • ECG • EEG • DRC dispensed • Seizure count • Recording of medications (Any ongoing medications [including AEDs and non-AEDs] at the time the subject completed N01349 should not be recorded in the N01266 eCRF. Changes in ongoing concomitant medications should be recorded in the eCRF.) • Recording of procedures • Recording of AEs (Any ongoing AEs at the time the subject completed N01349 should not be recorded in the N01266 eCRF. Worsening of the AE should be recorded as a	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		new AE.) • IVRS call • Study drug dispensed • Bayley-III scales (subjects enrolled in English-speaking countries) Other assessments listed in Table 5-1 will be obtained from N01349 (as footnoted in Table 5-1) and are not to be recorded in the N01266 eCRF.	
Section 8.3.1.2	Not applicable.	Header: Core study: EP0065 The following assessments will be performed at this visit: • Signing and dating of written Informed Consent by parent(s)/legal representative(s) • Signing and dating of the Assent form by the subject (if applicable, according to age and local requirements) • Subject identification card dispensing • Childbearing potential • Verification of inclusion/exclusion criteria • Demographic data • Epilepsy history • Psychiatric and mental status examination • Height	Add EV for subjects with EP0065 as the core study.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		• Head circumference • EEG • DRC dispensed • Recording of medications (Any ongoing medications [including AEDs and non-AEDs] at the time the subject completed EP0065 should not be recorded in the N01266 eCRF. Changes in ongoing concomitant medications should be recorded in the N01266 eCRF.) • Recording or procedures • Recording of AEs (Any ongoing AEs at the time the subject completed EP0065 should not be recorded in the N01266 eCRF. Worsening of the AE should be recorded as a new AE. • IVRS call • Study drug dispensed • Bayley-III scales (subjects enrolled in English-speaking countries and <18 months of age) • Achenbach CBCL (see Section 10.3.3) • BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (see Section 9.3.8) • PedsQL (see Section 10.3.5.) Other assessments listed in Table 5-1 will be obtained from EP0065 (as footnoted in Table 5-1)	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		and are not to be recorded in the N01266 eCRF.	
Section 8.3.1.3 (Section 8.3.1 of Amendment 4)	Header: LTFU subjects • Signing and dating of written Informed Consent by parent(s)/legal representative(s) • Signing and dating of Assent form by the subject (if applicable, according to age and local requirements) • Subject identification card dispensing • DRC dispensed • Verification of inclusion/exclusion criteria • Demographic data • Childbearing potential • IVRS call • Study drug dispensed • Recording of medications (Any ongoing medications [including AEDs and non-AEDs] at the time the subject completed the previous pediatric BRV study should not be recorded in the eCRF for N01266, unless there is a change regarding the administration of the medication. In this event, the start date corresponding to the date of change in administration should be recorded in the eCRF.) • Recording of AEs (Any ongoing AEs at the	Header: Core study: Other (not N01349 or EP0065) The following assessments will be performed at this visit: • Signing and dating of written Informed Consent by parent(s)/legal representative(s) • Signing and dating of Assent form by the subject (if applicable, according to age and local requirements) • Subject identification card dispensing • Childbearing potential • Verification of inclusion/exclusion criteria • Demographic data • DRC dispensed • Recording of medications (Any ongoing medications [including AEDs and non-AEDs] at the time the subject completed the core study should not be recorded in the N01266 eCRF. Changes in ongoing concomitant medications should be recorded in the N01266 eCRF). • Recording of AEs (Any ongoing AEs at the time the subject completed the core study should not be recorded in the N01266 eCRF. Worsening of the AE should be recorded as a	Update to align with revised presentation strategy in Table 5-1.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	time the subject completed the previous pediatric BRV study should not be recorded in the eCRF for N01266, unless there is a change in intensity or seriousness. In this event, the AE should be recorded in the eCRF for N01266, with the onset date corresponding to the date of change in condition.) • Appointment for the next visit according to the schedule described in Section 5.3 • The following data will be obtained from Baseline of the previous pediatric BRV study and should not be recorded in the eCRF for N01266:General medical and procedures history • Epilepsy history • AED history • Height • Bayley-III scales (for LTFU subjects <18 months of age at Baseline of N01263 or other pediatric BRV studies and only for subjects enrolled in English-speaking countries) • Achenbach CBCL score (see Section 10.3.3) • Laboratory assessments	new AE.) • IVRS call • Study drug dispensed Other assessments listed in Table 5-1 will be obtained from the core study (as footnoted in Table 5-1) and are not to be recorded in the N01266 eCRF.	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	– Endocrinology The following data will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266: • Recording of medications • Recording of procedures • Seizure count • EEG – For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: an EEG of at least 1 hour of recording (including hyperventilation and intermittent photic stimulation) must be performed – For subjects ≥1 month to <2 years of age on the day of the study visit: an EEG of at least 24 hours of recording (including sleeping and awakening periods) must be performed • ECG • Laboratory assessments for safety – Hematology – Biochemistry (including hepatic monitoring of ALT, AST, ALP, total		

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	bilirubin, and GGT) – Urinalysis (for subjects ≥4 years of age) – Urine pregnancy test (see Section 9.5.1) • Phenytoin plasma concentrations (if applicable) • Suicidality assessment (C-SSRS) (for subjects ≥6 years of age) • Vital signs • Body weight • Physical examination • Neurological examination • Psychiatric and mental status • Health care provider consultations not foreseen by the protocol • Hospital stays		

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Sections 8.3.2	• Body weight and height – Urinalysis – Urine pregnancy test (see Section 9.5.1)	• Body weight, height, and head circumference – Urinalysis (for subjects for whom sample collection is feasible) – Urine pregnancy test (see Section 9.2.1)	Clarify that head circumference is included as described above. Clarification that urinalysis is for all subjects for whom sample collection is feasible. Update of section number for pregnancy test.
Section 8.4	• Body weight and height • EEG (LTFU subjects only) – For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: an EEG of at least 1 hour of recording (including hyperventilation and intermittent photic stimulation) must be performed only at V4 (M3) as described in Section 10.2 – For subjects ≥1 month to <2 years of age on the day of the study visit: an EEG of at least 24 hours of recording (including sleeping and awakening periods) must be performed only at V4 (M3) as described in Section 10.2	• Body weight, height, and head circumference • Urine pregnancy test (see Section 9.2.1)	Removal of EEG at MEV. Clarify that head circumference is included as described above. Addition of pregnancy test to match Table 5-2.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 8.5	• Body weight and height • EEG – For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: an EEG of at least 1 hour of recording (including hyperventilation and intermittent photic stimulation) must be performed only at V5 (M6) as described in Section 10.2 – For subjects ≥1 month to <2 years of age on the day of the study visit: an EEG of at least 24 hours of recording (including sleeping and awakening periods) must be performed only at V5 (M6) as described in Section 10.2. – Urinalysis (for subjects ≥4 years of age) – Urine pregnancy test (see Section 9.5.1) • Bayley-III scales (for LTFU subjects <18 months of age at Baseline of N01263 or other pediatric BRV studies and only for subjects enrolled in English-speaking countries) • BRIEF-P (<5 years of age)/BRIEF (≥5 years of age) (see Section 9.38)	• Body weight, height, and head circumference • EEG (LTFU subjects only) – For subjects ≥2 years of age at V5 who have typical absence seizures, an EEG of at least 24 hours that includes hyperventilation and intermittent photic stimulation must be performed only at V5 and yearly thereafter. – For subjects <2 years of age at V5, an EEG of at least 24 hours of recording must be performed at V5 and yearly thereafter. – Urinalysis (for subjects for whom sample collection is feasible) – Urine pregnancy test (see Section 9.2.1) • Bayley-III scales (for LTFU subjects enrolled in English-speaking countries, <18 months of age at baseline of the core study, and <42 months of age) • BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (see Section 9.3.8)	Clarify that head circumference is included as described above. Clarify EEG requirements. Replace urinalysis for subjects ≥4 years of age, to urinalysis for all subjects for whom sample collection is feasible. Update of section number reference for pregnancy test. Clarification of age for Bayley-III. Clarification of age range for BRIEF-P/BRIEF.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 8.6	• Body weight and height • EEG – For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: an EEG of at least 1 hour of recording (including hyperventilation and intermittent photic stimulation) must be performed – For subjects ≥1 month to <2 years of age on the day of the study visit: an EEG of at least 24 hours of recording (including sleeping and awakening periods) must be performed – Urinalysis (for subjects ≥4 years of age) – Urine pregnancy test (Section 9.5.1) • Bayley-III scales (for LTFU subjects <18 months of age at Baseline of N01263 or other pediatric BRV studies and only for subjects enrolled in English-speaking countries) • BRIEF-P (<5 years of age)/BRIEF (≥5 years of age) (see Section 9.38)	• Body weight, height, and head circumference EEG deleted. – Urinalysis (for subjects for whom sample collection is feasible) – Urine pregnancy test (Section 9.2.1) • Bayley-III scales (for LTFU subjects enrolled in English-speaking countries, <18 months of age at baseline of the core study, and <42 months of age) • BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (see Section 9.3.8)	Clarify that head circumference is included as described above. Change in accordance with EEG schedule. Update of section number reference for pregnancy test. Clarification of age for Bayley-III. Replace urinalysis for subjects ≥4 years of age, to urinalysis for all subjects for whom sample collection is feasible. Clarification of age range for BRIEF-P/BRIEF.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 8.8	• Body weight and height • EEG – For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: an EEG of at least 1 hour of recording (including hyperventilation and intermittent photic stimulation) must be performed – For subjects ≥1 month to <2 years of age on the day of the study visit: an EEG of at least 24 hours of recording (including sleeping and awakening periods) must be performed. – Urinalysis (for subjects ≥4 years of age) – Serum pregnancy test (see Section 9.5.1) • Bayley-III scales (for LTFU subjects <18 months of age at Baseline of N01263 or other pediatric BRV studies and only for subjects enrolled in English-speaking countries) • BRIEF-P (<5 years of age)/BRIEF (≥5	• Body weight, height, and head circumference • EEG (for LTFU subjects only) – For subjects ≥2 years of age at V5 who have typical absence seizures, a 24-hour EEG may be performed at the Investigator's discretion. – For subjects <2 years of age at V5, a 24-hour EEG may be performed at the Investigator's discretion. – Urinalysis (for subjects for whom sample collection is feasible) – Urine pregnancy test (see Section 9.2.1) • Bayley-III scales (for LTFU subjects enrolled in English-speaking countries, <18 months of age at baseline of the core study, and <42 months of age) • BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (see Section 9.3.8)	Clarify that head circumference is included as described above. Clarify EEG requirements. Replace urinalysis for subjects ≥4 years of age, to urinalysis for all subjects for whom sample collection is feasible. Replace serum pregnancy test with urine pregnancy test and update section number. Clarification of age for Bayley-III. Clarification of age range for BRIEF-P/BRIEF.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	years of age) (see Section 9.3.8)		
Section 8.9	Not applicable.	Appointment for the next visit according to the schedule described in Section 5.2.	Update for intradocument consistency.
Section 8.10	• Body weight and height – Urinalysis (for subjects ≥4 years of age) – Serum pregnancy test (Section 9.5.1)	• Body weight, height, and head circumference – Urinalysis (for subjects for whom sample collection is feasible) – Urine pregnancy test (Section 9.2.1)	Clarify that head circumference is included as described above. Replace serum pregnancy test with urine pregnancy test and update section number. Replace urinalysis for subjects ≥4 years of age, to urinalysis for all subjects for whom sample collection is feasible..
Section 8.11	• Body weight and height • EEG – For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: an EEG of at least 1 hour of recording (including hyperventilation and intermittent photic stimulation) must be performed – For subjects ≥1 month to <2 years of	• Body weight, height, and head circumference • EEG (for LTFU subjects only) – For subjects ≥2 years of age at V5 who have typical absence seizures, an EEG of at least 24 hours that includes hyperventilation and intermittent photic stimulation must be performed – For subjects <2 years of age at V5, an EEG of at least 24 hours must be	Clarify that head circumference is included as described above. Clarify EEG requirements. Replace urinalysis for subjects ≥4 years of age, to urinalysis for all subjects for whom sample

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	age on the day of the study visit: an EEG of at least 24 hours of recording (including sleeping and awakening periods) must be performed. – Urinalysis (for subjects ≥4 years of age) – Urine pregnancy test (see Section 9.5.1) • Bayley-III scales (for LTFU subjects <18 months of age at Baseline of N01263 or other pediatric BRV studies and only for subjects enrolled in English-speaking countries) • BRIEF-P <5 years of age)/BRIEF (≥5 years of age) (see Section 9.6.8)	performed. – Urinalysis (for subjects for whom sample collection is feasible) – Urine pregnancy test (see Section 9.2.1) • Bayley-III scales (for LTFU subjects enrolled in English-speaking countries, <18 months of age at baseline of the core study, and <42 months of age) • BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (see Section 9.3.8)	collection is feasible. Clarification of age for Bayley-III. Update of section number for pregnancy test. Clarification of age range for BRIEF-P/BRIEF.

Section 9

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 9	For subjects who prematurely discontinue the study, the Evaluation Period will include the EV through the EDV, followed by a 4-week Down-Titration Period (maximum), and a 2-week study drug-free Safety Period.	For subjects who prematurely discontinue the study, the Evaluation Period will include the EV through the EDV, followed by a 4-week Down-Titration Period (maximum), and a 2-week Safety (Drug-Free) Period.	Update for intradocument consistency.
Section 9.1.1	Header: Definition of adverse event	Header: Definitions	Update to Sponsor template.
Section 9.1.1.1	Not applicable.	Header: Adverse event	Update to Sponsor template.
Section 9.1.1.2 (Section 9.2.1 of Amendment 4)	Header: Definition of serious adverse event	Header: Serious adverse event	Update to Sponsor template.
Section 9.1.1.2.1 (Section 9.4 of Amendment 4)	Header: Anticipated SAEs	Header: Anticipated serious adverse events Table 9-1: Added.	Update to Sponsor template. Update list of anticipated SAEs.
Section 9.1.1.3	Not applicable.	Header: Adverse events of special interest An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound. For this study, the AEs of special interest include: • Autoimmune nephritis • Nephritis • Nephritis allergic	Update to Sponsor template.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		• Tubulointerstitial nephritis • Tubulointerstitial nephritis and uveitis syndrome • Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.	
Section 9.1.2	For LTFU subjects, AEs ongoing at the time the subject completed the previous pediatric BRV study should not be recorded in the eCRF at the EV, or any subsequent visit, unless there is a change in intensity or seriousness.	For LTFU subjects, AEs ongoing at the time the subject completed the core study should not be recorded in the eCRF at the EV, or any subsequent visit. Worsening of the AE should be recorded as a new AE.	Update for intradocument consistency in terminology regarding core studies and AE reporting.
Section 9.1.2.2 (Section 9.1.5 of Amendment 4)	Not applicable.	Not applicable.	Update numbering.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 9.1.2.3 (Section 9.2.2 of Amendment 4)	Header: Procedures for reporting serious adverse events	Header: Additional procedures for reporting serious adverse events A blood sample for determination of BRV plasma concentration should be obtained for any subject who has an SAE.	Update to Sponsor template. Add text that previously appeared elsewhere in the document for clarification.
Section 9.1.3 (Section 9.1.4 of Amendment 4)	Not applicable.	Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.	Update to Sponsor template.
Section 9.1.4 (Section 9.1.6 of Amendment 4)	Not applicable.	Not applicable.	Update numbering.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 9.1.5	Not applicable.	Header: Suspected transmission of an infectious agent via a medicinal product A suspected transmission of infectious agent is defined as any infection that is temporally related to the administration of the medicinal product with no other likely cause. The Medical Monitor should be contacted immediately. No further medicinal product from that specific batch should be administered. Infections should be treated according to normal clinical practice. For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.	Update to Sponsor template.
Section 9.1.6 (Section 9.1.7 of Amendment 4)	Not applicable.	Not applicable.	Update section number.
Section 9.2.1 (Section 9.5.1 of Amendment 4)	Laboratory assessments for safety (including hematology, biochemistry, and endocrinology for all subjects, and urinalysis for subjects ≥4 years of age) will be conducted using standard methods at a central laboratory. For the table of laboratory paraemeters that appears in this section: β-HCG included in the urinalysis. [a] Urinalysis will be performed in subjects	Laboratory assessments for safety (including hematology, biochemistry, and endocrinology for all subjects, and urinalysis for subjects for whom sample collection is feasible) will be conducted using standard methods at a central laboratory. For the table of laboratory paraemeters that appears in this section: β-HCG deleted from the urinalysis column.	Replace urinalysis for subjects ≥4 years of age, to urinalysis for all subjects for whom sample collection is feasible. Provide consistency across BR pediatric program with

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	≥4 years of age. [d] All female subjects with a Tanner stage >1 should have urine pregnancy tests at the EV, YEVs/FV, and FEVs and serum pregnancy tests at the ScrV (directly enrolled subjects only), EDV, and SV. [e] Endocrinology testing will be performed at the ScrV (directly enrolled subjects only) and at the YEV/FV. For LTFU subjects, pregnancy testing (if applicable) will be performed at the EV and other laboratory safety assessments at the EV will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266. Laboratory safety assessments (hematology, biochemistry [including hepatic monitoring: total bilirubin, ALP, AST, ALT, and GGT], urinalysis [for subjects ≥4 years of age, and pregnancy testing [as applicable]) will be performed at the ScrV and EV (directly enrolled subjects only), FEV, YEV, FV, and at the EDV in the case of early discontinuation. Laboratory assessments will also be mandatory at the SV if the laboratory results at the EDV are abnormal. Only hepatic monitoring assessments will be performed at the final TV (directly enrolled subjects only), and the MEVs at V4 (M3) and V6 (M9) during the first year; no laboratory safety assessments will be performed at other MEVs. Endocrinology testing will be performed at the ScrV (directly	[a] Urinalysis will be performed for subjects for whom sample collection is feasible. [d] Urine pregnancy tests should be conductedat at the site for all female subjects of childbearing potential. All female subjects of childbearing potential should have urine pregnancy tests. A serum pregnancy test will be performed as backup if a urine sample is not available. A urine pregnancy test should be performed at any time during the study if a pregnancy is suspected. All urine pregnancy tests should be conducted at the site.	wording that pregnancy tests should to be childbearing potential. Remove information provided in Section 5.3 to decrease redundancy. Replace scheduled serum pregnancy tests with urine pregnancy tests with clarification that tests performed at the site.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	enrolled subjects only) and once a year at the YEV. For LTFU subjects, the Baseline endocrinology values will be taken from Baseline of the previous pediatric BRV study. All female subjects who have a Tanner stage >1 should have urine pregnancy tests at the EV, YEVs/FV, and FEVs and serum pregnancy tests at the ScrV (directly enrolled subjects only), EDV, and the SV. A serum pregnancy test will be performed as backup if a urine sample is not available. A urine pregnancy test should be performed at any time during the study if a pregnancy is suspected.		
Section 9.2.2 (No parallel section in Amendment 4.)	Not applicable.	Header: Evaluation of PDILI The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and Sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 9.1.1.3), and, if applicable, also reported as an SAE (see Section 9.1.2.3). Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 9-2 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 9.2.2.1). The local hepatologist is the expert usually consulted	Update to Sponsor template.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 9.2.2.4). The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and Sponsor. All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result. If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages. When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative. Rechallenge with a substance potentially causing	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
		drug-induced liver injury is dangerous, may be fatal, and must not occur. The table below summarizes the approach to investigate PDILI. Table 9-2: Added.	
Section 9.2.2.1 (No parallel section in Amendment 4.)	Not applicable.	Header: Consultation with Medical Monitor and local hepatologist Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 9.2.2.3) and SAE report (if applicable).	Update to Sponsor template.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 9.2.2.2 (No parallel section in Amendment 4.)	Not applicable.	Header: Immediate action: determination of IMP discontinuation All PDILI events require immediate action, testing, and monitoring. The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 9-2 for details). When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The Investigator should also consider dose reduction of medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 9.2.2.3 (No parallel section in Amendment 4.)	Not applicable.	Header: Testing: identification/exclusion of alternative etiology The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 9-3 (laboratory measurements) and Table 9-4 (additional information). Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable. All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory. The following measurements are to be assessed: Table 9-3: Added. The following additional information is to be collected: Table 9-4: Added.	

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 9.2.2.4 (No parallel section in Amendment 4)	Not applicable.	Header: Follow-up evaluation Potential drug-induced liver injury events will require follow-up monitoring as described in Table 9-2. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.	Update to Sponsor template.
Section 9.2.3 (Section 9.5.2 of Amendment 4)	Not applicable.	Not applicable.	Update numbering.
Section 9.2.3.1 (Section 9.5.2.1 of Amendment 4)	Blood samples for the analysis of BRV will be collected at the FEV, YEV, FV, and at the EDV in the case of early discontinuation. A blood sample for determination of BRV plasma concentration should be taken whenever the subject experiences an SAE.	Blood samples for the analysis of BRV concentrations will be collected at the visits designated in Table 5-2. Additionally, a blood sample for determination of BRV plasma concentration should be taken whenever the subject experiences an SAE.	Remove information provided in Section 5.2 to decrease redundancy.
Section 9.2.3.2 (Section 9.5.2.2 of Amendment 4)	Subjects receiving phenytoin as a concomitant AED during the study will have blood samples collected at the ScrV (directly enrolled subjects only), FEV, YEV, FV, and at the EDV in the case of early discontinuation to monitor phenytoin plasma concentrations. Blood samples will only be collected at the SV if the plasma levels of phenytoin are abnormal at the EDV.	Subjects receiving phenytoin as a concomitant AED during the study will have blood samples collected at the visits designated in Table 5-1, Table 5-2, and Table 5-3 to monitor phenytoin plasma concentrations.	Remove information provided in Section 5.2 to decrease redundancy.
Section 9.3 (Section 9.6 of Amendment 4)	Not applicable.	Other safety measurements will be performed at the visits indicated in Table 5-1, Table 5-2, and Table 5-3.	Provide navigational text for reader.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 9.3.1 (Section 9.6.1 of Amendment 4)	A standard 12-lead ECG will be performed at the ScrV, TV(s), and EV (directly enrolled subjects only), YEV, FV, and at the EDV in the case of early discontinuation. An ECG will be 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 previous pediatric BRV study and should not be recorded in the eCRF for N01266.	A standard 12-lead ECG will be performed.	Remove information provided in Section 5.2 to decrease redundancy.
Section 9.3.2 (Section 9.6.2 of Amendment 4)	Vital signs, including measurements of blood pressure, supine or sitting pulse rate, and body temperature, will be performed after 5 minutes of rest at the ScrV, TV(s), and EV (directly enrolled subjects only), MEV, FEV, YEV, FV, and at the EDV, 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 previous pediatric BRV study and should not be recorded in the eCRF for N01266.	Vital signs, including measurements of blood pressure, supine or sitting pulse rate, and body temperature, will be performed after 5 minutes of rest.	Remove information provided in Section 5.2 to decrease redundancy.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 9.3.3 (Section 9.6.3 of Amendment 4)	Header: Body weight and height Body weight (subject wearing light clothing without shoes) will be measured at the ScrV, TV(s), and EV (directly enrolled subjects only), MEV, FEV, YEV, FV, and at the EDV and the SV in the case of early discontinuation. For LTFU subjects, at the EV, body weight will be obtained from the final visit and height data will be obtained from Baseline of the previous pediatric BRV study and should not be recorded in the eCRF for N01266. Body height will be recorded at the ScrV (directly enrolled subjects only), MEV, FEV, YEV, FV, and at the EDV and the SV in the case of early discontinuation.	Header: Body weight, height, and head circumference Body weight (subject wearing light clothing without shoes), height (length may be used for this measure, as appropriate), and head circumference (occipital-frontal circumference) will be measured.	Remove information provided in Section 5.2 to decrease redundancy. Add information pertaining to the measurement of head circumference (in Amendment 4 this measurement was included in the neurological examination).
Section 9.3.4 (Section 9.6.4 in Amendment 4)	A standard physical examination will be performed at the ScrV and EV (directly enrolled subjects only), FEV, YEV, FV, and at the EDV and the SV in the case of early discontinuation. For LTFU subjects, at the EV, physical examination data will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266.	A standard physical examination will be performed.	Remove information provided in Section 5.2 to decrease redundancy.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 9.3.5 (Section 9.6.5 of Amendment 4)	A standard neurological examination will be performed at the ScrV and EV (directly enrolled 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 previous pediatric BRV study and should not be recorded in the eCRF for N01266. The neurological examination will include a measurement of the head size (occipital-frontal circumference). Clinically significant new or worsened abnormalities must be reported as AEs.	A standard neurological examination will be performed. Clinically significant new or worsened abnormalities in the neurological examination must be reported as AEs.	Remove information provided in Section 5.2 to decrease redundancy. Remove head circumference from this section with inclusion in Section 9.3.3.
Section 9.3.6 (Section 9.6.6 of Amendment 4)	Psychiatric and mental status will be reported by recording the presence or absence of psychiatric symptoms, mental impairment, and behavioral problems at the ScrV and EV (directly enrolled 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 will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266.	Psychiatric and mental status will be reported by recording the presence or absence of psychiatric symptoms, mental impairment, and behavioral problems.	Remove information provided in Section 5.2 to decrease redundancy.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 9.3.7 (Section 9.6.7 of Amendment 4)	Not applicable.	The C-SSRS is not validated for subjects <6 years of age and will not be used for this population. Subjects should be monitored for any changes in mood, ideas, or behavior for warning signs of depression. The Investigator should be aware of common warning signs that might be a signal for risk of depression. For common signs and symptoms of depression in children younger than 6 years old, reference should be made to the current version of the Diagnostic and Statistical Manual of Mental Disorders. Parents and caregivers should also be advised accordingly and effort should be made at clinic visits to specifically assess potential depression.	Update to Sponsor template.
Section 9.3.8 (Section 9.6.8 of Amendment 4)	The BRIEF-P/BRIEF will be completed at the ScrV (directly enrolled subjects only), FEV, YEV, FV, and the EDV in the case of early discontinuation. For LTFU subjects, at the EV, the BRIEF-P/BRIEF score will be obtained from Baseline of the previous pediatric BRV study and should not be recorded in the eCRF for N01266. For directly enrolled subjects, the Baseline BRIEF-P/BRIEF should be completed at the ScrV. 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.	Deleted.	Remove information provided in Section 5.2 to decrease redundancy.

Section 10

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 10	The EEG data will be reviewed by 3-month periods for the first 6 months and yearly thereafter.	The EEG data will be reviewed at 6 months and yearly thereafter.	Revise in accordance with EEG timing.
Section 10.2	At the EV, seizure data based on an EEG of at least 24 hours of recording (including sleeping and awakening periods) for subjects <2 years of age and data on absence seizure count (based on an EEG of at least 1 hour of recording for subjects ≥2 years of age suffering from absences) will be obtained from the final visit of the previous pediatric BRVstudy and should not be recorded in the eCRF for N01266. The EEGs will be performed according to the following specifications: • For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: an EEG of at least 1 hour of recording (including hyperventilation and intermittent photic stimulation) will be performed starting at V4 and at every 3-month visit for the first 6 months and then yearly thereafter. For subjects prematurely discontinuing from the study, an EEG of at least 1 hour of recording should also be performed at the EDV. • For subjects ≥1 month to <2 years of age on the day of the study visit: an EEG of at least	Deleted.	Remove information provided in Section 5.2 to decrease redundancy.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	24 hours of recording (including sleeping and awakening periods) will be performed every 3 months during the first 6 months of the study, then yearly thereafter, and at the FV or the EDV in the case of early discontinuation.		
Section 10.3	Not applicable.	Other assessments will be performed at the visits indicated in Table 5-1, Table 5-2, and Table 5-3.	Provide navigational text for reader.
Section 10.3.1.1	Concomitant medication information will be collected and recorded in the eCRF at the following visits: ScrV and TV(s) (directly enrolled subjects only), EV, MEV, FEV, YEV, UV, FV, and at the EDV, DTV, and the SV in the case of early discontinuation. For LTFU subjects, any ongoing medications (including AEDs and non-AEDs) at the time the subject completed the core study should not be recorded in the eCRF for N01266, unless there is a change regarding the administration of the medication.	Concomitant medication information will be collected and recorded. For LTFU subjects, any ongoing medications (including AEDs and non-AEDs) at the time the subject completed the core study should not be recorded in the N01266 eCRF. Changes in ongoing concomitant medications should be recorded in the N01266 eCRF.	Remove information provided in Section 5.2 to decrease redundancy. Provide intradocument consistency for “core study” terminology.
Section 10.3.1.2	Medical procedures will be recorded at the following visits: ScrV and TV(s) (directly enrolled subjects only), EV, MEV, FEV, YEV, UV, FV, and at the EDV, DTV, and the SV in the case of early discontinuation.	Deleted.	Remove information provided in Section 5.2 to decrease redundancy.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 10.3.1.3	At the TV(s) and EV (directly enrolled subjects only), MEV, FEV, YEV, UV, FV, and at the EDV, DTV, and the SV in the case of early discontinuation, health care provider consultations not foreseen by the protocol will be recorded in the eCRF. For LTFU subjects, at the EV, information on the health care provider consultations not foreseen by the protocol will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266.	Data collected for health care provider consultations not foreseen by the protocol will include the type of provider (general practitioner, specialist physician, nurse), the site of care (office-private, office-hospital, home, emergency room), and the reason leading to the consultation.	Remove information provided in Section 5.2 to decrease redundancy.
Section 10.3.1.4	During the TV(s) and EV (directly enrolled subjects only, MEV, FEV, YEV, UV, FV, and at the EDV, DTV, and the SV in the case of early discontinuation, data on hospital stays will be collected in the eCRF. It will include the reason leading to the hospitalization, the admission ward, transfers, and length of stay. For LTFU subjects, at the EV, information on hospital stays will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266.	Data collected for hospital stays will include the reason leading to the hospitalization, the admission ward, transfers, and length of stay.	Remove information provided in Section 5.2 to decrease redundancy.
Section 10.3.2	The Bayley-III scales are recognized internationally as one of the most comprehensive developmental assessment instruments (Sattler and Hoge, 2006) used to examine the major facets of a young child's development (Bayley, 2006). This scale is validated as a tool for assessment of neurological development in young children and is therefore considered appropriate for	The Bayley-III scales are validated as a tool for assessment of neurological development in young children and recognized internationally as one of the most comprehensive developmental assessment instruments (Sattler and Hoge, 2006) used to examine the major facets of a young child's development (Bayley, 2006). Children started on the Bayley-III scales at Baseline of the core study will also be assessed	Remove information provided in Section 5.2 to decrease redundancy. Remove information provided in Section 5.2 to decrease

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	N01266. The same scale has been completed by the Investigator or designee at Baseline (V1) of N01263 for children from 1 month to <18 months of age at Baseline enrolled in English-speaking countries. Children started on the Bayley-III scales at Baseline of N01263 will also be assessed using the Bayley-III scales in N01266 even if their age increases to ≥18 months. Bayley-III scale assessments are not applicable to directly enrolled subjects due to age-based considerations. At the EV, the Bayley-III scales will be obtained from Baseline of the previous pediatric BRV study if the subject was enrolled in an English-speaking country, and data should not be recorded in the eCRF in N01266. The Bayley-III scales will be completed at the FEV, YEV, FV, and at the EDV in the case of early discontinuation. The Bayley-III scales should be completed by the same person who completed the Bayley-III scales in the previous pediatric BRV study. At the EV, the Bayley-III scales will be obtained from Baseline of the previous pediatric BRV study if the subject was enrolled in an English-speaking country, and data should not be recorded in the eCRF in N01266. The Bayley-III scales will be completed at the FEV, YEV, FV, and at the EDV in the case of early discontinuation. The Bayley-III scales should be completed by the same person who completed the Bayley-III scales in the previous pediatric	using the Bayley-III scales in N01266 (if possible, by the same person who completed the scales in the core study) even if their age increases to ≥18 months. Bayley-III scale assessments are not applicable to directly enrolled subjects due to age-based considerations. The Bayley-III scales will be applied to subjects as described in Table 5-1 and Table 5-2. The Bayley-III scale is not applicable to directly enrolled subjects due the age of these subjects (≥4 years of age) at entry into N01266.	redundancy. Provide intradocument consistency for “core study” terminology.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	BRV study.		
Section 10.3.3	The Achenbach CBCL should be completed by the same parent(s)/legal representative(s) who completed the CBCL in the previous pediatric BRV study. The completion of the Achenbach CBCL will require approximately 45 minutes. The Achenbach CBCL will be completed at the ScrV (directly enrolled subjects only), FEV, YEV, FV, and at the EDV in the case of early discontinuation. For LTFU subjects, at the EV, the Achenbach CBCL score will be obtained from Baseline of the previous pediatric BRV study and should not be recorded in the eCRF for N01266.	The Achenbach CBCL should be completed by the same parent(s)/legal representative(s) who completed the CBCL in the core study, when possible. The completion of the Achenbach CBCL will require approximately 45 minutes.	Provide intradocument consistency for "core study" terminology. Remove information provided in Section 5.2 to decrease redundancy. Clarify that CBCL is to be completed by same person if possible.
Section 10.3.5	The PedsQL will be completed at the ScrV (directly enrolled subjects only), FEV, YEV, FV, and the EDV in the case of early discontinuation. For LTFU subjects, at the EV, the PedsQL score will be obtained from Baseline of the previous pediatric BRV study and will not be recorded in the eCRF in N01266. For directly enrolled subjects, the Baseline PedsQL will be completed at the ScrV.	Deleted.	Remove information provided in Section 5.2 to decrease redundancy.

Section 11

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 11.2.1	Not applicable.	Photocopies and/or printouts of eCRFs are not considered acceptable source documents.	Update to Sponsor template.
Section 11.3.1	This study will be performed using remote data capture.	This study will be performed using electronic data capture.	Update to Sponsor template.
Section 11.5	The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's study master file.	The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.	Update to Sponsor template.

Section 12

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 12.2	Not applicable.	Analyses may also be summarized for direct enrollers, as well as by core study (eg, EP0065 and N01349).	Provide additional information about possible data summaries.
Section 12.5	The Achenbach CBCL, the Bayley-III scores (LTFU subjects only), BRIEF-P/BRIEF, PedsQL, and change from Baseline scores (previous BRV study for LTFU subjects and ScrV for directly enrolled subjects) will be analyzed in a descriptive manner.	The Achenbach CBCL, the Bayley-III scores (LTFU subjects only), BRIEF-P/BRIEF, PedsQL, and change from Baseline scores (core study for LTFU subjects and ScrV for directly enrolled subjects) will be analyzed in a descriptive manner.	Provide intradocument consistency for "core study" terminology.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 12.9	The original number was based upon the assumption that 90% of the subjects having completed a previous pediatric study with BRV as adjunctive treatment in epilepsy will rollover into the present study. With Protocol Amendment 3, enrollment was expanded to include up to 100 directly enrolled subjects (≥4 years to <17 years of age) with POS, thus increasing possible enrollment up to 600 subjects. With Protocol Amendment 4, the number of directly enrolled subjects is increased to at least 100 subjects with the planned total enrollment of approximately 600 subjects.	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 directly enrolled subjects, with no change in the assumption regarding core study completion.	Update to provide clarity regarding current design with no change to sample size. Provide clarity regarding definition of "core study."

Section 13

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 13.1	Prior to participation in the study, the written Informed Consent form should be signed and personally dated by the subject's parent(s)/legal representative(s), and by the person who conducted the informed consent discussion (Investigator [or designee]).	Prior to participation in the study, the Informed Consent form should be signed and personally dated by the subject's parent(s)/legal representative(s), and by the person who conducted the informed consent discussion (Investigator [or designee]).	Update to Sponsor template.

Section 15

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 15	Dulac O. Epilepsy in children. Curr Opin Neurol. 1994;7:102-6. Engel J, Pedley TA. Epilepsy: a comprehensive textbook. Philadelphia: Lippincott-Raven; 1998.	Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: a systematic review and meta-analysis. Neurology. 2011; 77(10): 1005–12.	Update of references cited in text.

Section Impacted	Key components of previous text	Key components of amended text	Rationale
	Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia. 1993;34:453-68. Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. Epilepsia. 2001;42:1255-60. Loiseau J, Loiseau P, Guyot M, Duche B, Dartigues JF, Aublet B. Survey of seizure disorders in the French southwest. I. Incidence of epileptic syndromes. Epilepsia. 1990;31:391-6. Nasreddine W, Beydoun A, Atweh S, Abou-Khalil B. Emerging drugs for partial onset seizures. Expert Opin Emerg Drugs. 2010;15:415-31. Perucca E. Established antiepileptic drugs. Baillieres Clin Neurol. 1996;5:693-722. Sander JW, Shorvon SD. Epidemiology of the epilepsies. J Neurol Neurosurg Psychiatry. 1996;61:433-43.		

Section 18

Section Impacted	Key components of previous text	Key components of amended text	Rationale
Section 18	Not applicable.	Header: Sponsor Declaration I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.	Update to Sponsor template.

Specific changes to tables in Section 5:

With Amendment 5, Amendment 4 Table 5-1 (see below) was divided into 2 tables (Table 5-1 and Table 5-2) in order to include all Entry Visits in one table (Table 5-1) and subsequent visits in another table (Table 5-2). With this change, the Entry Visits in Amendment 4 Table 5-1 were retained in Table 5-1 and the remaining contents of Amendment 4 Table 5-1 (with exceptions noted below) were included in Table 5-2. The rationales for the changes are noted in the table above.

Amendment 4 Table 5-1 is provided below for reference.

Amendment 4 Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	**Evaluation**							**Down-Titration**	**Safety (Drug-free)**
Visit	**Entry Visit**		**Minimal Evaluation Visit**	**Full Evaluation Visit**	**Yearly Evaluation Visit/Final Visit**	**Unscheduled Visit**	**Early Discontinuation Visit**	**Down-Titration Visit**	**Safety Visit**
	(EV)		**(MEV)**	**(FEV)**	**(YEV/FV[b])**	**(UV)**	**(EDV)**	**(DTV)[c]**	**(SV)**
Subjects	**LTFU[a]**	**DE**	**All**						
Assessment									
Written informed consent/assent	X								
Subject identification card dispensing	X								
Childbearing potential	X	X	X	X	X		X		
Verification inclusion/exclusion criteria	X								
Demographic data	X								
Physical and neurological examinations	X[a]	X		X	X		X		X

Amendment 4 Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	**Evaluation**							**Down-Titration**	**Safety (Drug-free)**
Visit	**Entry Visit**		**Minimal Evaluation Visit**	**Full Evaluation Visit**	**Yearly Evaluation Visit/Final Visit**	**Unscheduled Visit**	**Early Discontinuation Visit**	**Down-Titration Visit**	**Safety Visit**
	(EV)		**(MEV)**	**(FEV)**	**(YEV/FV[b])**	**(UV)**	**(EDV)**	**(DTV)[c]**	**(SV)**
Subjects	**LTFU[a]**	**DE**	**All**						
Assessment									
Psychiatric and mental status	X[a]	X		X	X		X		X
Vital signs[d]	X[a]	X	X	X	X		X	X	X
Body weight and height	X[a]	X	X	X	X		X		X
ECG[e]	X[a]	X			X		X		X[f]
EEG[g]	X[a]		X	X	X		X		
DRC dispensed	X	X	X	X	X[h]		X	X	
DRC retrieved		X	X	X	X		X	X	X
Seizure count	X[a]	X	X	X	X		X	X	X
Assessment of seizure types[i]				X	X				

Amendment 4 Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	**Evaluation**							**Down-Titration**	**Safety (Drug-free)**
Visit	**Entry Visit**		**Minimal Evaluation Visit**	**Full Evaluation Visit**	**Yearly Evaluation Visit/Final Visit**	**Unscheduled Visit**	**Early Discontinuation Visit**	**Down-Titration Visit**	**Safety Visit**
	(EV)		**(MEV)**	**(FEV)**	**(YEV/FV[b])**	**(UV)**	**(EDV)**	**(DTV)[c]**	**(SV)**
Subjects	**LTFU[a]**	**DE**	**All**						
Assessment									
Recording of medications[j]	X[a]	X	X	X	X	X	X	X	X
Recording of procedures	X[a]	X	X	X	X	X	X	X	X
Recording of AEs[k]	X[a]	X	X	X	X	X	X	X	X
IVRS	X	X	X	X	X	X	X	X	X
Study drug dispensed	X	X	X	X	X[h]		X		
Study drug returned[l]		X	X	X	X		X	X	
Study drug compliance		X	X	X	X		X	X	
Laboratory assessments for safety[m]	X[a]	X	X[n]	X	X		X		X[f]
BRV plasma concentrations[o]				X	X		X		

Amendment 4 Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	**Evaluation**							**Down-Titration**	**Safety (Drug-free)**
Visit	**Entry Visit**		**Minimal Evaluation Visit**	**Full Evaluation Visit**	**Yearly Evaluation Visit/Final Visit**	**Unscheduled Visit**	**Early Discontinuation Visit**	**Down-Titration Visit**	**Safety Visit**
	(EV)		**(MEV)**	**(FEV)**	**(YEV/FV[b])**	**(UV)**	**(EDV)**	**(DTV)[c]**	**(SV)**
Subjects	**LTFU[a]**	**DE**	**All**						
Assessment									
Phenytoin plasma concentrations, if applicable	X[a]			X	X		X		X[f]
C-SSRS[p]	X[a]	X	X	X	X		X	X	X
Bayley-III scales[q]				X	X		X		
Achenbach CBCL[r]				X	X		X		
BRIEF-P/BRIEF[s]				X	X		X		
PedsQL[t]				X	X		X		
Health care provider consultations not foreseen by protocol	X[a]	X	X	X	X	X	X	X	X
Hospital stays[u]	X[a]	X	X	X	X	X	X	X	X
End of study status					X[v]				X

Amendment 4 Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	Evaluation							Down-Titration	Safety (Drug-free)
Visit	Entry Visit		Minimal Evaluation Visit	Full Evaluation Visit	Yearly Evaluation Visit/Final Visit	Unscheduled Visit	Early Discontinuation Visit	Down-Titration Visit	Safety Visit
	(EV)		(MEV)	(FEV)	(YEV/FV[b])	(UV)	(EDV)	(DTV)[c]	(SV)
Subjects	LTFU[a]	DE	All						
Assessment									

AE=adverse event; AED=antiepileptic drug; ALP=alkaline phosphatase; ALT=alanine aminotransferase; 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; C-SSRS=Columbia-Suicide Severity Rating Scale; DE=directly enrolled; DRC=daily record card; DTV=Down-Titration Visit; ECG=electrocardiogram; eCRF=electronic case report form; EDV=Early Discontinuation Visit; EEG=electroencephalogram; EV=Entry Visit; FEV= Full Evaluation Visit; FV=Final Visit; GGT=gamma-glutamyltransferase; IVRS=interactive voice response system; LTFU=long-term follow-up; M=Month; MEV=Minimal Evaluation Visit; PedsQL=Pediatric Quality of Life Inventory; SAE=serious adverse event; SV=Safety Visit; TV=Titration Visit; UV=Unscheduled Visit; V=Visit; YEV=Yearly Evaluation Visit

[a] For LTFU subjects, the following data will be obtained from Baseline of the previous pediatric BRV study and should not be recorded on the eCRF for N01266: general medical and procedure history, epilepsy history, AED history, height, Bayley-III scales, the Achenbach CBCL, BRIEF-P/BRIEF, and PedsQL scores. The following data will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266: AEs, recording of medications, recording of procedures, seizure count, EEG, ECG, laboratory assessments for safety, including phenytoin plasma concentrations (if applicable), the C-SSRS, vital signs, body weight, physical and neurological examinations, psychiatric and mental status, and data on health care provider consultations not foreseen by the protocol and hospital stays. The EV is also the final evaluation visit of the previous pediatric BRV study.

[b] For subjects staying in the study until it ends, the same procedures as for a YEV should be performed at the subject's FV.

[c] Visit should be scheduled at the end of the Down-Titration Period. The duration of the Down-Titration Period will depend on when the final dose of the study drug was taken during the Evaluation Period, with a maximum duration of 4 weeks.

[d] Vital sign measurements include blood pressure, pulse rate, and body temperature.

[e] An ECG has to be scheduled once a year at the YEV and at the EDV in the case of early discontinuation.

[f] At the SV, ECGs, laboratory assessments for safety, and determination of phenytoin plasma concentration will be performed only if abnormal at the EDV.

Amendment 4 Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	Evaluation							Down-Titration	Safety (Drug-free)
Visit	Entry Visit		Minimal Evaluation Visit	Full Evaluation Visit	Yearly Evaluation Visit/Final Visit	Unscheduled Visit	Early Discontinuation Visit	Down-Titration Visit	Safety Visit
	(EV)		(MEV)	(FEV)	(YEV/FV[b])	(UV)	(EDV)	(DTV)[c]	(SV)
Subjects	LTFU[a]	DE	All						
Assessment									

[g] EEG (for LTFU subjects only)

- For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: every 3 months during the first 6 months (starting at V4), and then yearly thereafter: an EEG of at least 1 hour of recording including hyperventilation and intermittent photic stimulation must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, an EEG of at least 1 hour of recording should also be performed at the EDV.
- For subjects ≥1 month to <2 years of age on the day of the study visit: every 3 months during the first 6 months (starting at V4), then yearly thereafter: an EEG of at least 24 hours of recording including sleeping and awakening periods must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, an EEG of at least 24 hours of recording should also be performed at the EDV.

[h] No DRC or study drug will be dispensed at the FV.

[i] The assessment of seizure types will be done at 6-monthly intervals (at the FEV and the YEV) for subjects <2 years of age.

[j] For LTFU subjects, any ongoing medications (including AEDs and non-AEDs) at the time the subject completed the previous pediatric BRV study should not be recorded in the eCRF for N01266, unless there is a change regarding the administration of the medication. In this event, the start date corresponding to the date of change in administration should be recorded in the eCRF.

[k] For LTFU subjects, any ongoing AEs at the time the subject completed the previous pediatric BRV study should not be recorded on the eCRF for N01266, unless there is a change in intensity or seriousness. In this event, the AE should be recorded in the eCRF for N01266, with the onset date corresponding to the date of change in condition.

[l] Drug return includes study medication intake recording and accountability.

[m] Full laboratory assessments for safety include hematology, biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT), and endocrinology for all subjects and urinalysis for subjects ≥4 years of age as described in Section 9.5.1. Female subjects with a Tanner stage >1 should have a urine pregnancy test performed at all laboratory assessment visits, except for the EDV and the SV, when a serum pregnancy test will be performed. Endocrinology testing will be performed at the YEV/FV.

[n] Laboratory assessments are to be done only at the MEV at V4 (M3) and V6 (M9) and are to include only hepatic monitoring (ALT, AST, ALP, total

Amendment 4 Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	Evaluation							Down-Titration	Safety (Drug-free)
Visit	Entry Visit		Minimal Evaluation Visit	Full Evaluation Visit	Yearly Evaluation Visit/Final Visit	Unscheduled Visit	Early Discontinuation Visit	Down-Titration Visit	Safety Visit
	(EV)		(MEV)	(FEV)	(YEV/FV[b])	(UV)	(EDV)	(DTV)[c]	(SV)
Subjects	LTFU[a]	DE	All						
Assessment									

bilirubin, and GGT).

[o] In addition to the scheduled assessments, a pharmacokinetic sample for determination of BRV plasma concentration should be taken whenever a subject experiences an SAE.

[p] The C-SSRS will be administered to subjects ≥6 years of age. The "Since Last Visit" version of the C-SSRS will be used, with the following exception: If a subject turns 6 years of age during N01266, the "Already Enrolled" version of the C-SSRS should be completed at the first visit after the sixth birthday, and the "Since Last Visit" version of the C-SSRS should be completed at subsequent visits.

[q] The cognition scale (Bayley-III) to be used in N01266 for subjects <18 months to 42 months of age and enrolled in English-speaking countries will be the same as the one used in the previous pediatric BRV study. If the subject reaches 18 months of age in this study, the subject will still be assessed using the Bayley-III to allow for an evaluation of the change from Baseline even if his/her age increases to ≥18 months.

[r] The version of the Achenbach CBCL (CBCL/1½-5 or CBCL/6-18) should be in accordance with the subject's age, with the following exception: If a subject completed the Achenbach CBCL/1½-5 at the Baseline assessment (previous pediatric BRV study for LTFU subjects and ScrV for directly enrolled subjects) 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.

[s] The BRIEF-P should be used for subjects ≥2 years to <5 years of age and the BRIEF should be used for subjects ≥5 years of age, with the following exception: For subjects who completed the BRIEF-P at the Baseline assessment (previous pediatric BRV study for LTFU subjects and ScrV for directly enrolled subjects) 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.

[t] The version of the PedsQL used should be consistent with the subject's age at each visit when it is administered with the following exception: If a subject ages up to the next PedsQL between the Baseline assessment (previous pediatric BRV study for LTFU subjects and ScrV for directly enrolled subjects) and the initial YEV, the PedsQL that was used at the Baseline assessment should be completed through and including the initial YEV, and subsequently the PedsQL consistent with the age at the time of assessment should be completed.

[u] This refers to any hospital stay that occurs during the study. Data recorded in the eCRF include the reason for the hospitalization, the admission ward,

Amendment 4 Table 5-1: Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Period	Evaluation							Down-Titration	Safety (Drug-free)
Visit	Entry Visit		Minimal Evaluation Visit	Full Evaluation Visit	Yearly Evaluation Visit/Final Visit	Unscheduled Visit	Early Discontinuation Visit	Down-Titration Visit	Safety Visit
	(EV)		(MEV)	(FEV)	(YEV/FV[b])	(UV)	(EDV)	(DTV)[c]	(SV)
Subjects	LTFU[a]	DE	All						
Assessment									

transfers, and length of stay.

[v] End of study status only for subjects who continue in the study until it ends and for whom the visit corresponds to the final evaluation visit or FV.

Table 5-1:

Change 1:

The title:

Schedule of all study assessments for LTFU subjects and assessments subsequent to the final TV for directly enrolled subjects

Was changed to:

Schedule of assessments for the Entry Visit (EV) (all subjects)

Change 2:

Entry Visit assessments for subjects from core studies EP0065 and N01349 were added (see Table 5-1 for display of assessments added).

Change 3:

The following rows were added:

- General medical history
- Procedure history
- Epilepsy history
- AED history
- Head circumference

Change 4:

The following rows were deleted:

- Assessment of seizure types
- BRV plasma concentrations
- End of study status

Change 5:

The following row entries were split into separate rows as follows:

- Written informed consent/assent

  Split and revised to:

  – Written informed consent

  – Assent form (if applicable, according to age and local requirements)

- Body weight and height

  Split into:

  – Body weight

  – Height

Change 6:

The following footnote was deleted:

[a] For LTFU subjects, the following data will be obtained from Baseline of the previous pediatric BRV study and should not be recorded on the eCRF for N01266: general medical and procedure history, epilepsy history, AED history, height, Bayley-III scales, the Achenbach CBCL, BRIEF-P/BRIEF, and PedsQL scores. The following data will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266: AEs, recording of medications, recording of procedures, seizure count, EEG, ECG, laboratory assessments for safety, including phenytoin plasma concentrations (if applicable), the C-SSRS, vital signs, body weight, physical and neurological examinations, psychiatric and mental status, and data on health care provider consultations not foreseen by the protocol and hospital stays. The EV is also the final evaluation visit of the previous pediatric BRV study.

And replaced with the following:

[a] "Other" core studies include those other than EP0065 and N01349.

[b] To be obtained from the final visit of the core study and not recorded in the N01266 eCRF.

[c] To be obtained from baseline of the core study and not recorded in the N01266 eCRF.

Change 7:

The following footnotes were deleted:

[e] An ECG has to be scheduled once a year at the YEV and at the EDV in the case of early discontinuation.

[f] At the SV, ECGs, laboratory assessments for safety, and determination of phenytoin plasma concentration will be performed only if abnormal at the EDV.

[g] EEG (for LTFU subjects only)

- For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: every 3 months during the first 6 months (starting at V4), and then yearly thereafter: an EEG of at least 1 hour of recording including hyperventilation and intermittent photic stimulation must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, an EEG of at least 1 hour of recording should also be performed at the EDV.
- For subjects ≥1 month to <2 years of age on the day of the study visit: every 3 months during the first 6 months (starting at V4), then yearly thereafter: an EEG of at least 24 hours of recording including sleeping and awakening periods must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, an EEG of at least 24 hours of recording should also be performed at the EDV.

And replaced with the following:

[f] Any ongoing AEs at the time the subject completed the core study should not be recorded in the N01266 eCRF. Worsening of the AE should be recorded in the N01266 eCRF as a new AE. A pharmacokinetic sample for determination of BRV plasma concentration should be taken whenever a subject experiences an SAE.

[g] Drug return includes study medication intake recording and accountability.

Change 8:

The following footnotes were deleted:

[h] No DRC or study drug will be dispensed at the FV.

[i] The assessment of seizure types will be done at 6-monthly intervals (at the FEV and the YEV) for subjects <2 years of age.

Change 9:

The following footnotes:

[j] For LTFU subjects, any ongoing medications (including AEDs and non-AEDs) at the time the subject completed the previous pediatric BRV study should not be recorded in the eCRF for N01266, unless there is a change regarding the administration of the medication. In this event, the start date corresponding to the date of change in administration should be recorded in the eCRF.

[k] For LTFU subjects, any ongoing AEs at the time the subject completed the previous pediatric BRV study should not be recorded on the eCRF for N01266, unless there is a change in intensity or seriousness. In this event, the AE should be recorded in the eCRF for N01266, with the onset date corresponding to the date of change in condition.

Were replaced with the following as shown in Change #7):

[e] Any ongoing concomitant medications at the time the subject completed the core study should not be recorded in the N01266 eCRF. Changes in ongoing concomitant medications should be recorded in the N01266 eCRF.

[f] Any ongoing AEs at the time the subject completed the core study should not be recorded on the N01266 eCRF. Worsening of the AE should be recorded in the N01266 eCRF as a new AE. A pharmacokinetic sample for determination of BRV plasma concentration should be taken whenever a subject experiences an SAE.

Change 10:

The following footnote was relettered to “g”:

[l] Drug return includes study medication intake recording and accountability.

Change 11:

The following footnote:

[m] Full laboratory assessments for safety include hematology, biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT), and endocrinology for

all subjects and urinalysis for subjects ≥4 years of age as described in Section 9.5.1. Female subjects with a Tanner stage >1 should have a urine pregnancy test performed at all laboratory assessment visits, except for the EDV and the SV, when a serum pregnancy test will be performed. Endocrinology testing will be performed at the YEV/FV.

Was replaced with:

[h] Full laboratory assessments for safety include hematology and biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT) for all subjects, endocrinology for LTFU subjects, and urinalysis for all subjects for whom sample collection is feasible as described in Section 9.2.1. Female subjects of childbearing potential will have a urine pregnancy test done at the site.

Change 12:

The following footnotes were deleted:

[n] Laboratory assessments are to be done only at the MEV at V4 (M3) and V6 (M9) and are to include only hepatic monitoring (ALT, AST, ALP, total bilirubin, and GGT).

[o] In addition to the scheduled assessments, a pharmacokinetic sample for determination of BRV plasma concentration should be taken whenever a subject experiences an SAE.

Change 13:

The following footnotes:

[p] The C-SSRS will be administered to subjects ≥6 years of age. The "Since Last Visit" version of the C-SSRS will be used, with the following exception: If a subject turns 6 years of age during N01266, the "Already Enrolled" version of the C-SSRS should be completed at the first visit after the sixth birthday, and the "Since Last Visit" version of the C-SSRS should be completed at subsequent visits.

[q] The cognition scale (Bayley-III) to be used in N01266 for subjects <18 months to 42 months of age and enrolled in English-speaking countries will be the same as the one used in the previous pediatric BRV study. If the subject reaches 18 months of age in this study, the subject will still be assessed using the Bayley-III to allow for an evaluation of the change from Baseline even if his/her age increases to ≥18 months.

[r] The version of the Achenbach CBCL (CBCL/1½-5 or CBCL/6-18) should be in accordance with the subject's age, with the following exception: If a subject completed the Achenbach CBCL/1½-5 at the Baseline assessment (previous pediatric BRV study for LTFU subjects and ScrV for directly enrolled subjects) 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.

[s] The BRIEF-P should be used for subjects ≥2 years to <5 years of age and the BRIEF should be used for subjects ≥5 years of age, with the following exception: For subjects who completed the BRIEF-P at the Baseline assessment (previous pediatric BRV study for LTFU subjects and ScrV for directly enrolled subjects) 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.

[t] The version of the PedsQL used should be consistent with the subject's age at each visit when it is administered with the following exception: If a subject ages up to the next PedsQL between the Baseline assessment (previous pediatric BRV study for LTFU subjects and ScrV for directly enrolled subjects) and the initial YEV, the PedsQL that was used at the Baseline assessment should be completed through and including the initial YEV, and subsequently the PedsQL consistent with the age at the time of assessment should be completed.

Were revised as follows:

[i] The C-SSRS will be administered to subjects ≥6 years of age. The "Since Last Visit" version of the C-SSRS will be used. If a subject turns 6 years of age during the study, the "Already Enrolled" version of the C SSRS should be completed at the first visit after the sixth birthday.

[j] The Bayley-III is applicable to subjects enrolled in English-speaking countries only and as follows:

- Core study N01349: all subjects
- Core study EP0065: subjects <18 months of age at baseline (Screening)
- Other core studies: subjects <18 months of age at baseline for the core study (as indicated in footnote c).

[k] The version of the Achenbach CBCL (CBCL/1½-5 or CBCL/6-18) should be in accordance with the subject's age.

[l] The BRIEF-P should be used for subjects ≥2 years to <5 years of age and the BRIEF should be used for subjects ≥5 years of age.

[m] The version of the PedsQL used should be consistent with the subject's age.

Change 14:

The following footnotes were deleted:

[u] This refers to any hospital stay that occurs during the study. Data recorded in the eCRF include the reason for the hospitalization, the admission ward, transfers, and length of stay.

[v] End of study status only for subjects who continue in the study until it ends and for whom the visit corresponds to the final evaluation visit or FV.

Table 5-2:

Change 1:

The title was updated to:

Schedule of all study assessments for the Evaluation, Down-Titration, and Safety (Drug-Free) Periods (all subjects)

Change 2:

The row containing "Subjects" and "All" was removed.

Change 3:

The following entries and associated assessment times were removed (with retention of information in Table 5-1):

- Written informed consent/assent
- Subject identification card dispensing
- Verification inclusion/exclusion criteria
- Demographic data

Change 4:

The Entry Visit columns were removed (with retention of information to Table 5-1)

Change 5:

The following entry:

Body weight and height

Was changed to:

Body weight, height, and head circumference

Change 6:

The X for the EEG assessment was removed from the MEV column.

Change 7:

An X^p was added for the Unscheduled Visit for the C-SSRS.

Change 8:

The following footnote was removed and subsequent footnotes relettered accordingly (both below and within the table):

[a] For LTFU subjects, the following data will be obtained from Baseline of the previous pediatric BRV study and should not be recorded on the eCRF for N01266: general medical and procedure history, epilepsy history, AED history, height, Bayley-III scales, the Achenbach CBCL, BRIEF-P/BRIEF, and PedsQL scores. The following data will be obtained from the final visit of the previous pediatric BRV study and should not be recorded in the eCRF for N01266: AEs, recording of medications, recording of procedures, seizure count, EEG, ECG, laboratory assessments for safety, including phenytoin plasma concentrations (if applicable), the C-SSRS, vital signs, body weight, physical and neurological examinations, psychiatric and mental status, and data on health care provider consultations not foreseen by the protocol and hospital stays. The EV is also the final evaluation visit of the previous pediatric BRV study.

Change 9:

The following footnote:

[g] EEG (for LTFU subjects only)

- For subjects ≥2 years of age on the day of the study visit and with typical absence seizures: every 3 months during the first 6 months (starting at V4), and then yearly thereafter: an EEG of at least 1 hour of recording including hyperventilation and intermittent photic stimulation must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, an EEG of at least 1 hour of recording should also be performed at the EDV.
- For subjects ≥1 month to <2 years of age on the day of the study visit: every 3 months during the first 6 months (starting at V4), then yearly thereafter: an EEG of at least 24 hours of recording including sleeping and awakening periods must be performed for efficacy assessment. For subjects prematurely discontinuing from the study, an EEG of at least 24 hours of recording should also be performed at the EDV.

Was changed to:

[f] EEG (for LTFU subjects only)

- For subjects ≥2 years of age at V5 who have typical absence seizures, an EEG of at least 24 hours that includes hyperventilation and intermittent photic stimulation must be performed at V5 and yearly threafter. For subjects prematurely discontinuing from the study, a 24-hour EEG may be performed at the EDV at the Investigator's discretion.
- For subjects <2 years of age at V5, an EEG of at least 24 hours must be performed for efficacy assessment at V5 and yearly thereafter until subjects reach 2 years of age. For subjects prematurely discontinuing from the study, a 24-hour EEG may be performed at the EDV at the Investigator's discretion.

Change 10:

The following footnote:

[j] For LTFU subjects, any ongoing medications (including AEDs and non-AEDs) at the time the subject completed the previous pediatric BRV study should not be recorded in the eCRF for N01266, unless there is a change regarding the administration of the medication. In this event, the start date corresponding to the date of change in administration should be recorded in the eCRF.

Was changed to:

[i] For subjects enrolled in N01266 who volunteered to participate in EP0065 and then returned to N01266, changes to ongoing concomitant medications during EP0065 will be recorded in the N01266 eCRF.

Change 11:

The following footnote:

[m] Full laboratory assessments for safety include hematology, biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT), and endocrinology for all subjects and urinalysis for subjects ≥4 years of age as described in Section 9.5.1. Female subjects with a Tanner stage >1 should have a urine pregnancy test performed at all laboratory assessment visits, except for the EDV and the SV, when a serum pregnancy test will be performed. Endocrinology testing will be performed at the YEV/FV.

Was changed to:

[l] Full laboratory assessments for safety include hematology, biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT), and endocrinology for all subjects and urinalysis for subjects for whom sample collection is feasible as described in Section 9.2.1. Female subjects of childbearing potential should have a urine pregnancy test done at the site at all laboratory assessment visits. Endocrinology testing will be performed at the YEV/FV.

Change 12:

The following footnote:

[n] Laboratory assessments are to be done only at the MEV at V4 (M3) and V6 (M9) and are to include only hepatic monitoring (ALT, AST, ALP, total bilirubin, and GGT).

Was changed to:

[m] Laboratory assessments (hepatic monitoring [ALT, AST, ALP, total bilirubin, and GGT only] are to be done only at the MEV at V4 (M3) and V6 (M9). Urine pregnancy tests are to be done at the site for female subjects of childbearing potential at all visits.

Change 13:

The following footnote was added:

[p] If an unscheduled visit is conducted due to safety or efficacy reasons, the C-SSRS will be performed for subjects ≥6 year of age.

Change 14:

The following footnote:

[q] The cognition scale (Bayley-III) to be used in N01266 for subjects <18 months to 42 months of age and enrolled in English-speaking countries will be the same as the one used in the previous pediatric BRV study. If the subject reaches 18 months of age in this study, the subject will still be assessed using the Bayley-III to allow for an evaluation of the change from Baseline even if his/her age increases to ≥18 months.

Was changed to:

[q] The Bayley-III is applicable to subjects who meet all of the following criteria: are enrolled English-speaking countries, were <18 months of age at baseline of the core study, and are <42 months of age.

Table 5-3:

With Amendment 5, the Amendment 4 Table 5-2 was renumbered to Table 5-3 and the following changes were made:

Change 1:

The title:

Schedule of study assessments for directly enrolled subjects only from the ScrV through the final TV

Was changed to:

Schedule of study assessments from the ScrV through the final TV (directly enrolled subjects only)

Change 2:

The entry:

body weight and height

Was changed to:

body weight, height, and head circumference

Change 3:

The entry:

IVRS

Was changed to:

IVRS call

Change 4:

The footnote:

[c] Height will be recorded only at the ScrV.

Was changed to:

[c] Height and head circumference will be recorded only at the ScrV.

Change 5:

The following sentence in footnote i:

[i] The ScrV laboratory assessments for safety will include hematology, biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT), urinalysis, endocrinology, and a serum pregnancy test (for female subjects with a Tanner stage >1).

Was changed to:

[i] The ScrV laboratory assessments for safety will include hematology, biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT), urinalysis

(for subjects for whom sample collection is feasible), endocrinology, and a urine pregnancy test at the site (for female subjects of childbearing potential).

Table 5-4:

The following footnote:

[b] For LTFU subjects, the EV is the final evaluation visit of the previous pediatric study. For directly enrolled subjects, the EV represents the point of entry into the Evaluation Period.

Was changed to:

[b] For directly enrolled subjects, the EV represents the point of entry into the Evaluation Period.

16.6 Protocol Amendment 6

Rationale for the amendment

The main purposes of this substantial protocol amendment are to:

- Update language for Bayley-III scales to include countries where a validated translation is available
- Remove reference to central reading of EEGs to provide flexibility
- Remove EEG assessment for the EV (all subjects)
- Update inclusion criteria to align language enhancements provided in country-specific amendment (Czech Republic) (ie, diagnosis of epilepsy and contraceptive language)
- Update language in regards to partner pregnancy to align with Sponsor's SOP and protocol templates
- Add blood draw volumes for children <2 years of age
- Clarify PedsQL age range (≥2 years of age) as this assessment will not be used in children <2 years of age
- Clarify for all other EEGs (ie, V5 and yearly thereafter) the duration in subjects >2 years of age

Modifications and changes

Global changes

These following changes are considered administrative in nature and are not included as separate listings in the table of specific changes below:

- Stylistic changes and minor editorial changes have been made and are of no consequence to the meaning of content.

Specific changes

The following table provides a list of specific changes to the protocol. Specific changes to the tables in Section 5.2 (Table 5-1, Table 5-2, and Table 5-3) are provided immediately after the table and are not included in the table itself.

Section Impacted	Key components of previous text	Key components of amended text
Study contact information	Sponsor Study Physician Address: UCB Biosciences GmbH Alfred Nobel Strabe 10 40789 Monheim Germany Phone: [redacted] FAX: [redacted]	Sponsor Study Physician Address: UCB Biosciences GmbH Alfred Nobel Strabe 10 40789 Monheim am Rhein Germany Phone: [redacted] FAX: [redacted]
	Clinical Project Manager Name: [redacted] Address: UCB BioPharma sprl Allée de la Recherche 60 B-1070 Bruxelles Belgium Phone: [redacted] Fax: [redacted]	Clinical Project Manager Name: [redacted] Address: UCB Biosciences GmbH Alfred-Nobel-Straße 10 40789 Monheim Germany Phone: [redacted] Fax: [redacted]
	Clinical Trial Biostatistician: Name: [redacted] Phone: [redacted]	Clinical Trial Biostatistician: Name: [redacted] Phone: [redacted]

Section 1

Section Impacted	Key components of previous text	Key components of amended text
Section 1	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 directly enrolled 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 ≥1 month of age at the Baseline of the core study and for all directly enrolled 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 <18 months of age at Baseline of the core study; the Bayley-III will not be used to assess directly enrolled subjects since all are to be ≥4 years of age. 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.	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 directly enrolled 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 directly enrolled 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 directly enrolled subjects since all are to be ≥4 years of age. 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 countries where a validated translation is available.

Section 3

Section Impacted	Key components of previous text	Key components of amended text
Section 3.3	• To assess the effect of BRV on cognition using the Bayley-III scales in subjects <18 months of age (applicable only to LTFU subjects enrolled in English-speaking countries)	• To assess the effect of BRV on cognition using the Bayley-III scales in subjects <18 months of age (applicable only to LTFU subjects enrolled in English-speaking countries and in countries where a validated translation is available)
	• To explore the effect of BRV on health-related quality of life (HRQoL) using the PedsQL in subjects ≥1 month of age	• To explore the effect of BRV on health-related quality of life (HRQoL) using the PedsQL in subjects ≥2 years of age

Section 4

Section Impacted	Key components of previous text	Key components of amended text
Section 4.3	• Change from the 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)	• Change from the 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 in countries where a validated translation is available)
	• Change from Baseline in PedsQL for subjects ≥1 month of age (age at initiation of study drug in N01266 or core study)	• Change from Baseline in PedsQL for subjects ≥2 years of age (age at initiation of study drug in N01266 or core study)

Section 5

Section Impacted	Key components of previous text	Key components of amended text
Section 5.1	A central reader will perform a review of the EEG recordings.	Deleted

Section 6

Section Impacted	Key components of previous text	Key components of amended text
Section 6.1.1	-Abstinence from sexual intercourse	Deleted
Section 6.1.2	3a. Male or female subjects having participated in a core study and for whom a reasonable benefit from long-term administration of BRV is expected.	3a. Male or female subjects having participated in a core study with a confirmed diagnosis of epilepsy and for whom a reasonable benefit from long-term administration of BRV is expected.

Section 8

Section Impacted	Key components of previous text	Key components of amended text
Section 8.3.1.1 & Section 8.3.1.2	• EEG	Deleted
Section 8.3.1.1 & Section 8.3.1.2 & Section 8.5 & Section 8.6 & Section 8.8 & Section 8.11	• Bayley-III scales (subjects enrolled in English-speaking countries)	• Bayley-III scales (subjects enrolled in English-speaking countries and in countries where a validated translation is available)
Section 8.5 &	• EEG (for LTFU subjects only) – For subjects ≥2 years of age at V5 who have typical absence seizures, an EEG of at least 24 hours that includes hyperventilation and intermittent photic stimulation must be performed only at V5 and yearly thereafter.	• EEG (for LTFU subjects only) – For subjects ≥2 years of age at V5 who have typical absence seizures, an EEG of at least 1 hour that includes hyperventilation and intermittent photic stimulation must be performed only at V5 and yearly thereafter.
Section 8.8	• EEG (LTFU subjects only) For subjects ≥2 years of age at V5 who have typical absence seizures, a 24-hour EEG may be performed at the Investigator's discretion.	• EEG (LTFU subjects only) For subjects ≥2 years of age at V5 who have typical absence seizures, a 1-hour EEG may be performed at the Investigator's discretion.
Section 8.11	• EEG (for LTFU subjects only) – For subjects ≥2 years of age at V5 who have typical absence seizures, an EEG of at least 24 hours that includes hyperventilation and intermittent photic stimulation must be performed	• EEG (for LTFU subjects only) – For subjects ≥2 years of age at V5 who have typical absence seizures, an EEG of at least 1 hour that includes hyperventilation and intermittent photic stimulation must be performed

Section 9

Section Impacted	Key components of previous text	Key components of amended text
Section 9.1.4	In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, UCB will ask the Investigator or designee to contact the subject and his partner to request consent via the Partner Pregnancy Consent form. If the partner agrees to provide additional information, the Pregnancy Report and Outcome form will be forwarded to the subject's partner for completion. The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed-up using the Pregnancy Report and Outcome form in which the Investigator has to report on the health of the mother and of the child. The health of the child must be followed for 12 months after birth for any significant medical issues.	In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the investigator site file. In case of questions about the consent process, the investigator may contact the UCB/contract research organization (CRO) contract monitor for the study. The investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see Serious Adverse Event reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.
Section 9.2.1	The total blood volume drawn for clinical laboratory assessments will be a maximum of 11mL per sampling, which includes 3mL for hematology and 8mL for biochemistry. Further details will be provided in the laboratory manual.	The total blood volume drawn for clinical laboratory assessments in subjects ≥2 years of age will be a maximum of 11mL per sampling, which includes up to 3mL for hematology and up to 8mL for biochemistry. For subjects <2 years of age, the blood volume drawn will be typically much smaller and in the range of 1mL to 2.5mL. Further details will be provided in the laboratory manual.

Section10

Section Impacted	Key components of previous text	Key components of amended text
Section 10.2	A central reader will review and assess all EEGs in a standardized manner.	Deleted
Section 10.3.2	The Bayley-III scales are validated only in English.	The Bayley-III scales are provided in English and in countries where a validated translation is available.
Section 10.3.5	The PedsQL Measurement Model consists of developmentally appropriate forms for pediatric subjects 1 month to 24 months, ≥2 years to ≤4 years, ≥5 years to ≤7 years, ≥8 years to ≤12 years, and ≥13 years to ≤18 years of age.	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.

Specific changes to tables in Section 5

The rationales for the changes are noted in the rationale section above.

Details of updates to Table 5-1 are as follows:

Change # 1:

EEG assessment was removed.

Change #2

Footnote

[j] The Bayley-III is applicable to subjects enrolled in English-speaking countries only and as follows:

- Core study N01349: all subjects
- Core study EP0065: subjects <18 months of age at baseline (Screening)
- Other core studies: subjects <18 months of age at baseline for the core study (as indicated in footnote c)

Has been changed to:

[k] The Bayley-III is applicable to subjects enrolled in countries where a validated translation is available only and as follows:

- Core study N01349: all subjects
- Core study EP0065: subjects <18 months of age at baseline (Screening)
- Other core studies: subjects <18 months of age at baseline for the core study (as indicated in footnote c)

Details of updates to Table 5-2 are as follows:

Change #1

Footnote

[f] EEG (for LTFU subjects only)

- For subjects ≥2 years of age at V5 who have typical absence seizures, an EEG of at least 24 hours that includes hyperventilation and intermittent photic stimulation must be performed at V5 and yearly thereafter. For subjects prematurely discontinuing from the study, a 24-hour EEG may be performed at the EDV at the Investigator's discretion.
- For subjects <2 years of age at V5, an EEG of at least 24 hours must be performed for efficacy assessment at V5 and yearly thereafter until subjects reach 2 years of age. For subjects prematurely discontinuing from the study, a 24-hour EEG may be performed at the EDV at the Investigator's discretion.

Has been changed to:

[f] EEG (for LTFU subjects only)

- For subjects ≥2 years of age at V5 who have typical absence seizures, an EEG of at least 1 hour that includes hyperventilation and intermittent photic stimulation must be performed at V5 and yearly thereafter. For subjects prematurely discontinuing from

the study, a at least 1-hour EEG may be performed at the EDV at the Investigator's discretion.

- For subjects <2 years of age at V5, an EEG of at least24hours must be performed for efficacy assessment at V5 and yearly thereafter until subjects reach 2 years of age. For subjects prematurely discontinuing from the study, an at least 24-hour EEG may be performed at the EDV at the Investigator's discretion.

Change #2

Footnote

[m] Laboratory assessments (hepatic monitoring [ALT, AST, ALP, total bilirubin, and GGT only] are to be done only at the MEV at V4 (M3) and V6 (M9). Urine pregnancy tests are to be done at the site for female subjects of childbearing potential at all visits.

Has been changed to:

[m] Additional hepatic monitoring laboratory assessments (ALT, AST, ALP, total bilirubin, and GGT only) are to be done only at the MEV at V4 (M3) and V6 (M9). Urine pregnancy tests are to be done at the site for female subjects of childbearing potential at all visits.

Change #3

Footnote

[q] The Bayley-III is applicable to subjects who meet all of the following criteria: are enrolled English-speaking countries, were <18 months of age at baseline of the core study, and are <42 months of age.

Has been changed to:

[q] The Bayley-III is applicable to subjects who meet all of the following criteria: are enrolled English-speaking countries and in countries where a validated translation is avaiable, were <18 months of age at baseline of the core study, and are <42 months of age.

16.7 Protocol Amendment 7

Rationale for the amendment

The text in the Section 9.1.4 Pregnancy has been updated to clarify that the Pregnancy Report and Outcome form should be completed for all pregnancies.

Modifications and changes

The following table provides a list of specific changes to the protocol.

Section Impacted	Key components of previous text	Key components of amended text
Section 9.1.4	In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/contract research organization contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see SAE reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow-up. A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. Those SAEs must be additionally reported using the Investigator SAE Report form.	The Investigator will complete the Pregnancy Report and Outcome form for any pregnancy and send it to UCB's PS department (for contact details see SAE reporting information at the beginning of this protocol). A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. Those SAEs must be additionally reported using the Investigator SAE Report form. In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/contract research organization contract monitor for the study. If the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form, the Pregnancy Report and Outcome form will be completed. UCB's PS department is the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow-up.

16.8 Protocol Amendment 8

Rationale for the amendment

The study variables have been reorganized into primary, secondary, and other variables in compliance with reporting registries. This recategorization does not affect the type or processing of data collected and reported in the study report, as they will be assessed as initially planned. The option for subjects to transition to another BRV study has been added, and information regarding down-titration for subjects who do not continue BRV treatment after completing the study has been added. Text describing the maximum dose of BRV has been clarified.

Modifications have been made to the study conduct to ensure the safety of subjects in response to the COVID-19 pandemic.

Administrative changes include the update of the Sponsor Study Physician and Clinical Trial Biostatistician contact details and typographical corrections.

Modifications and changes

The following table provides a list of specific changes to the protocol.

Section impacted	Key components of previous text	Key components of amended text	Rationale
Study contact information	Sponsor Study Physician Name: [redacted] Address: UCB Biosciences GmbH Alfred-Nobel-Straße 10 40789 Monheim Germany Phone: [redacted] Fax: [redacted]	Sponsor Study Physician Name: [redacted] Address: UCB Biosciences GmbH Alfred-Nobel-Straße 10 40789 Monheim Germany Phone: [redacted] Fax: [redacted]	Administrative change
	Clinical Trial Biostatistician Name: [redacted] Address: 8010 Arco Corporate Drive, [redacted] Raleigh, NC 27617 United States Phone: [redacted] Fax: [redacted]	Clinical Trial Biostatistician Name: [redacted] Address: 8010 Arco Corporate Drive, [redacted] Raleigh, NC 27617 United States Phone: [redacted] Fax: [redacted]	Administrative change
List of abbreviations	Not applicable.	COVID-19 coronavirus (SARS-CoV-2) disease 2019 SARS-CoV-2 severe acute respiratory syndrome coronavirus-2	Administrative change
Section 1	The maximum allowable BRV dose is 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg.	The maximum allowable BRV dose is 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day.	Removal of unnecessary text for clarification

Section impacted	Key components of previous text	Key components of amended text	Rationale
Section 1 Section 2.3	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, or until the investigational product development in the related age range of the pediatric population is stopped by the Sponsor, whichever comes first.	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.	To allow subjects to transition to another BRV study

Section impacted	Key components of previous text	Key components of amended text	Rationale
Section 4.1	Safety variables The safety variables include the following: • AE reporting • Safety laboratory tests (hematology, biochemistry including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT, and endocrinology for all subjects and urinalysis for subjects for whom sample collection is feasible) (See Section 9.2.1) • Plasma concentrations of BRV and phenytoin (if applicable) • ECG • Physical (Tanner scale, if applicable depending on subject's developmental status) and neurological examinations • Psychiatric and mental status • Vital signs (blood pressure, pulse rate, and body temperature) • Body weight, height, and head circumference	Primary variables • Treatment-emergent AEs • Treatment-emergent serious adverse events (SAEs)	To reorganize the study variables in compliance with reporting registries
Section 4.2	Efficacy variables For subjects <2 years of age (based on EEG data [recorded at least 24 hours]) or subjects with absence seizures (based on EEG data): • Responder rate for total POS defined as the percentage of subjects with a ≥50% reduction in ADF (average daily frequency) of POS	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	To reorganize the study variables in compliance with reporting registries

Section impacted	Key components of previous text	Key components of amended text	Rationale
	recorded on EEG (subjects with POS only) • Absolute and percent reduction in ADF of POS (subjects with POS only) • 50% responder rate for total seizures (all types) • Absolute and percent reduction in ADF of total seizures (all types) • Seizure freedom (rate and proportion) • Worsening of other types of seizures (absolute and percent) In addition, the following efficacy variables will be repeated for subjects <2 years of age or subjects with absence seizures based on the 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 and percent worsening in ADF of total seizures (all types) A descriptive summary of seizure frequency by visit based on the DRC data will be also provided for these subjects. The efficacy variables planned for analysis of subjects ≥2 years of age will be based on DRC data and will include the following:	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)	

Section impacted	Key components of previous text	Key components of amended text	Rationale
	• Responder rate (the percentage of subjects who have a ≥50% reduction in seizure frequency per 28 days from Baseline for POS) • Absolute and percent reduction in seizure frequency (POS) per 28 days from Baseline to the end of the Evaluation Period • 50% responder rate for total seizures (all types) • Absolute and percent reduction in seizure frequency (total seizures) per 28 days from Baseline to the end of the Evaluation Period • Seizure freedom rate over the Evaluation Period • Proportion of seizure-free days over the Evaluation Period		
Section 4.3	Other variables The other variables include the following: • Direct cost parameters: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays • Change 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)	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	To reorganize the study variables in compliance with reporting registries

Section impacted	Key components of previous text	Key components of amended text	Rationale
	• Change 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 the 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 in 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)	• Seizure freedom over the Evaluation Period • Proportion of seizure-free days over the Evaluation Period For subjects <2 years of age or subjects with absence seizures based on the 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 seizures (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 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)	

Section impacted	Key components of previous text	Key components of amended text	Rationale
		• 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 absence seizures: • Number and type of nonabsence seizure For all subjects: • Physical (including Tanner staging, if applicable depending on subject's developmental status) • Neurological examinations • Psychiatric and mental status • Laboratory tests (hematology, biochemistry including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT, 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) (See Section 9.2.1) • ECG • Vital signs (blood pressure, pulse rate, and body temperature)	

Section impacted	Key components of previous text	Key components of amended text	Rationale
		• 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 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 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 the 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 in 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)	

Section impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.1	For all subjects enrolled in N01266, the maximum BRV dose is 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg.	For all subjects enrolled in N01266, the maximum BRV dose is 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day.	Removal of unnecessary text for clarification
	Following the EDV, subjects will have their BRV dose reduced by a maximum of half the dose every week for a maximum of 4 weeks until a dose of 1mg/kg/day (50mg/day for subjects with body weights >50kg) is reached.	Following the EDV, or following the FV for subjects who complete the study but do not continue BRV treatment, subjects will have their BRV dose reduced by a maximum of half the dose every week for a maximum of 4 weeks until a dose of 1mg/kg/day (50mg/day for subjects with body weights >50kg) is reached.	To add down-titration information for subjects who do not continue BRV treatment after completing the study
Section 5.1.1	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, or until the investigational product development in the related age range of the pediatric population is stopped by the Sponsor, whichever comes first.	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.	To allow subjects to transition to another BRV study
Table 5-2	[g] No DRC or study drug will be dispensed at the FV.	[g] No DRC or study drug will typically be dispensed at the FV. However, for subjects who complete the study but do not continue BRV treatment, study drug for down-titration will be dispensed.	To add down-titration information for subjects who do not continue BRV treatment after completing the study
Section 5.4	The maximum allowable BRV dose in N01266 is 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg.	The maximum allowable BRV dose in N01266 is 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day.	Removal of unnecessary text for clarification

Section impacted	Key components of previous text	Key components of amended text	Rationale
Section 5.5	Not applicable.	Section 5.5 Study conduct due to coronavirus (severe acute respiratory syndrome coronavirus-2) disease 2019 The following applies where normal study conduct is impacted by coronavirus (severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2]) disease 2019 (COVID-19). The protocol visit schedule should be followed to the extent possible, considering the individual benefit-risk assessment by the Investigator. If necessary, remote visits may be conducted and the subjects or caregivers will be contacted by telephone or videoconference. Remote follow-up, at minimum with a telephone call after 3 months, must be done (preferably more frequently and as needed to follow-up on subject safety assessments). If a subject needs to be discontinued and cannot come into the study site, then appropriate down-titration instructions will be provided, and a visit will be scheduled to perform safety assessments as soon as possible (see Section 7.2.3 for down-titration instructions). In situations where a subject is unable to return to the study site, Investigators will assess and document the subject's safety via telephone contact. Based on information gathered from the telephone contact, Investigators will confirm whether the subject could continue the current study treatment based upon the outcome of the safety assessment. Subjects' agreement to implement this procedure should be obtained and documented prior to implementing any changes. Changes in the study treatment supply in this	To mitigate risk related to COVID-19

Section impacted	Key components of previous text	Key components of amended text	Rationale
		situation are described in Section 7.2.4. Ad hoc subject contact may be warranted to understand the current health status of the subjects, follow up on AEs and inform them of any protective measures taken by the study site as a result of the COVID-19 pandemic (eg, any measures which may limit access to the site or may require additional actions by the subject prior to entry to the site). Investigators and study coordinators may use discretion when determining the need to perform a home visit (eg, for safety laboratory parameters or PK samples). If subjects are unable to return to the study site, protocol deviations will occur (even if the study visit is replaced by a home visit or remote visit) (Section 12.6). Investigators must carefully document the occurrence of these and any other deviations, clearly noting deviations which occurred during and in accordance to the COVID-19 pandemic. If a subject visits another facility for a medical issue (or has to switch sites for some COVID-19-related reason), the Investigator should request contact with the physician providing care to provide a detailed explanation of the subject's condition and his/her participation in the study. Subjects or caregivers shall be reminded to completely collect and keep records of this visit. In case laboratory assessments cannot be conducted via central laboratory vendor due to restricted site access or home visits by Investigators are not an option, local laboratory	

Section impacted	Key components of previous text	Key components of amended text	Rationale
		safety assessment may need to be conducted, in a format that allows the Investigator to receive and review these results and include as source documentation. Deviations to data collection including inability to perform some assessments such as EEG, ECG or blood collection for safety laboratory assessments and PK, or alternative methods of assessment such as phone calls should be recorded in the source documentation and notated as "not done" in the electronic case report form (eCRF). In cases where subjects cannot return to the study site, and it will not be possible to dispense a new DRC, subjects will be instructed to continue recording of seizures in a manner that is mutually agreed with the Investigator (eg, hand-written notes, taking notes on a smart device). Any recording of seizures in a manner outside of the study DRC must be carefully documented in the source medical records (copies or printouts of these recordings will be brought to and retained at site).	
Section 7.2.2	The maximum BRV dose will be 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg.	The maximum BRV dose will be 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day.	Removal of unnecessary text for clarification
Section 7.2.3	All subjects who prematurely discontinue the study should complete an EDV and have their BRV dose down titrated by a maximum of half the dose every week for a maximum of 4 weeks until a dose of 1mg/kg/day (50mg/day for subjects with body weights >50kg) is reached.	All subjects who prematurely discontinue the study should complete an EDV and have their BRV dose down titrated by a maximum of half the dose every week for a maximum of 4 weeks until a dose of 1mg/kg/day (50mg/day for subjects with body weights >50kg) is reached. Equally, all subjects completing the study but switching to treatment	To add down-titration information for subjects who do not continue BRV treatment after completing the study

Section impacted	Key components of previous text	Key components of amended text	Rationale
		other than BRV should have their BRV dose down titrated.	
Section 7.2.4	Not applicable.	Section 7.2.4 Alternative study treatment supply due to COVID-19 When a subject can no longer return to the study site but will continue in the study, the following methods may be used to provide study treatment: • Site to subject: In instances where site staff can ship study treatment dispensed from the site or pharmacy supply directly to the subject, or • Depot to subject: In instances where it is not possible for the site staff to access study treatment and/or ship study treatment dispensed from the site or pharmacy supply directly to the subject.	To mitigate risk related to COVID-19
Section 7.7	The IMP (oral solution or oral tablets) will be supplied to the subject/parent(s)/legal representative(s) at the TV(s) (directly enrolled subjects only), EV, MEV, FEV, YEV, and at the EDV in the case of early discontinuation.	The IMP (oral solution or oral tablets) will be supplied to the subject/parent(s)/legal representative(s) at the TV(s) (directly enrolled subjects only), EV, MEV, FEV, YEV, and at the EDV in the case of early discontinuation. The IMP for down-titration will be dispensed at the FV for subjects who complete the study but do not continue BRV treatment.	To add down-titration information for subjects who do not continue BRV treatment after completing the study
Section 8.11	Not applicable.	• Appointment for the next visit should be scheduled for the end of the 4-week Down-Titration Period (maximum) if BRV treatment is not continued after study completion (FV), and study drug for down-titration should be dispensed	To add down-titration information for subjects who do not continue BRV treatment after completing the study

Section impacted	Key components of previous text	Key components of amended text	Rationale
Section 9.1.2.1	Not applicable.	Occurrence of COVID-19 in subjects should be reported as either "suspected COVID-19" or "confirmed COVID-19." For subjects where COVID-19 is still suspected despite a negative viral test, please report as "suspected COVID-19."	To document adverse events of suspected or confirmed COVID-19
Section 11.2	UCB (or designee) will monitor the study to meet the Sponsor's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a contract research organization or a contract monitor.	UCB (or designee) will monitor the study to meet the Sponsor's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a contract research organization or a contract monitor. Remote monitoring visits may be conducted during the COVID-19 pandemic or under other exceptional circumstances as deemed appropriate to ensure subjects' safety.	To mitigate risk related to COVID-19
Section 12.6	Not applicable.	Protocol deviations (eg, missing assessments or visits) related to COVID-19 will be documented.	To clarify that protocol deviations related to COVID-19 will be documented

17 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed Name	Date/Signature

18 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Approval Signatures

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Document Approvals	
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