A MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF BRIVARACETAM IN STUDY PARTICIPANTS 2 TO 26 YEARS OF AGE WITH CHILDHOOD ABSENCE EPILEPSY OR JUVENILE ABSENCE EPILEPSY

PROTOCOL EP0132 AMENDMENT 2

PHASE 3

SHORT TITLE:

A long-term safety, tolerability, and efficacy study of brivaracetam in study participants 2 to 26 years of age with childhood absence epilepsy or juvenile absence epilepsy.

Sponsor:
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Regulatory agency identifying number(s):

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Confidential Material

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Amendment 2	29 Mar 2021	Substantial
Amendment 1	08 Sep 2020	Substantial
Original Protocol	15 Jun 2020	Not applicable

Amendment 2 (29 Mar 2021)

Overall Rationale for the Amendment

EP0132 Protocol Amendment 2, dated 29 Mar 2021, was completed to:

- Address Health Authority feedback
- Correct minor errors/inconsistencies
- Provide additional clarifying information

EP0132 Protocol Amendment History is detailed in Section 10.11.

Section # and Name	Description of Change	Brief Rationale
Synopsis	Text was added to the key inclusion/exclusion criteria description to include end-stage kidney disease requiring dialysis and hepatic impairment in the list of exclusion criteria noted.	Clarification, as well as to note the newly added exclusion criterion (Section 5.2).
Section 1.2 (Schema)	Revised the study schema to add visit windows for the MEV, FEV, YEV, and FV and frequency for the MEV, FEV, YEV, and SV. Additional dosing information was added for participants weighing less than 50kg.	Clarification of the EP0132 study design.
Section 1.3 (Schedule of Activities)	Added text to footnote "c" describing the Down-titration Period to clarify that study participations who require down-titration will complete their daily seizure diaries during the Down-titration Period. Added "X's" to Table 1–2 to denote that participant diaries would be dispensed and retrieved during the Down-titration Period.	Clarification of procedures for completion of the seizure diary.
Section 1.3 (Schedule of Activities)	Removed former footnote "d" and revised footnote "k" (previously footnote "l") to remove text that stated a BRV plasma concentration should be taken within 1 day of the occurrence of an SAE. There are no	Error correction; not applicable for this study.

Section # and Name	Description of Change	Brief Rationale
	time approximation points to relate SAEs to BRV plasma concentrations for this study	
Section 1.3 (Schedule of Activities)	Edited footnote "d" (previously footnote "e"), which stated no study drug will be dispensed at the FV or EDV to clarify that study drug will only be dispensed at these visits if the study participant is discontinuing study drug and requires down-titration.	Error correction and further clarification of the procedures at the FV or EDV.
Section 1.3 (Schedule of Activities)	Removed inclusion of body weight/height and psychiatric/mental status assessments from footnotes "f" and "g" (previously footnotes "g" and "h") describing complete and brief physical and neurological examinations as these assessments are presented as separate line items in Table 1–2.	Body weight, height, and psychiatric/mental status assessments are included in Table 1-2 as separate line items so need not be noted in the descriptions of brief and complete physical/neurological exams.
Section 1.3 (Schedule of Activities)	Added EEG assessments to FEV and YEV/EDV/FV to align with the text provided in Section 7.3.1 detailing seizure data based on EEG.	Error correction.
Section 1.3 (Schedule of Activities)	Added text to footnote "m" (previously footnote "n") describing assessments conducted for Unscheduled Visits.	Clarification that, in addition to the assessments noted in the Schedule of Activities table, additional assessments can be performed per the Investigator's discretion.
Section 2.3 (Benefit/risk assessment)	Added text and supportive publications describing the current approved treatments for absence seizure and their limitations. Text was added to include the risk assessment regarding the potential interaction if concomitant use of BRV and a COVID-19 vaccination were to occur.	Response to Health Authority feedback. Inclusion of the risk assessment for concomitant use of a COVID-19 vaccine and BRV.
Section 5.2 (Exclusion criteria)	Added an exclusion criteria for clinically relevant ECG abnormalities. Added a hepatic impairment exclusion criterion, with Child Pugh Score A, B, or C as the basis for determination by the Investigator. Added a new exclusion criterion for participants with known fructose intolerance or hypersensitivity to any of the ingredients in BRV oral solution.	Consistency with parent study, N01269 Response to Health Authority feedback.

Section # and Name	Description of Change	Brief Rationale
	Added a new exclusion criterion for participants with end-stage kidney disease requiring dialysis.	
Section 5.3 (Lifestyle restrictions)	Added text to note that concomitant intake of alcohol is prohibited.	Response to Health Authority feedback.
Section 6.1.1 (Alternative study treatment supply due to COVID-19)	Removed "depot to participant" as a method for providing IMP to a study participant who is unable to return to the site but wishes to remain in the study.	This method is not permitted due to privacy issues.
Section 6.5.2 (Prohibited concomitant treatments [medications and therapies])	Added text that use of substrates of alcohol dehydrogenase is prohibited.	Response to Health Authority feedback.
Section 6.5.3 (Rescue medication)	Revised text to specify that rescue medication includes any treatment with permitted AEDs, including benzodiazepines.	Clarification that benzodiazepines are permitted as rescue medication.
Section 7.3.1 (Seizure data based on EEG)	Removed sentence stating the further information on EEG evaluation will be detailed in the EEG manual.	Error correction; there is no manual for locally read EEGs.
Section 7.3.2 (Seizure diary)	Added text to clarify that study participations who require down-titration will complete their daily seizure diaries during the Down-titration Period	Clarification of procedures for completion of the seizure diary.
Section 8.1.2 (Body weight and height)	Section added for body weight and height, and moved the applicable text from its former location in Section 8.1.1 (Physical examination).	Body weight and height are assessed on a different schedule than for physical examinations; these assessments are presented separately in Table 1–2.
Section 8.1.4 (Psychiatric and mental status evaluation)	Section added to provide information regarding the psychiatric and mental status evaluation conducted as a part of each complete neurological examination.	Alignment with the schedule of activities and the CRF.
Section 8.1.5 (Vital signs)	Revised text to state that 1 pulse and 1 blood pressure measurement will be recorded instead of an average of 3 consecutive blood pressure measurements.	Alignment with the CRF.
Section 8.1.8 (Suicidal risk monitoring)	Revised text to clarify administration of the C-SSRS consistently throughout the protocol.	Consistent presentation of C-SSRS administration.

Section # and Name	Description of Change	Brief Rationale
Section 8.2.5 (Pregnancy), Section 10.4 (Contraceptive guidance and collection of pregnancy information).	Revised text to clarify that a pregnancy will be followed for at least 30 days after the birth of the child and, in certain circumstances, for up to 12 months.	Clarification and consistency of this information across sections of the protocol.
Section 8.4 (Treatment of overdose)	Revised text to specify that an overdose should be reported "within 24 hours" instead of "immediately."	Alignment with the 24-hour requirement for reporting of SAEs.
Section 8.5 (Pharmacokinetics)	Revised text to specify that drug concentration information that may unblind **N01269** will not be reported to investigative sites or blinded personnel until the study has completed (last patient last visit).	Clarification of previously ambiguous text.
Section 9.2 (General statistical considerations)	Minor text revisions to refer to all AE outputs and not just AE tables, and remove "blinded" from the description of the data evaluation meeting.	Clarification and error correction.
Section 10.1.6 (Source documents)	Provide study-specific details regarding the electronic source document system that will be used for direct data capture.	Clarification and alignment with ICH-GCP.
Section 10.2 (Appendix 2: Clinical laboratory tests)	Revised text to specify that laboratory results that could unblind N01269 will not be reported to investigative sites or blinded personnel until the study has been unblinded.	Clarification of previously ambiguous text.

AE=adverse event; AED=antiepileptic drug; BRV=brivaracetam; COVID-19=coronavirus disease 2019; CRF=case report form; C-SSRS=Columbia-Suicide Severity Rating Scale; EDV=Early Discontinuation Visit; EEG=electroencephalogram; FEV=Full Evaluation Visit; FV=Final Visit; GCP=Good Clinical Practice; ICH=International Council for Harmonisation; IMP=investigational medicinal product; MEV=Minimal Evaluation Visit; MHRA=Medicines and Healthcare Products Regulatory Agency; RA=Regulatory Authority; SAE=serious adverse event; SV=Safety Visit; YEV=Yearly Evaluation Visit

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **US and Canada:** +1 800 880 6949 or +1 866 890 3175
Email	**Global:** DS_ICT@ucb.com

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title: A Multicenter, Open-label, Single-arm Study to Evaluate Long-term Safety, Tolerability, and Efficacy of Brivaracetam in Study Participants 2 to 26 Years of Age with Childhood Absence Epilepsy or Juvenile Absence Epilepsy

Short Title: A long-term safety, tolerability, and efficacy study of brivaracetam in study participants 2 to 26 years of age with childhood absence epilepsy or juvenile absence epilepsy.

Rationale: In a proof of principle study in study participants with photosensitive epilepsy, brivaracetam (BRV) showed dose-dependent efficacy with complete abolishment of the evoked generalized photoparoxysmal electroencephalogram (EEG) response after treatment of study participants with an 80mg single dose (Kasteleijn-Nolst Trenité et al, 2007). The effect compared favorably to the effect seen in a previous study with levetiracetam (LEV) using the same model. Response to treatment in the photosensitivity model may be more indicative of efficacy in generalized epilepsy rather than focal epilepsy (Yuen and Sims, 2014) and both childhood absence epilepsy (CAE) and juvenile absence epilepsy (JAE) are types of generalized epilepsy. Given the limited current treatment options for CAE and JAE, BRV has the potential to be a valuable alternative to the monotherapy treatments currently available for patients with typical absence seizures. An antiepileptic drug (AED) used in monotherapy is preferable as it may improve adherence and tolerability, compared to the use as adjunctive therapy. Brivaracetam treatment is well tolerated and is easy to use without the need for titration.

Objectives and Endpoints

Objectives	**Endpoints/Estimands**
Primary objective	**Primary endpoints**
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• Treatment-emergent adverse events Estimand 1. Population: population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population who receive at least 1 dose of BRV during the study. 2. Study participant-level outcome: TEAE occurrence. 3. Intercurrent event handling: The intercurrent event of concomitant medication use is handled by using a treatment policy strategy in which all TEAE data are included, regardless of receipt of any concomitant medication. The intercurrent event of treatment discontinuation is handled by using a while-on-treatment strategy where observation ends at 14 days after treatment is stopped.

	4. Population-level summary measure: incidence rates of TEAEs or incidence rates of TEAEs leading to discontinuation.
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• Treatment-emergent adverse events leading to discontinuation of study drug Estimand 1. Population: population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population who receive at least 1 dose of BRV during the study. 2. Study participant-level outcome: TEAE leading to discontinuation occurrence. 3. Intercurrent event handling: The intercurrent event of concomitant medication use is handled by using a treatment policy strategy in which all TEAE data are included, regardless of receipt of any concomitant medication. 4. Population-level summary measure: incidence rates of TEAEs or incidence rates of TEAEs leading to discontinuation.
Primary objective	**Secondary endpoints**
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• SAEs • Study drug-related TEAEs Estimand 1. Population: population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population who receive at least 1 dose of BRV during the study. 2. Study participant-level outcome: occurrence of events in the list above. 3. Intercurrent event handling: The intercurrent event of concomitant medication use is handled by using a treatment policy strategy in which all TEAE data are included, regardless of receipt of any concomitant medication. The intercurrent event of treatment discontinuation is handled by using a while-on-treatment strategy where observation ends at 14 days after treatment is stopped. 4. Population-level summary measure: incidence rates.

Primary objective	Other endpoints
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• TEAEs requiring a change in BRV dose • Maximum intensity TEAE experienced (mild, moderate, and severe) • Drug-related serious TEAEs • Fatal AEs • TEAEs by maximum relationship (related and not related to BRV) • SAEs by maximum relationship (related and not related to BRV) Occurrence of other seizure types, including GTCS, based on diary or EEG: • Nonabsence seizures based on 1-hour EEG • Nonabsence seizures based on diary Estimand: 1. Population: population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population who receive at least 1 dose BRV during the study. 2. Study participant-level outcome: occurrence of events in the list of endpoints above. 3. Intercurrent event handling: the intercurrent event of concomitant medication use is handled by using a treatment policy strategy in which all TEAE data are included, regardless of receipt of any concomitant medication. The intercurrent event of treatment discontinuation is handled by using a while-on-treatment strategy where observation ends at 14 days after treatment is stopped. • Population-level summary measure: incidence rates.
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• Change from Baseline to each applicable visit in safety laboratory tests • Change from Baseline to each applicable visit in ECG parameters • ECG findings at each applicable visit • Physical and neurological examinations findings at each applicable visit

	• Psychiatric and mental status at each applicable visit • Changes from Baseline to each applicable visit in vital signs (blood pressure, pulse rate, body temperature) • Changes from Baseline to each applicable visit in body weight and height
Secondary objective	**Secondary endpoints**
To investigate long-term efficacy of BRV in pediatric study participants with CAE or JAE	• Absence seizure freedom within 4 days prior to or during the 1-hour EEG at each applicable visit Estimand: 1. Population: the study participant population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population. 2. Study participant-level outcome: seizure freedom response while awake on 1-hour EEG at each applicable visit. 3. Intercurrent event handling: The intercurrent event of concomitant use of any permitted AED, including benzodiazepines, within 4 days prior to or during the 1-hour EEG is handled in the definition of the participant-level variable implementing a composite strategy in which receiving any permitted concomitant AED, including benzodiazepines, within 4 days prior to or during the 1-hour EEG is counted as nonresponse (ie, considered as having absence seizures during the EEG). 4. Population-level summary measure: percentage of study participants free from absence seizures.
To investigate long-term efficacy of BRV in pediatric study participants with CAE or JAE	• Absence seizure freedom based on diary over the entire evaluation period and by 3-month time intervals Estimand 1. Population: the study participant population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population. 2. Study participant-level outcome: seizure freedom response on diary over the evaluation period and by 3-month time intervals. 3. Intercurrent event handling: The intercurrent event of concomitant use of any permitted AED, including benzodiazepines, during each applicable 3-month period is handled in the definition of the participant-level variable implementing a composite strategy in which receiving any

	permitted concomitant AED, including benzodiazepines, in the 3-month period or during the visit is counted as nonresponse (ie, considered as having absence seizures). The intercurrent event of diary completion during each applicable period is handled in the definition of the participant-level variable implementing a composite strategy in which completing less than 80% of diaries during the 3-month period is counted as nonresponse (ie, considered as having absence seizures). 4. Population-level summary measure: percentage of study participants free from clinical absence seizures.
Secondary objective	**Other endpoints**
To investigate long-term efficacy of BRV in pediatric study participants with CAE or JAE	• Consecutive absence seizure freedom in 6-month periods based on EEG • Consecutive absence seizure freedom in 6-month periods based on diary
Tertiary/Exploratory	**Other endpoints**
To investigate the long-term effect of BRV on behavior, cognition, and quality of life in pediatric study participants with CAE or JAE	• Change from Baseline to each applicable visit in the EpiTrack Junior scores (for study participants 6 to <18 years old) • Change from Baseline to each applicable visit in PedsQL Generic Core scale scores from the study participant self-reports (separate questionnaires for participants age in years: 5 to ≤7, 8 to ≤12, 13 to ≤17 years) • Change from Baseline to each applicable visit in PedsQL Generic Core scale scores from the parent proxy-reports (separate questionnaires for participants age in years: 2 to ≤4, 5 to ≤7, 8 to ≤12, 13 to ≤17 years)

AE=adverse event; AED=antiepileptic drug; BRV=brivaracetam; CAE=childhood absence epilepsy; ECG=electrocardiogram; EEG=electroencephalogram; GTCS=generalized tonic-clonic seizure; JAE=juvenile absence epilepsy; PedsQL=Pediatric Quality of Life; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Key inclusion/exclusion criteria

Study participants who previously participated in N01269 and qualify for entry into EP0132 with a confirmed diagnosis of CAE or JAE, and for whom a reasonable benefit from long-term administration of BRV is expected, in the opinion of the Investigator, are eligible to participate. Study participants must not have severe medical, neurological, or psychiatric disorders or laboratory values, which could, at the discretion of the Investigator, affect safe participation in the study or would preclude appropriate study participation. Study participants must also not

have end-stage kidney disease requiring dialysis, hepatic impairment, active suicide ideation, or a lifetime history of suicide attempt.

Overall design

This is a Phase 3, open-label, single-arm, multicenter, long-term follow-up study to evaluate the safety, tolerability, and efficacy of BRV in pediatric study participants with CAE or JAE. The study is designed for study participants in the age range of 2 to 26 years of age, who have participated in study N01269 and qualify for entry into EP0132.

Upon enrollment, eligible study participants will enter the Evaluation Period and start on a BRV dose of 100mg/day (or equivalent dose of 2mg/kg/day for study participants weighing less than 50kg). The dose may be adjusted after 3 days in the range of 50 to 200mg/day (or equivalent dose of 1 to 4mg/kg/day for study participants weighing less than 50kg) based on the individual needs.

The Entry Visit (EV) is the first study visit and is equivalent to last study visit of the core study as defined in the study protocol of N01269. Two weeks (±2 days) after study start, the study participant will be contacted by phone to check on the appropriateness of the BRV dose. Within each year of study participation during the Evaluation Period, Minimal Evaluation Visits (MEVs) will be performed at Months 3 and 9, Full Evaluation Visits (FEVs) will be performed at Month 6, and Yearly Evaluation Visits (YEVs) will be performed at Month 12. At any time, the study participant may have an Unscheduled Visit if the Investigator or the participant and/or parent(s)/legal representative(s) consider it necessary. For study participants who continue in the study until it ends, the Evaluation Period will last from the EV to the Final Visit (FV). For study participants who prematurely discontinue the study, the Evaluation Period will last from the EV until the Early Discontinuation Visit (EDV).

For study participants who transition to another BRV study or a managed access program or similar type of program or who convert to commercial BRV (if, when, and where available), the FV instead of the EDV will need to be completed; however, down-titration and the Safety Visit (SV) will not be applicable.

For study participants who will discontinue BRV treatment following the EDV or FV, the BRV dose will be 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 study participants with body weight >50kg) is reached (Down-Titration Period). A Down-Titration Visit (DTV) will be performed at the end of the Down-Titration Period, and study drug will be discontinued at the DTV. After 2 weeks free of study drug (Safety Period), study participants will complete the SV.

Number of Participants

Approximately 140 study participants may enroll in this study, based upon the rollover expectations from N01269 into EP0132.

Treatment Groups and Duration

Brivaracetam (tablet or oral solution) will be administered twice per day in equal doses. Twice daily dosing with equivalent morning and evening doses approximately 12 hours apart is recommended to achieve more regular exposure over the 24-hour interval; however, the dosing amount and schedule may be adjusted as needed to improve tolerability and efficacy in consultation with the Investigator.

Upon enrollment, eligible study participants will enter the Evaluation Period and start on a BRV dose of 100mg/day (or equivalent dose of 2mg/kg/day for study participants weighing less than 50kg). The dose may be adjusted after 3 days in the range of 50 to 200mg/day (or equivalent dose of 1 to 4mg/kg/day for study participants weighing less than 50kg) based on the individual needs. The maximum allowed daily dose in EP0132 is 200mg/day (or equivalent dose of 4mg/kg/day for study participants weighing less than 50kg). Dose adjustments of BRV and/or concomitant AEDs based on clinical judgment are allowed at any time, 3 days after study start and onwards.

The duration of the study per study participant will be 2 years at minimum, until approval of BRV for the indication of CAE or JAE has been obtained for pediatric participants 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 indication is stopped by the Sponsor, whichever comes first.

1.2 Schema

Table 1–1: EP0132 schema

Study Period	Evaluation Period								Down-Titration Period	Safety Period
Visit Type	**EV**	**TC[a]**	**MEV**	**FEV**	**MEV**	**YEV**	**FV**	**EDV**	**DTV**	**SV**
Visit Timing	Y1, D1	Y1, D14	Y1, M3/ Y2, M15	Y1, M6/ Y2, M18	Y1, M9/ Y2, M21	Y1, M12	Y2, M24[c]	As needed		
Visit Window	±7 Days	±2 Days	±7 Days	±7 Days	±7 Days	±7 Days	±7 Days			
Frequency			3 months after EV and 3 months after YEV for every year of participation	6 months after EV and 6 months after YEV for every year of participation	9 months after EV and 9 months after YEV for every year of participation	12 months after EV				2 weeks after last dose of study drug
BRV Treatment	100mg/day (2mg/kg/day for participants weighing less than 50kg)	Individual dose[b]							Reduce max dose by ½ until 1mg/kg/day	BRV-free period
Duration	≥2 years[c]								Up to 4 weeks	2 weeks

BRV=brivaracetam; CAE=childhood absence epilepsy; D=Day; DTV=Down-titration Visit; EDV=Early Discontinuation Visit; EV=Entry Visit; FEV=Full Evaluation Visit; FV=Final Visit; JAE=juvenile absence epilepsy; max=maximum; M=month; MEV=Minimal Evaluation Visit; SV=Safety Visit; TC=telephone call; Y=treatment year; YEV=Yearly Evaluation Visit

[a] Study participants will be contacted after 2 weeks (±2 days) to check for appropriateness of dose.

[b] Participants will receive 100mg/day upon entry into EP0132. The dose may be adjusted after 3 days in the range of 50 to 200mg/day (or equivalent dose of 1 to 4mg/kg/day for study participants weighing less than 50kg) based on the individual needs.

[c] The duration of the study per study participant will be 2 years at minimum, until approval of BRV for the indication of CAE or JAE has been obtained for pediatric participants 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 indication is stopped by the Sponsor, whichever comes first.

1.3 Schedule of activities

Table 1–2: Schedule of activities

Study period	**Evaluation Period**						**Down-Titration Period**	**Safety Period**
Visit	**EV**[a]	**TC**	**MEV**	**FEV**	**YEV/EDV**[b]**/FV**	**UV**	**DTV**[c]	**SV**
Frequency		**After 2 weeks ± 2 days**	**Months 3 and 9 during each year of participation**	**Month 6 during each year of participation**	**Month 12 during each year of participation (YEV)/ Month 24 or later (FV)**			
Procedures								
Written informed consent	X							
Assent form (if applicable)	X							
Study participant identification card	X							
Inclusion/exclusion criteria	X							
Prior and concomitant medications and medical procedures	X		X	X	X	X	X	X
IXRS	X		X	X	X	X	X	X
Recording of AEs	X	X	X	X	X	X	X	X
Study drug dispensed	X	X (as applicable)	X	X	X[d]	X (as applicable)		
Study drug returned[e]			X	X	X	X (as applicable)	X	
Participant diary dispensed	X		X	X	X[d]		X	

Study period	**Evaluation Period**						**Down-Titration Period**	**Safety Period**
Visit	**EV**[a]	**TC**	**MEV**	**FEV**	**YEV/EDV**[b]**/FV**	**UV**	**DTV**[c]	**SV**
Frequency		**After 2 weeks ± 2 days**	**Months 3 and 9 during each year of participation**	**Month 6 during each year of participation**	**Month 12 during each year of participation (YEV)/ Month 24 or later (FV)**			
Procedures								
Participant diary retrieved			X	X	X		X	
Assessment of childbearing potential			X	X	X			
Complete physical/neurological examination[f]				X	X			X
Brief physical/neurological examination[g]			X			X		
Psychiatric and mental status				X	X			X
Vital signs[h]			X	X	X		X	X
Dose adaptation (optional)		X	X	X	X	X		
Body weight, height			X	X	X			
Laboratory assessments for safety[i]			X	X	X			X[j]
BRV plasma concentration[k]				X	X			
C-SSRS[l]			X	X	X	X[m]	X	X
EpiTrack Junior[n]				X	X			X
PedsQL[n]				X	X			
ECG[o]					X			X[j]

Study period	**Evaluation Period**						**Down-Titration Period**	**Safety Period**
Visit	**EV**[a]	**TC**	**MEV**	**FEV**	**YEV/EDV**[b]**/FV**	**UV**	**DTV**[c]	**SV**
Frequency		**After 2 weeks ± 2 days**	**Months 3 and 9 during each year of participation**	**Month 6 during each year of participation**	**Month 12 during each year of participation (YEV)/ Month 24 or later (FV)**			
Procedures								
EEG (1h EEG/HV)[p]				X	X	X (as applicable)		
End of study status					X[q]			X

AE=adverse event; AED=antiepileptic drug; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BRV=brivaracetam; C-SSRS=Columbia-Suicide Severity Rating Scale; 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; HV=hyperventilation; IXRS=interactive voice or web response system; MEV=Minimal Evaluation Visit; PedsQL=Pediatric Quality of Life Inventory; PK=pharmacokinetic; S=on-site visit; SAE=serious adverse event; SV=Safety Visit; TC=telephone call; UV=Unscheduled Visit; YEV=Yearly Evaluation Visit

[a] The EV is also the last completed study visit of N01269. The following Baseline data will be obtained from N01269 and should not be recorded on the eCRF for this study's EV: demographics, general medical and procedure history, epilepsy history, AED history, seizure count/ absence seizure count, ECG, laboratory assessments for safety, vital signs, body weight, height, physical and neurological examinations, psychiatric and mental status, and recording of epileptic seizures.

[b] Participants who discontinue from the study before Month 24 will complete an EDV, unless the participant is transitioning to another BRV study, in which case an FV will be completed (see Section 4.1).

[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. Study participants requiring down titration will complete their daily seizure diaries during the Down-titration Period.

[d] No study participant diary will be dispensed at the FV or EDV. Study drug will only be dispensed at the FDV or EDV if the study participant is discontinuing study drug and requires down titration.

[e] Drug return includes study drug intake recording and accountability and recording of concomitant AEDs.

[f] A complete physical examination will include, at a minimum, general appearance; eyes, ear, nose, and throat; skin; and assessments of the cardiovascular, respiratory, gastrointestinal, and musculoskeletal systems. A complete neurological examination will include, at a minimum, assessments of cranial nerves, motor and sensory systems, deep tendon reflexes, coordination, and gait.

[g] A brief physical examination will include, at a minimum, general appearance; assessments of the skin, respiratory system, and cardiovascular systems; and abdomen (liver and spleen). A brief neurological examination will include, at a minimum, assessments of cranial nerves, motor system, coordination, and gait.

[h] Vital sign measurements include blood pressure and pulse rate.

[i] Full laboratory assessments for safety include hematology and biochemistry (including hepatic monitoring of ALT, AST, ALP, total bilirubin, and GGT) for all study participants and urinalysis for study participants for whom sample collection is feasible. Female study participants of childbearing potential should have a urine pregnancy test done at all laboratory assessment visits. Endocrinology testing will be performed for all study participants <18 years of age at the YEV/FV. For study participants on study drug for more than 12 months, laboratory assessments at MEV can be omitted.

[j] At the SV, ECGs and laboratory assessments for safety will be performed only if abnormal at the EDV or FV.

[k] At the FEV and YEV/EDV/FV Visits, when PK sampling is planned, study participants should not take their morning BRV dose prior to arriving in the clinic.

[l] The C-SSRS will be completed by study participants ≥6 years of age. The "Since Last Visit" version of the C-SSRS will be used, with the following exception: If study participant turns 6 years of age during EP0132, 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.

[m] If an Unscheduled Visit is needed, the assessments noted will be performed. Additional assessments can be performed at the Investigator's discretion. If an unscheduled visit is conducted due to safety or efficacy reasons, the C-SSRS will be performed for study participants ≥6 year of age.

[n] Additional details for the patient-reported outcomes (ie, versions and ages) are provided in Table 8–1.

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

[p] The investigator/designated EEG reader should attempt to keep the study participant awake for the duration of the 1-hour EEG; a minimum of 30 minutes of awake time will be required for evaluability.

[q] End of study status only for study participants who continue in the study until it ends (SV) and for whom the visit corresponds to the FV.

2 INTRODUCTION

2.1 Study rationale

Childhood absence epilepsy (CAE) and Juvenile absence epilepsy (JAE) present with typical absences and are classified by the International League Against Epilepsy (ILAE) as idiopathic generalized epilepsy types (ILAE, 2019). Treatment options are limited: Ethosuximide (ESM) is considered effective against absence but not against other types of seizures like generalized tonic clonic or myoclonic seizures. Valproic acid (VPA) is a broad-spectrum and effective treatment but there are important safety issues, including negative impact on attention and cognitive development, liver and bone marrow toxicity, and teratogenesis, which raises important concerns for the treatment of females. Lamotrigine (LTG) is an alternative, even though not approved for the treatment of absence seizures in the US; however, it is less efficacious than VPA and ESM and needs a very long titration time due to the risk of severe cutaneous reactions. Further, LTG has a high potential for relevant drug-drug interactions, including oral hormonal contraceptives. This limits the value of LTG in female patients of childbearing potential. Moreover, in CAE, approximately one-third of patients continue to have seizures despite an initial and second therapy, meeting the criteria for drug resistance (Cnaan et al, 2017). The seizure outcomes of patients with JAE is even less favorable (Tovia et al, 2006). Therefore, there is a need for additional monotherapy treatments.

N01269 is a multicenter, double-blind, placebo-controlled, parallel-group study with an adaptive design to evaluate the efficacy, safety, and tolerability of brivaracetam (BRV) monotherapy in study participants 2 to 25 years of age with CAE or JAE. An AED used in monotherapy is preferable as it may improve treatment adherence and tolerability as compared with its use as adjunctive therapy. Brivaracetam treatment is well tolerated and is easy to use with no titration. Given limited current treatment options, BRV has the potential to be a valuable addition to monotherapy treatment of patients with typical absence seizures.

EP0132 is Phase 3, multicenter, open-label, single-arm study to evaluate the long-term safety, tolerability, and efficacy of BRV in pediatric study participants with CAE or JAE, who are rolling over from study N01269 (core study). Study participants who participated in N01269 and qualify for entry into EP0132 and for whom a reasonable benefit from long-term administration of BRV is expected will get the opportunity to participate.

2.2 Background

Brivaracetam ((2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1*H*-pyrrol-1-yl]butanamide) is a 2-pyrrolidone derivative. Brivaracetam 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.

The recommended starting dosage for adjunctive therapy in focal seizures in adults is 50mg twice daily (bid; 100mg/day) with 100mg bid (200mg/day) being the maximum recommended dose. The dosage may be adjusted between 25mg bid (50mg/day) and 100mg bid (200mg/day) based on individual patient tolerability and therapeutic response.

Between 2016 and 2019, marketing authorization for the use of oral and intravenous (iv) BRV as adjunctive treatment for partial-onset seizures (POS) was granted in the EU, US, Turkey, Mexico, Australia, Argentina, Brazil, Taiwan, Israel, United Arab Emirates, Qatar, Hong Kong,

and Saudi Arabia for patients 16 years of age and older with epilepsy and in Switzerland and Canada for patients 18 years of age and older with epilepsy. In addition, use of oral BRV was approved in Russia, India, Colombia, Lebanon, Korea, and Kuwait.

Brivaracetam has been approved in the US as monotherapy, based on extrapolation, for the treatment of POS in patients with epilepsy aged 16 years and older. An application for the extension of indication to the pediatric population from 4 years of age in the EU (adjunctive) and the US (adjunctive and monotherapy) based on the concept of extrapolation of efficacy data from the adult population was approved in 2018. In Taiwan, BRV was approved as monotherapy and adjunctive therapy for POS in adults and children aged 4 years and older in 2019. Of note, in the US and in Taiwan, iv BRV is indicated for the treatment of POS only in adult patients (16 years of age and older). The extension of the indication to the pediatric population from 4 years of age in Israel and Australia (adjunctive) based on the concept of extrapolation of efficacy data from the adult population was approved in 2019. In Argentina, BRV has been approved as monotherapy and adjunctive therapy for POS in adults aged 16 years and older.

2.3 Benefit/risk assessment

According to the current approved indication, BRV is indicated as monotherapy and adjunctive therapy for focal/POS with or without secondary generalization in patients from 4 years of age with epilepsy. The approved indications for BRV may vary according to the countries of authorization.

Four antiseizure medications have been approved for the treatment of absence seizures, namely ethosuximide, valproate, lamotrigine and clonazepam, with the first 3 being commonly used as initial monotherapy (Glauser et al, 2010). While ethosuximide is usually effective against absence seizures, it is not considered effective against other seizure types such as tonic-clonic seizures, limiting its use for patients with JAE, in which this type of seizure is common. Ethosuximide's use, especially in children, is also limited by gastrointestinal side effects and the need for monitoring liver function. Valproate is a broad-spectrum antiseizure medication, however, there are significant safety concerns with its use, including the negative impact on attention, liver and bone marrow toxicity, and teratogenicity. Lamotrigine is limited by its very long up-titration needs, the high potential for drug-drug interactions, and the potential for severe cutaneous adverse reactions. Moreover, a number of patients with CAE are drug resistant to the 3 commonly used antiseizure medications, as shown in a large multicenter study, in which approximately one third of patients with CAE met ILAE criteria for drug resistance (Cnaan et al, 2017). Due to the limitations in currently available treatments, UCB believes BRV could be a valuable addition.

Clinical development is ongoing for the following indications in relation to epilepsy: monotherapy and adjunctive therapy of POS in children and infants aged from 1 month to ≤4 years of age with epilepsy, treatment of neonatal seizures, and treatment of CAE and JAE.

Cumulatively, approximately 4536 study participants have been enrolled in the BRV clinical development program; an estimated 4087 study participants were exposed to BRV in completed and ongoing clinical trials as of the current safety update report data lock point of 14 Jan 2020. Additionally, there were: 194 study participants exposed in the ongoing blinded study EP0083 where the randomization scheme is 1:1:1 (placebo:BRV 50mg/day:BRV 200mg/day);
47 Japanese study participants exposed in the ongoing long-term follow-up (LTFU) study

(EP0085); and 44 study participants in ongoing open-label study of iv BRV (EP0065). Based on marketing experience, the exposure to BRV is estimated at 88,532 patient-years during this reporting interval and at 188,177 patient-years cumulatively since the International Birth Date.

In total, 263 pediatric study participants (1 month to <17 years of age) received BRV in other studies, of which 44 were from EP0065, 99 were from N01263, and 120 were directly enrolled into N01266. Based on the information supplied in the pediatric efficacy supplement where the pharmacokinetics (PK), efficacy, and safety profiles have been established for pediatric patients with POS 4 years to <16 years of age, it was determined that the benefits of BRV treatment for pediatric patients are similar to those for adults. In general, the safety profile of BRV in the pediatric population is similar to that reported in adults with POS and the risks characterized in the adult population are applicable to the pediatric population.

Brivaracetam seems a promising candidate for the treatment of typical absence seizures. Both BRV and levetiracetam (LEV), an AED with a similar mechanism of action as BRV, have been shown to be active in a preclinical rat model for absence seizures (genetic absence epilepsy rat from Strasbourg), with BRV being more efficacious compared with LEV (Matagne et al, 2008). Furthermore, in a proof-of-concept study in participants with photosensitive epilepsy, BRV showed dose-dependent efficacy with complete abolishment of photosensitive epilepsy after treatment of study participants with an 80mg single dose (Kasteleijn-Nolst Trenité et al, 2007). In addition, LEV was effective in treating typical absence seizures in a randomized placebo-controlled study with newly diagnosed CAE and JAE study participants (Fattore et al, 2011).

In conclusion, given the study design, patient population, and safety monitoring proposed, it is UCB's opinion that the anticipated therapeutic benefits of BRV will outweigh any potential risks possibly associated with this Phase 2/3 study. This study is part of a larger pediatric development program which aims to evaluate the safety and tolerability of BRV in pediatric subjects, which will ultimately provide relevant information of potential benefit and risk to this population of patients with a recognized medical need.

Furthermore, and in face of the current SARS-CoV-2 (COVID-19) pandemic, there are no expected interactions between brivaracetam and COVID-19 vaccines, based on the mechanism of action of BRV. Therefore, the benefit-risk profile of BRV remains favorable.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of BRV may be found in the Investigator's Brochure (IB) or Summary of Product Characteristics.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints/Estimands
Primary objective	**Primary endpoints**
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• Treatment-emergent adverse events Estimand 1. Population: population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient

Objectives	Endpoints/Estimands
	population who receive at least 1 dose of BRV during the study. 2. Study participant-level outcome: TEAE occurrence. 3. Intercurrent event handling: The intercurrent event of concomitant medication use is handled by using a treatment policy strategy in which all TEAE data are included, regardless of receipt of any concomitant medication. The intercurrent event of treatment discontinuation is handled by using a while-on-treatment strategy where observation ends at 14 days after treatment is stopped. 4. Population-level summary measure: incidence rates of TEAEs or incidence rates of TEAEs leading to discontinuation.
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• Treatment-emergent adverse events leading to discontinuation of study drug Estimand 1. Population: population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population who receive at least 1 dose of BRV during the study. 2. Study participant-level outcome: TEAE leading to discontinuation occurrence. 3. Intercurrent event handling: The intercurrent event of concomitant medication use is handled by using a treatment policy strategy in which all TEAE data are included, regardless of receipt of any concomitant medication. 4. Population-level summary measure: incidence rates of TEAEs or incidence rates of TEAEs leading to discontinuation.
Primary objective	**Secondary endpoints**
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• SAEs • Study drug-related TEAEs Estimand 1. Population: population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient

Objectives	Endpoints/Estimands
	population who receive at least 1 dose of BRV during the study. 2. Study participant-level outcome: occurrence of events in the list above. 3. Intercurrent event handling: The intercurrent event of concomitant medication use is handled by using a treatment policy strategy in which all TEAE data are included, regardless of receipt of any concomitant medication. The intercurrent event of treatment discontinuation is handled by using a while-on-treatment strategy where observation ends at 14 days after treatment is stopped. 4. Population-level summary measure: incidence rates.
Primary objective	**Other endpoints**
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• TEAEs requiring a change in BRV dose • Maximum intensity TEAE experienced (mild, moderate, and severe) • Drug-related serious TEAEs • Fatal AEs • TEAEs by maximum relationship (related and not related to BRV) • SAEs by maximum relationship (related and not related to BRV) Occurrence of other seizure types, including GTCS, based on diary or EEG: • Nonabsence seizures based on 1-hour EEG • Nonabsence seizures based on diary Estimand: 1. Population: population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population who receive at least 1 dose BRV during the study. 2. Study participant-level outcome: occurrence of events in the list of endpoints above. 3. Intercurrent event handling: the intercurrent event of concomitant medication use is handled by using a treatment

Objectives	Endpoints/Estimands
	policy strategy in which all TEAE data are included, regardless of receipt of any concomitant medication. The intercurrent event of treatment discontinuation is handled by using a while-on-treatment strategy where observation ends at 14 days after treatment is stopped. • Population-level summary measure: incidence rates.
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• Change from Baseline to each applicable visit in safety laboratory tests • Change from Baseline to each applicable visit in ECG parameters • ECG findings at each applicable visit • Physical and neurological examinations findings at each applicable visit • Psychiatric and mental status at each applicable visit • Changes from Baseline to each applicable visit in vital signs (blood pressure, pulse rate, body temperature) • Changes from Baseline to each applicable visit in body weight and height
Secondary objective	**Secondary endpoints**
To investigate long-term efficacy of BRV in pediatric study participants with CAE or JAE	• Absence seizure freedom within 4 days prior to or during the 1-hour EEG at each applicable visit Estimand: 1. Population: the study participant population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population. 2. Study participant-level outcome: seizure freedom response while awake on 1-hour EEG at each applicable visit. 3. Intercurrent event handling: The intercurrent event of concomitant use of any permitted AED, including benzodiazepines, within 4 days prior to or during the 1-hour EEG is handled in the definition of the participant-level variable implementing a composite strategy in which receiving any permitted concomitant AED, including benzodiazepines, within 4 days prior to or during the 1-hour EEG is counted as nonresponse (ie, considered as having absence seizures during the EEG).

Objectives	Endpoints/Estimands
	4. Population-level summary measure: percentage of study participants free from absence seizures.
To investigate long-term efficacy of BRV in pediatric study participants with CAE or JAE	• Absence seizure freedom based on diary over the entire evaluation period and by 3-month time intervals Estimand 1. Population: the study participant population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population. 2. Study participant-level outcome: seizure freedom response on diary over the evaluation period and by 3-month time intervals. 3. Intercurrent event handling: The intercurrent event of concomitant use of any permitted AED, including benzodiazepines, during each applicable 3-month period is handled in the definition of the participant-level variable implementing a composite strategy in which receiving any permitted concomitant AED, including benzodiazepines, in the 3-month period or during the visit is counted as nonresponse (ie, considered as having absence seizures). The intercurrent event of diary completion during each applicable period is handled in the definition of the participant-level variable implementing a composite strategy in which completing less than 80% of diaries during the 3-month period is counted as nonresponse (ie, considered as having absence seizures). 4. Population-level summary measure: percentage of study participants free from clinical absence seizures.
Secondary objective	**Other endpoints**
To investigate long-term efficacy of BRV in pediatric study participants with CAE or JAE	• Consecutive absence seizure freedom in 6-month periods based on EEG • Consecutive absence seizure freedom in 6-month periods based on diary
Tertiary/Exploratory	**Other endpoints**
To investigate the long-term effect of BRV on behavior, cognition, and quality of life in pediatric	• Change from Baseline to each applicable visit in the EpiTrack Junior scores (for study participants 6 to <18 years old)

Objectives	Endpoints/Estimands
study participants with CAE or JAE	• Change from Baseline to each applicable visit in PedsQL Generic Core scale scores from the study participant self-reports (separate questionnaires for participants age in years: 5 to ≤7, 8 to ≤12, 13 to ≤17 years) • Change from Baseline to each applicable visit in PedsQL Generic Core scale scores from the parent proxy-reports (separate questionnaires for participants age in years: 2 to ≤4, 5 to ≤7, 8 to ≤12, 13 to ≤17 years)

AE=adverse event; AED=antiepileptic drug; BRV=brivaracetam; CAE=childhood absence epilepsy; ECG=electrocardiogram; EEG=electroencephalogram; GTCS=generalized tonic-clonic seizure; JAE=juvenile absence epilepsy; PedsQL=Pediatric Quality of Life; SAE=serious adverse event; TEAE=treatment-emergent adverse event

4 STUDY DESIGN

4.1 Overall design

This is a Phase 3, open-label, single-arm, multicenter, LTFU study to evaluate the safety, tolerability, and efficacy of BRV in pediatric study participants with CAE or JAE. The study is designed for study participants in the age range of 2 to 26 years of age who have participated in study N01269 and qualify for entry into EP0132.

Upon enrollment, eligible study participants will enter the Evaluation Period and start on a BRV dose of 100mg/day (or equivalent dose of 2mg/kg/day for study participants weighing less than 50kg). The dose may be adjusted after 3 days in the range of 50 to 200mg/day (or equivalent dose of 1 to 4mg/kg/day for study participants weighing less than 50kg) based on the individual needs.

The Entry Visit (EV) is the first study visit and is equivalent to last study visit of the core study as defined in the study protocol of N01269. Two weeks (±2 days) after study start, the study participant will be contacted by phone to check on the appropriateness of the BRV dose. Within each year of study participation during the Evaluation Period, Minimal Evaluation Visits (MEVs) will be performed at Months 3 and 9, Full Evaluation Visits (FEVs) will be performed at Month 6, and Yearly Evaluation Visits (YEVs) will be performed at Month 12. At any time, the study participant may have an Unscheduled Visit if the Investigator or the participant and/or parent(s)/legal representative(s) consider it necessary. For study participants who continue in the study until it ends, the Evaluation Period will last from the EV to the Final Visit (FV). For study participants who prematurely discontinue the study, the Evaluation Period will last from the EV until the Early Discontinuation Visit (EDV).

For study participants who transition to another BRV study or a managed access program or similar type of program or who convert to commercial BRV (if, when, and where available), the FV instead of the EDV will need to be completed; however, down-titration and the Safety Visit (SV) will not be applicable.

For study participants who will discontinue BRV treatment following the EDV or FV, the BRV dose will be 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 study participants with body weight >50kg) is reached

(Down-Titration Period). A Down-Titration Visit (DTV) will be performed at the end of the Down-Titration Period, and study drug will be discontinued at the DTV. After 2 weeks free of study drug (Safety Period), study participants will complete the SV.

Brivaracetam (tablet and oral solution) will be administered twice per day in equal doses. The maximum allowed daily dose in EP0132 is 200mg/day (4mg/kg/day). Dose adjustments of BRV and/or concomitant AEDs based on clinical judgment are allowed at any time, 3 days after study start and onwards.

The duration of the study per study participant will be 2 years at minimum, until approval of BRV for the indication of CAE or JAE has been obtained for pediatric participants 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 indication is stopped by the Sponsor, whichever comes first.

This study will be conducted using a site-based model; all study assessments will be conducted at the study site.

4.1.1 Study conduct due to coronavirus disease

The protocol-mandated 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 study participants or caregivers will be contacted by telephone or videoconference. Remote follow-up, at a minimum with telephone call after 3 months, must be done (preferably more frequently and as needed to follow-up on participant safety assessments).

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

Under COVID-19 circumstances, a maximum of 2 visits that are required to be on-site visits (FEV/YEV) is considered acceptable to be conducted remotely. Participants who miss more than the defined visits will need to discontinue study participation.

If a participant must be discontinued and cannot come into the clinic, then appropriate tapering instructions will be provided, and a visit will be scheduled to perform safety assessments as soon as possible.

In situations where a study participant is unable to return to the study site, Investigators will assess and document the study participant's safety via telephone contact. Based on information gathered from the telephone contact, Investigators will confirm whether the participant could continue the current study treatment based upon the outcome of the safety assessment. Study participants' 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 6.1.1.

If a study participant 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 study participant's condition and his/her participation in the study. Study participants 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 and home visits by study health care providers are not an option, local laboratory safety assessments 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, 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 study participants cannot return to the clinic, and it will not be possible to dispense a new seizure diary, study participants will be instructed to continue recording of seizures in a manner that is mutually agreed with the Investigator (eg, hand-written notes, recording on a smart device). Any recording of seizures in a manner outside of the study seizure diary must be carefully documented in the source medical records (copies or printouts of these recordings will be brought to and retained at site).

4.2 Scientific rationale for study design

This Phase 3, multicenter, open-label, single-arm study will allow evaluation of long-term data to establish the long-term safety, tolerability, and efficacy of BRV in pediatric study participants with CAE or JAE who are rolling over from study N01269 (core study). Study participants who participated in N01269 and qualify for entry into EP0132 and for whom a reasonable benefit from long-term administration of BRV is expected will get the opportunity to participate. Study participants will begin the open-label study on 100mg/day (or equivalent dose of 2mg/kg/day for study participants weighing less than 50kg). The study participant's dose can be adapted in the range of 50 to 200mg/day (or equivalent dose of 1 to 4mg/kg/day for study participants weighing less than 50kg) based on safety and efficacy as it would be done in clinical practice.

For the estimands to address the primary objective, the treatment policy strategy has been selected as the approach for the handling of the intercurrent event of concomitant medication because use of concomitant medications is allowed in the study and reflects clinical practice, and in addition for the TEAE primary endpoint only, the while-on-treatment strategy has been selected for the approach for handling of the intercurrent event of treatment discontinuation to capture all AEs occurring after the end of BRV treatment.

For the estimands to address the secondary objective, the treatment policy strategy has been selected as the approach for the intercurrent event handling because the use of concomitant antiepileptic drugs (AEDs), including benzodiazepines, is allowed in the study and the treatment effect will therefore reflect the effectiveness of BRV in the real world.

4.3 Justification for dose

Based on the labeling of other AEDs and published data, the BRV doses selected for this study are in the range of the currently labeled BRV doses for POS. Further, in the study in participants with photosensitive epilepsy, BRV showed dose-dependent efficacy with complete abolishment of photosensitive epilepsy after treatment of study participants with an 80mg single dose

(Kastelijn-Nolst Trenité et al, 2007). As this model is considered predictive for generalized seizures, the dose used in that study is also used as a guidance.

4.4 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Assessments (Table 1–2) for the last participant in the study globally.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of participant and disease characteristics

1. Participants who previously participated in N01269 and qualify for entry into EP0132 as per N01269 protocol with a confirmed diagnosis of CAE or JAE, and for whom a reasonable benefit from long-term administration of BRV is expected, in the opinion of the Investigator.

Sex

2. Male and female
   - A sexually active male study participant must agree to use contraception as detailed in Appendix 4 (Section 10.4) of this protocol during the treatment period and for at least 2 days, corresponding to the time needed to eliminate study treatment, after the last dose of study treatment and refrain from donating sperm during this period.
   - A female study participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4]), not breastfeeding, and at least 1 of the following conditions applies:
     - The study participant is premenarchal
       OR
       A woman of childbearing potential (WOCBP) who agrees to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least 2 days after the last dose of study medication, corresponding to the time needed to eliminate study treatment.

Informed consent

3. Study participant is capable of and provides consent/assent, and the study participant's parent/legal representative/caregiver provides signed informed consent for minor study participants, as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

1. Study participant has a history or presence of paroxysmal nonepileptic seizures.
2. Study participant has severe medical, neurological, or psychiatric disorders or laboratory values, which could, at the discretion of the Investigator, affect safe participation in the study or would preclude appropriate study participation.
3. Study participant has a clinically relevant ECG abnormality in the opinion of the Principal Investigator.
4. Study participant has hepatic impairment (Child Pugh Score A, B, or C) based on the Investigator's assessment.
5. Study participant has active suicidal ideation prior to study entry as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia Suicide Severity Rating Scale (C-SSRS) (for study participants 6 years or older) or clinical judgment (for study participants younger than 6 years). The study participant should be referred immediately to a Mental Healthcare Professional.
6. Study participant has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt). The Investigator must immediately refer the study participant to a Mental Healthcare Professional.
7. Participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
8. Participant has known fructose intolerance or a known hypersensitivity to any components of BRV or excipients or a drug with similar chemical structure. Note that the tablets contain lactose.
9. Study participant has end-stage kidney disease requiring dialysis.

Prior/Concomitant therapy

10. Concomitant use of carbamazepine, felbamate, gabapentin, oxcarbazepine, phenobarbital, phenytoin, tiagabine, or vigabatrin.

Prior/Concurrent clinical study experience

11. Study participant has planned participation in any clinical study on an investigational drug or device.

Other exclusions

12. Study participant has poor compliance with the visit schedule or medication intake in the core study in the opinion of the Investigator.

5.3 Lifestyle restrictions

Concomitant intake of alcohol is prohibited.

5.4 Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

6 STUDY TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Treatments administered

Brivaracetam (tablet [10, 25, or 50mg] or oral solution [10mg/mL]) will be administered twice per day in equal doses in the range of 50 to 200mg/day (or equivalent doses of 1 to 4mg/kg/day for study participants weighing less than 50kg, not to exceed 200mg/day [or equivalent dose of 4mg/kg/day for participants weighing less than 50kg]). Study participants will be treated in the study for at least 2 years. Twice daily dosing with equivalent morning and evening doses approximately 12 hours apart is recommended to achieve more regular exposure over the 24-hour interval; however, the dosing amount and schedule may be adjusted as needed to improve tolerability and efficacy in consultation with the Investigator.

This is an open-label study; no reference therapy will be used.

6.1.1 Alternative study treatment supply due to COVID-19

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

- Site to participant: Where possible, site staff can ship study treatment dispensed from the site pharmacy supply directly to the study participant.

6.2 Preparation, handling, storage, and accountability requirements

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

The Investigator (or designee) will instruct the participant to store the study medication following the instructions on the label.

Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

6.2.1 Drug accountability/device accountability

The case report form (CRF) will be used to record study medication dispensing and return information on a by-participant basis and will serve as source documentation during the course of the study. Details of any study medication 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.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of study medication 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 study medication 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 study medication must be reconciled and either destroyed at the site according to local laws, regulations, and UCB standard operating procedures 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.

6.3 Measures to minimize bias: randomization and blinding

This is an open-label study. There is no randomization or blinding.

Each participant will start on a BRV dose of 100mg/day (or equivalent dose of 2mg/kg/day for study participants weighing less than 50kg).

To enroll a participant (EV), the Investigator will contact the interactive voice or web response system (IXRS) and provide brief details about the participant to be enrolled. Participants will continue with the 5-digit study participant number assigned by the IXRS in the core study. The study participant number will be required in all communication between the Investigator (or designee) and the IXRS regarding a particular participant. Participants' status and the dispensing of IMP (bottle numbers) will be tracked via the IXRS.

6.4 Treatment compliance

At each visit after study medication is dispensed, participants must return all unused study medication and empty study medication containers. Drug accountability must be done in the participant'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 participant is found to be persistently noncompliant (defined as taking <85% or >115% of prescribed dose), the Sponsor, in conjunction with the Investigator, will make a decision as to whether the participant should be withdrawn from the study.

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

All concomitant medications except those specified in Section 6.5.2 are permitted during the study.

6.5.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- Carbamazepine
- Felbamate
- Gabapentin
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Tiagabine
- Vigabatrin

The use of substrates of alcohol dehydrogenase is prohibited.

6.5.3 Rescue medication

Rescue medication in this study is considered as any treatment with permitted AEDs, including benzodiazepines. Rescue medication can be given at any time if considered necessary by the Investigator. The study site may supply locally obtained rescue medication as per the Investigator's assessment/recommendation.

The date of rescue medication onset and end as well as the name and dosage regimen of the rescue medication must be recorded.

6.6 Dose modification

Study participants will start on a BRV dose of 100mg/day (or equivalent dose of 2mg/kg/day for study participants weighing less than 50kg). The dose may be adjusted after 3 days in the range of 50 to 200mg/day (or equivalent dose of 1 to 4mg/kg/day for study participants weighing less than 50kg) based on the individual needs.

For study participants who will discontinue BRV treatment following the EDV or FV, the BRV dose will be 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 study participants with body weight >50kg) is reached (Down-Titration Period). A DTV will be performed at the end of the Down-Titration Period, and study drug will be discontinued at the DTV. After 2 weeks free of study drug (Safety Period), study participants will complete the SV.

For study participants who transition to another BRV study or a managed access program or similar type of program or who convert to commercial BRV (if, when, and where available), the FV instead of the EDV will need to be completed; however, down-titration and the SV will not be applicable.

6.7 Treatment after the end of the study

After their participation in EP0132 is complete, study participants may transition without down-titration to another BRV study; may be initiated without down-titration in a managed access program, named patient program, compassionate use program, or similar type of access program as allowed per country-specific requirements in addition to legal and regulatory guidelines; or convert to commercial BRV (if, when, and where available).

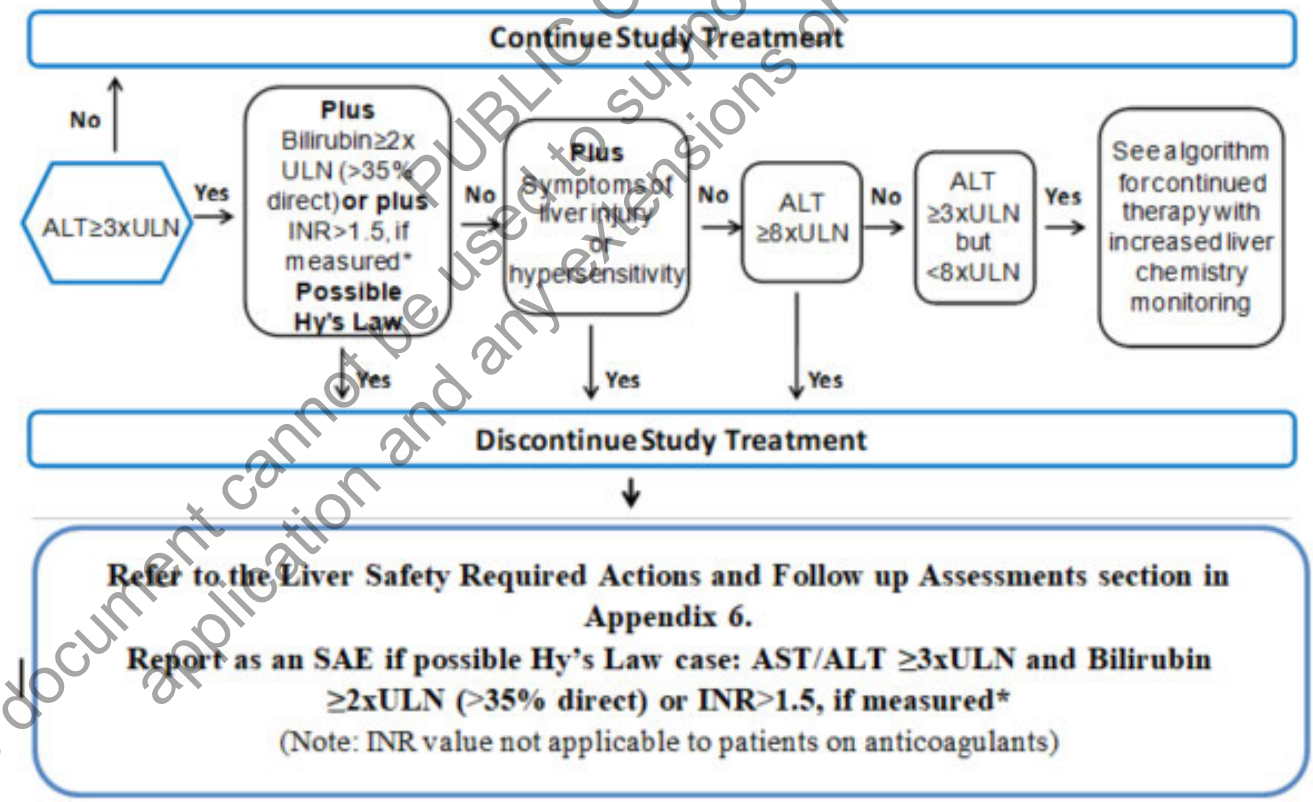
7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study medication

7.1.1 Liver chemistry stopping criteria

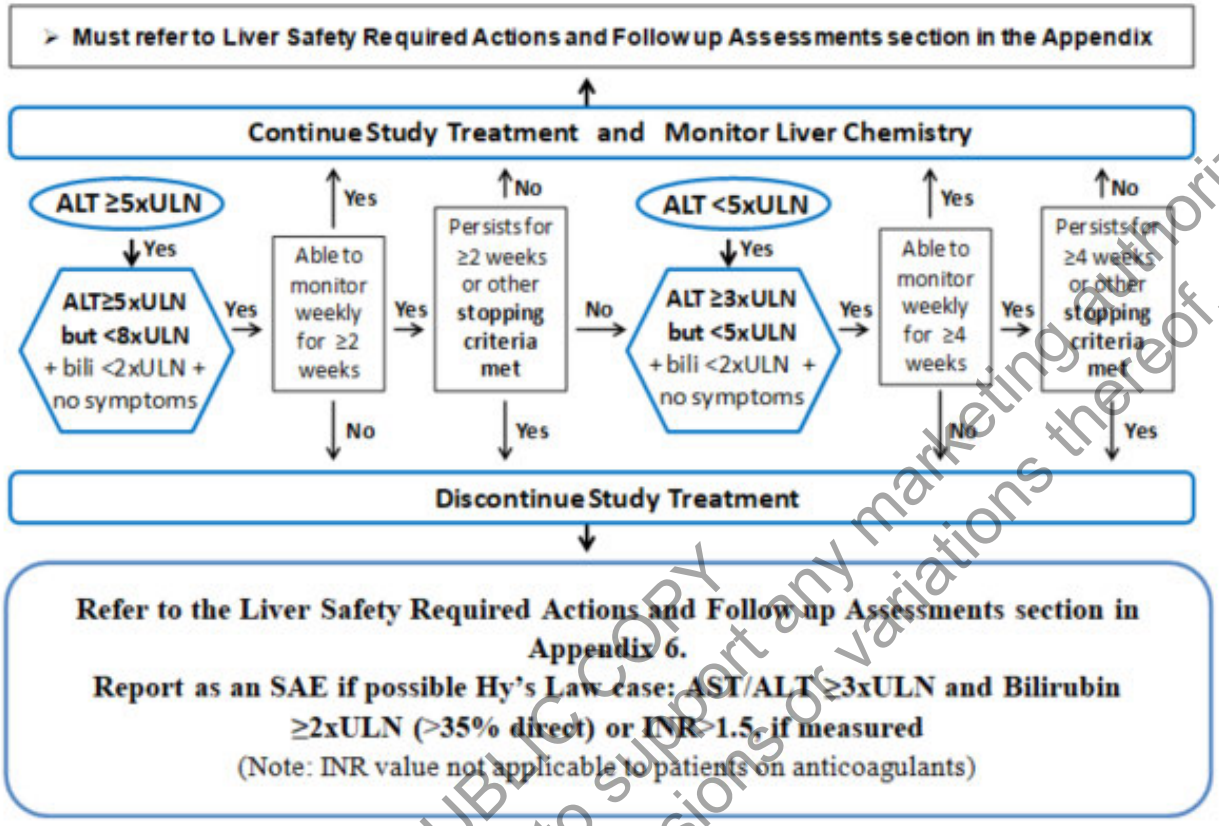
Discontinuation of study treatment for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Figure 7–1 or if the Investigator believes that it is in best interest of the participant. The increased monitoring algorithm and continued study intervention for study participants with alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN) but <8xULN is presented in Figure 7–2.

Figure 7–1: Phase 3 liver chemistry stopping criteria and increased monitoring algorithm



ALT=alanine transaminase; AST=aspartate aminotransferase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal

Figure 7–2: Liver chemistry increased monitoring algorithm with continued study intervention for participants with ALT ≥3xULN but <8xULN



ALT=alanine transaminase; AST=aspartate aminotransferase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal

Specific assessments and follow up actions for potential drug-induced liver injury (PDILI) are provided in Appendix 6 (Section 10.6).

7.1.2 QTc stopping criteria

If a clinically significant finding is identified, including, but not limited to changes from Baseline in QT interval (corrected using Bazett's formula) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE and should be followed up as deemed necessary by the Investigator.

See the Schedule of Assessments (Table 1–2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.2 Participant discontinuation/withdrawal from the study

Participants are free to withdraw from the study at any time, without prejudice to their continued care.

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

See the Schedule of Assessments (Table 1–2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Participants should be withdrawn from the study if any of the following events occur:

1. Study participant develops any medical or psychiatric condition that, in the opinion of the Investigator, could negatively impact the study participant's safety.
2. Study participant 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.
3. Participant is noncompliant with the study procedures or medications in the opinion of the Investigator.
4. Participant takes prohibited concomitant medications as defined in this protocol.

Participants must be withdrawn from the study if any of the following events occur:

1. Study participant (or parent[s] or legal representative[s]) withdraws his/her consent (or assent, if applicable).
2. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
3. The Sponsor or a regulatory agency requests withdrawal of the participant.
4. Investigator decides that withdrawal from further participation would be in the study participant’s best interest.
5. Study participant has active suicidal ideation since study start as indicated by a positive response (“Yes”) to either Question 4 or Question 5 of the C-SSRS (for study participants 6 years or older) or clinical judgment (for study participants younger than 6 years). The study participant should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.
6. Study participant has a history of suicide attempt since study start (including an active attempt, interrupted attempt, or aborted attempt). The study participant should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a participant in advance. Refer to Section 6.6 for down-titration instructions.

7.3 Efficacy assessments

Planned time points for all efficacy assessments are provided in Table 1–2.

7.3.1 Seizure data based on EEG

For the assessment of the secondary and other efficacy endpoints, a 1-hour EEG will be performed at FEVs, YEVs, and EDV or FV (as applicable). The awake time from the EEG will be analyzed for absence seizures. The awake and asleep time from the EEG will be analyzed for other seizure types. Every 1-hour EEG will include hyperventilation as a standard provocation test at the beginning of the EEG. The investigator/designated EEG reader should attempt to keep the study participant awake for the duration of the 1-hour EEG; a minimum of 30 minutes of awake time will be required for evaluability.

7.3.2 Seizure diary

During the study, study participants will keep a diary to record daily seizure activity from the EV until the EDV or FV (as applicable). Study participants who discontinue study drug and require down titration will also complete their daily seizure diaries during the Down-titration Period. Study participants will be reminded to bring their diary with them to each clinic visit.

The written information is discussed with the study participants at each visit in order to ensure completeness and accuracy. As a result of the discussion, the Investigator will assess and confirm the seizures according to the ILAE codes and record the seizure types in the eCRF/diary; he/she will also confirm the presence of AEs, if applicable.

Study participants will record all types of seizures that occur in their diaries and will be educated to complete their diary entries after each seizure or at least once a day. A parent or caregiver may assist in completing the diary if necessary.

7.4 Lost to follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (at least 1 phone call and 1 written message to the participant), 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 reason(s) for removing the participant, must be recorded in the source documents. The CRF must document the primary reason for withdrawal.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up documented in the CRF.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Assessments (Table 1–2).

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 3% of the participant's total blood volume within 4 weeks. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Safety assessments

Planned time points for all safety assessments are provided in Table 1–2.

8.1.1 Physical examination

A complete physical examination is performed at FEVs, YEVs, EDV or FV (as applicable), and SVs. A brief physical examination is performed at MEVs and UVs.

A complete physical examination will include, at a minimum, general appearance; eyes, ear, nose, and throat; skin; and assessments of the respiratory, cardiovascular, gastrointestinal, and musculoskeletal systems.

A brief physical examination will include, at a minimum, general appearance; assessments of the skin, respiratory, and cardiovascular systems; and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Clinically relevant findings or worsening of previous findings will be recorded as AEs.

8.1.2 Body height and weight

Body weight and height will be measured and recorded during the Evaluation Period at MEV, FEV, YEV, EDV, and FV.

8.1.3 Neurological examination

A complete neurological examination is performed at FEVs, YEVs, EDV or FV (as applicable), and SVs. A brief neurological examination is performed at MEVs and UVs.

A complete neurological examination will include, at a minimum, assessments of:

- Psychiatric and mental status evaluation
- Cranial nerves
- Motor and sensory systems
- Deep tendon reflexes
- Coordination
- Gait

A brief neurological examination will include, at a minimum, assessments of cranial nerves, motor system, coordination, and gait.

8.1.4 Psychiatric and mental status

An examination of psychiatric and mental status is performed as part of the complete neurological examination at FEVs, YEVs, EDV, or FV (as applicable) and SVs, as noted in Table 1–2. At a minimum, the presence of psychiatric symptoms, mental impairment, and behavioral problems should be assessed.

8.1.5 Vital signs

Oral temperature, pulse rate, respiratory rate, body weight, and blood pressure (systolic and diastolic) will be assessed.

Blood pressure and pulse measurements will be assessed in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs should be obtained prior to blood collection for safety laboratory assessments per Schedule of Activities (Table 1–2). Only 1 measurement of blood pressure and pulse rate are required.

8.1.6 Electrocardiograms

A standard 12-lead ECG will be obtained as outlined in the Schedule of Assessments (Table 1–2) to capture abnormalities during the study. If abnormal values were detected during N01269, prior to the participant's entry into EP0132, or during EP0132, the ECG will be repeated until the participant's values return to normal or Baseline, or are no longer considered clinically significant by the Investigator or Medical Monitor. Clinically significant abnormalities will be reported as TEAEs. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

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

8.1.7 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the Schedule of Assessments (Table 1–2) for the timing and frequency. The possibly clinically significant treatment-emergent (PCST) criteria are provided in the Statistical Analysis Plan (SAP).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal from any point after administration of first IMP until the end of the Safety Period should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or Medical Monitor. Participants who enter EP0132 from N01269 with clinically significantly abnormal values will be monitored during EP0132.

If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the Schedule of Assessments.

If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.1.8 Suicidal risk monitoring

Brivaracetam is considered to be an AED. Suicidal ideation and behavior have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomized placebo-controlled studies of AEDs has also shown a small increased risk of suicidal ideation and behavior. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for BRV.

Participants being treated with IMP should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing IMP in participants who experience signs of suicidal ideation or behavior.

Families and caregivers of participants being treated with IMP should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study Investigator.

Treatment-emergent suicidal ideation and behavior will be monitored by trained study personnel using the C-SSRS for all study participants ≥6 years of age at the time of enrollment into EP0132. The "Since Last Visit" version of the C-SSRS will be used at each visit unless the participant turns 6 years of age while enrolled in EP0132. If the participant turns 6 years of age during enrollment, the "Already Enrolled" version of the C-SSRS should be completed at the first visit after the participant's sixth birthday. Thereafter, the "Since Last Visit" version of the C-SSRS should be completed at all subsequent visits as indicated in the Schedule of Activities (Table 1–2).

8.1.9 Participant- or caregiver-reported outcomes

The patient- or parent-reported outcomes that will be assessed in this study are summarized in Table 8–1 and described in the following subsections.

Table 8–1: Participant- or caregiver-reported outcomes

Assessment	Time points assessed	Participant age at assessment[a]
EpiTrack Junior	FEV, YEV, and EDV or FV (as applicable)	6 to <18 years
PedsQL Core Module	FEV, YEV, and EDV or FV (as applicable)	Participant self-report: 5 to ≤7, 8 to ≤12, and 13 to ≤17 years Parent proxy-report: 2 to ≤4, 5 to ≤7, 8 to ≤12, and 13 to ≤17 years

EDV=Early Discontinuation Visit; FEV=Full Evaluation Visit; FV=Final Visit; PedsQL=Pediatric Quality of Life; YEV=Yearly Evaluation Visit

Note: Whole years are considered when determining participant age; ie, a 5-year-old is considered 5 until they turn 6 years old.

[a] The version of the assessment test should be in accordance with the study participant's age at the time of the assessment. If the participant has aged into a different version of the assessment test since the initial assessment in N01269, then the same version of the assessment should be completed at the initial assessment in EP0132, and subsequently, the version of the assessment test in accordance with the study participant's age at the time of the assessment should be used.

8.1.9.1 EpiTrack Junior

The EpiTrack Junior is a 15-minute screening tool intended to assess and track the cognitive side effects of AEDs in children with epilepsy. This will be conducted at FEVs, YEVs, EDV or FV (as applicable), and SV for study participants between 6 and 18 years old at the time of assessment. Study participants who become 6 years old after Baseline (EV), will be assessed for all visits they are aged 6 or above. The screening tool consists of 6 subtests, which will each be scored from 1 to 7 with greater differentiation in the lower range, thus aiming more at deficits: Speed, Flexibility, Planning, Response Inhibition, Word Fluency, and Working Memory. Overall EpiTrack Junior score will be calculated by summing the scores of the 6 domains and correcting for age at study entry. EpiTrack age correction is presented in the SAP and comes from the Helmstaedter et al (2010) manuscript. The same age correction (age at EV) will be applied at all visits even if a study participant changes age category during the study. If a study participant is missing any of the raw scores then the subtest and EpiTrack total score will be missing.

8.1.9.2 Pediatric Quality of Life Inventory

The Pediatric Quality of Life (PedsQL) Measurement Model is a modular approach to measuring health-related quality of life in healthy children and adolescents and those with acute and chronic health conditions (Varni et al, 2001).

The 23-item **Generic core module** is reliable and valid, has been used in a variety of health conditions and is responsive to change over time.

Two versions are available: Study Participant Self-Report Ages 5 to ≤7, 8 to ≤12, and 13 to ≤18; Parent Proxy-Report Ages 2 to ≤4, 5 to ≤7, 8 to ≤12, and 13 to ≤18. In study participants aged 2 to 4 years at the time of assessment, the caregiver will complete the Parent Proxy Report for 2 to ≤4 years old. In study participants aged 5 to 7 years at the time of assessment, the participant will complete the Study Participant Self-Report PedsQL for 5 to ≤7 years old, and the caregiver will complete the Parent Proxy Report for 5 to ≤7 years old. In study participants aged 8 to 12 years at the time of assessment, the participant will complete the Study Participant Self-Report PedsQL for 8 to ≤12 years old, and the caregiver will complete the Parent Proxy

Report for 8 to ≤12 years old. In study participants aged 13 to 17 years at the time of assessment, the participant will complete the Study Participant Self-Report PedsQL for 13 to ≤18 years old, and the caregiver will complete the Parent Proxy Report for 13 to ≤18 years old.

The version of the PedsQL used should be consistent with the study participant's age at the time of assessment with the following exception: If a study participant ages up to the next PedsQL between the initial assessment in the core study and the initial assessment in EP0132, the PedsQL that was used at the initial assessment in the core study should be completed through and including the initial assessment in EP0132, and subsequently the PedsQL consistent with the age at the time of assessment should be completed. The assessment will be done in study participants from 2 to ≤17 years of age.

The following scores will be computed:

- Physical, Emotional, Social, School Functioning; total score, physical health summary score, and psychosocial health summary score

PedsQL data will be collected at FEVs, YEVs, and EDV or FV (as applicable) using the 1-week recall period version.

The underlying score values 0 to 4 (representing responses of: never/not at all [0], almost never [1], sometimes [2], often [3], and almost always/a lot [4]) will be transformed by the function: (100 – [response x 25]) in order to generate scores of 0, 25, 50, 75, and 100, where a higher value represents a better quality of life.

8.1.10 Nonabsence seizures

8.1.10.1 Nonabsence seizure incidence after first BRV treatment during the study based on EEG

All nonabsence seizure types observed while awake or asleep on EEG (1-hour) will be categorized into 1 of 3 nonabsence seizure types:

- Partial seizures: 'POS'
- Tonic clonic seizures: 'Tonic clonic'
- All other seizure types

8.1.10.2 Nonabsence seizure incidence after first BRV treatment during the study based on study participant diary

The identification of nonabsence seizures described in Section 8.1.10.1 will be repeated using all nonabsence seizures observed from the study participant diary.

8.2 Adverse events and serious adverse events

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3). Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study medication or study procedures, or that caused the participant to discontinue IMP or EP0132 (see Section 7).

Occurrence of COVID-19 in participants should be reported as either "suspected COVID-19" or "confirmed COVID-19" along with all available relevant data including diagnostic and laboratory data. For participants where COVID-19 is still suspected despite a negative viral test, please report as "suspected COVID-19" and provide relevant data to support the diagnosis as well as the test results.

8.2.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the SV, at the time points specified in the Schedule of Assessments (Table 1–2).

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

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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 study medication), up to 30 days from the end of the study for each participant, and to also inform participants of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the study medication must be reported to UCB regardless of the time between the event and the end of the study.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.2.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.2.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AEs of special interest (as defined in Section 8.2.6), will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.2.4 Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.2.5 Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 2 days (ie, 5 half-lives) after the last dose of study medication.

If a pregnancy is reported, the Investigator must immediately inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

Should a participant become pregnant during the study, she should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The participant should return for an EDV.
- The participant should immediately stop the intake of the study medication or be down-titrated as instructed at the EDV.
- An SV should be scheduled 2 weeks after the participant has discontinued her study medication.

Every reasonable attempt should be made to follow the health of the child for at least 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period up to 12 months. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.2.6 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 BRV, the following events require immediate reporting (within 24 hours regardless of seriousness) to UCB:

- Autoimmune nephritis
- Nephritis

- Nephritis allergic
- Tubulointerstitial nephritis
- Tubulointerstitial nephritis and uveitis syndrome
- Potential Hy's Law, defined as ≥3xULN ALT or aspartate aminotransferase with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase, 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 participants.

8.2.7 Anticipated serious adverse events

The Anticipated SAEs in Table 8–2 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 8.2.1 and Appendix 3 (Section 10.3).

Table 8–2: Anticipated SAEs 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 study participant.

8.3 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 study medication so that Investigators, clinical study participants, 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 study medication, medically qualified personnel at UCB may identify additional safety measures

(eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

8.4 Treatment of overdose

For this study, any dose of BRV greater than that prescribed in the protocol will be considered an overdose. Overdose events are only considered AEs or SAEs if there are associated clinical signs and/or symptoms or if the act of taking the excess study medication itself is an AE or SAE (eg, suicide attempt).

UCB does not recommend specific treatment for an overdose. In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor within 24 hours.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically (at least 2 days).
3. Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 Pharmacokinetics

Blood samples of approximately 2 mL will be collected for measurement of BRV plasma concentration as specified in the Schedule of Assessments (Table 1–2). At the FEV and YEV/EDV/FV Visits, when PK sampling is planned, study participants should not take their morning BRV dose prior to arriving in the clinic.

A topical anesthetic (EMLA® or similar product) can be used locally prior to venipuncture or insertion of a catheter. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Each plasma sample will be divided into 2 aliquots (1 each for PK, and a back-up).

Drug concentration information that may unblind the N01269 study will not be reported to investigative sites or blinded personnel until the completion of the study (last patient last visit).

8.6 Genetics

Genetics are not evaluated in this study.

8.7 Pharmacodynamics

The efficacy assessments described in Section 7.3 may be used in pharmacodynamic analyses.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Health economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and will be described in more detail in the SAP.

9.1 Definition of analysis sets

The analysis sets will be defined as follows:

- The All Study Participants Screened Set will consist of all screened study participants who gave informed consent (and informed assent where required).
- The Safety Set (SS) will consist of all enrolled study participants who took at least 1 dose of study drug in the LTFU study. All analyses will be performed on the SS, except where specifically noted.
- The PK analysis set will consist of all enrolled study participants who during the study took at least 1 dose of study drug in the LTFU study and had at least 1 PK measurement.

9.2 General statistical considerations

All computations for the non-PK analyses will be performed using SAS® version 9.3 or later (SAS Institute, NC, USA).

Descriptive statistics, such as the mean, standard deviation, median, 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. No hypothesis testing will be conducted.

All outputs will be produced for all participants. Adverse event outputs will be produced for the Evaluation Period, 3-month periods within the Evaluation Period, the Down-Titration Period, and the Safety Period. Selected outputs may also be produced by modal dose, maximum BRV dose, exposure duration, 3-month periods during the Evaluation Period and study period.

Statistical outliers are defined as values that are discordant with other values and are clinically implausible. Exclusion of outliers from an analysis requires thorough justification based on statistical and clinical grounds. In such cases, unless otherwise specified, the analysis may be run both with and without the values. Any outliers will be reviewed during the data evaluation meeting. Study participant data listings will be provided and will present source data and key derived variables for statistical analyses, outliers excluded from analysis will be clearly marked.

9.3 Planned efficacy analyses

9.3.1 Analysis of the secondary efficacy endpoint

All efficacy outcomes will be summarized with descriptive statistics only on the SS:

- Absence seizure freedom on 1-hour ambulatory awake EEG at each applicable visit
- Absence seizure freedom based on diary over the evaluation period and by 3-month time intervals

All EEG and diary data will be reported individually using data listings.

9.4 Planned safety and other analyses

9.4.1 Safety analyses

Adverse event summary tables will be presented over the Evaluation Period, by 3-month intervals during the Evaluation Period, the Down-Titration Period, and Safety Period for the SS.

All safety variables will be analyzed by descriptive methods on the SS. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Treatment-emergent AEs (TEAEs) will be summarized by MedDRA System Organ Class and Preferred Term. The incidence of TEAEs, SAEs, TEAEs leading to discontinuation, and study treatment-related TEAEs will also be summarized.

Other safety variables, including laboratory values, vital signs, weight and height will be summarized by scheduled visit. All PCST abnormalities for laboratory values, vital signs and weight will be summarized by scheduled visit and listed. All ECG findings, as well as physical and neurological examination findings and psychiatric/mental status, will be listed.

The nonabsence seizure incidence will be summarized descriptively based on EEG and participant diary at each scheduled visit.

9.4.2 Pharmacokinetic analyses

Descriptive statistics will be used to describe the plasma concentration data on the PK analysis set. Data may be used for additional PK and PK-pharmacodynamic analyses, either as a standalone analysis or in combination with data from other relevant studies. In that case, a separate Data Analysis Plan will be written.

9.4.3 Other analyses

The questionnaire scores and change scores for EpiTrack Junior and PedsQL will be summarized in a descriptive manner by visit. Change from Baseline will be calculated only if the questionnaire is the same version at both time points.

9.5 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 study participant. The criteria for identifying important protocol deviations and the classification of important protocol deviations are defined within the project Data Cleaning Plan. To the extent feasible, the rules for identifying protocol deviations are 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 are implemented algorithmically to ensure consistency in the classification of important protocol deviations across all study participants.

9.6 Handling of dropouts or missing data

Study participants who prematurely discontinue the study will be evaluated based on the data collected at each visit attended.

No imputation of missing values associated with an individual date or visit is planned for the safety analysis, with the exception of partial date information for AEs and concomitant medications in order to determine whether they are treatment emergent.

9.7 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.

9.8 Determination of sample size

No formal sample size calculation was performed for this study. Approximately 140 study participants may enroll in this study, based upon the rollover expectations from N01269 into EP0132.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, International Council for Harmonisation (ICH)-Good Clinical Practice (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, ICF, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant-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 participants or others, and any protocol deviations, to eliminate immediate hazards to participants.

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 participants. 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 IRB/IEC requirements), at intervals appropriate to the degree of participant 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.

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the Investigator and/or contract research organization agreements, as applicable.

10.1.3 Informed consent process

Participant's 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 to the participant in both oral and written form by the Investigator (or designee). Parent(s), legal representative(s), and study participant, if applicable, will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the ICF should be signed and personally dated by the participant, or his/her parent/legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). Adult study participants will provide consent; minor study participants will provide assent and consent will be provided by the parent/caregiver. As the definitions of "adult" and "minor" vary by location/region, the appropriate ICF assent/consent will be achieved by each site based upon its location and the applicable definitions. The participant or his/her legal representative must receive a copy of the signed and dated ICF. As part of the consent process, each participant must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the ICF 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 ICF 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 Authorization form.

The participant may withdraw his/her consent to participate in the study at any time. A participant is considered as enrolled in the study when he/she has signed the ICF, whether or not any study procedures are actually performed; in the event that no study procedures are performed after the ICF is signed, the participant would be recorded as a screen failure. A CRF must not be started, nor may any study specific procedure be performed for a given participant, without having obtained his/her written consent to participate in the study.

10.1.4 Data protection

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

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 participant'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 participant's study participation, and autopsy reports for deaths occurring during the study).

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Data quality assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, legible, contemporaneous, original, and attributable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements. Remote monitoring visits may be conducted during the COVID-19 pandemic or under other exceptional circumstances as deemed appropriate to ensure study participants' safety.

All essential documents must be retained by the Investigator for the minimum retention period mandatory under the applicable local laws and regulations. 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.

Quality tolerance limits will be established for the study using parameters related to patient safety reporting and reliability of study results. The parameters will be monitored throughout the study to identify systematic issues. Parameters used, parameter values, important deviations from the quality tolerance limits, and actions taken will be summarized in the clinical study report.

10.1.5.1 Case report form completion

Unless specified otherwise, eCRFs will be used in this study. For assessments that require paper CRFs (eg, patient-reported outcomes), the information will be collected and loaded into the electronic data capture system. The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the CRFs and in all required reports. Corrections made after the Investigator's review and approval of the completed CRF will be re-signed and dated by the Investigator (via a password/electronic signature for eCRFs), and must be accompanied by a reason for the change.

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

Detailed instructions will be provided in the CRF Completion Guidelines.

10.1.5.2 Apps

Not applicable.

10.1.6 Source documents

This study will be utilizing an electronic source document system (e-Source) for direct data capture. As applicable, sites will utilize e-Source to enter original records in the data capture system to which raw data are first recorded. Information to be originally captured and reviewed electronically shall include details of the study participant visit and the protocol-required assessments performed. These data will be collected into a system that is secured and fully validated. Data recorded in the e-Source will be monitored directly from the system and will not require additional source data verification (SDV). Access to data from e-Source can be obtained using the system portal once appropriate training has been completed and designated study staff has been assigned. Investigators and study staff will be responsible for ensuring the quality and integrity of the data entered into the e-Source system.

In the event data cannot be captured in e-Source, alternative source documents may be utilized. All source documents must meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) for both paper and e-Source. 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). These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, quality of life questionnaires, or video. Source documents that are computer generated and stored electronically must be printed for review by the monitor for SDV. Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the participant's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the data capture to ensure all data are consistent.

10.1.7 Study and site closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study medication development

10.1.8 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in the table below will be performed by a central laboratory.
- Local laboratory results are only anticipated in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	AST/SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
Endocrinology tests	The following tests will be collected in study participants <18 years of age: • Follicle-stimulating hormone • Luteinizing hormone • Thyroid-stimulating hormone • Triiodothyronine • Thyroxine			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) • Urine hCG pregnancy test (as needed for women of childbearing potential)[2]			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; hCG=human chorionic gonadotropin; IEC=Independent Ethics Committee; INR=international normalized ratio; IRB=Institutional Review Board; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SAE=serious adverse event; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell

NOTES:

[1] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Appendix 6 (Section 10.6). All events of ALT ≥3×ULN and bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN and INR >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[2] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the N01269 study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 Appendix 3: Adverse events – definitions and procedures for recording, evaluating, follow-up, and reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study medication, whether or not considered related to the study medication. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study medication administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the study participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to UCB in lieu of completion of the UCB/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UCB.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met).

The National Cancer Institute Common Terminology Criteria for Adverse Events should be used as a supportive standardization instrument to evaluate AEs and SAEs but the final intensity grading by the Investigator must be mild, moderate, or severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.

- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to UCB. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UCB.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- 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 participant is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide UCB with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the UCB within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to UCB via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to UCB will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the UCB Study Physician by telephone.
- Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

SAE Reporting to UCB via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the UCB Study Physician. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories **are not considered WOCBP**:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception guidance

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following and for 5 half-lives (2 days) after the last dose of study medication:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition male participants must refrain from donating sperm for the duration of the study and for 2 days after the last dose of study medication.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for 2 days after the last dose of study medication.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods[a]

Highly Effective Contraceptive Methods That Are User Dependent[b] Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[c] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[c]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

NOTES:

a) In case of newly started contraception pills/IUDs, the Principal Investigator should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instruction as when these newly started methods would become effective.

b) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

c) Hormonal contraception may be susceptible to interaction with the study medication, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 2 days after the last dose of study medication

Pregnancy testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test.
- Pregnancy testing will be performed as specified in the Schedule of Assessments (Table 1–2) during the study and 2 days after the last dose of study medication, or as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 1 working day of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be at least 30 days and up to 12 months after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- Any female participant who becomes pregnant while participating in the study will discontinue study medication or be withdrawn from the study.
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 1 working day of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, the follow-up will be at least 30 days and up to 12 months after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study medication by the Investigator will be reported to the Sponsor as described in Section 8.2.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.5 Appendix 5: Genetics

Not applicable.

10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments

Participants with PDILI must be assessed to determine if study medication must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

Investigators should attempt to obtain information on study participants in the case of study medication discontinuation to complete the final evaluation.

Study participants 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 study medication discontinuation and/or participant withdrawal (if applicable), must be recorded in the source documents. The CRF must document the primary reason for discontinuation of study medication.

A specific monitoring plan must be agreed between the UCB Study Physician and the Investigator for study participants who have ALT >5 ULN. The monitoring plan should include any necessary follow-up assessments (until resolution of the abnormal lab values).

Phase 3-4 liver chemistry stopping criteria and follow-up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks ALT ≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin[a,b]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[b]	ALT ≥3xULN **and** INR >1.5, if INR measured
Cannot Monitor	ALT ≥5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[c]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study medication. • Report the event to UCB within **24 hours.** • Complete the liver event CRF, and complete a SAE data collection tool if the event also met the criteria for an SAE.[b] • Perform liver chemistry follow-up assessments. • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to Baseline (see **MONITORING**).	• Viral hepatitis serology[d] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen), quantitative hepatitis B DNA and hepatitis delta antibody[e]

Liver Chemistry Stopping Criteria	
• **Do not restart/rechallenge** participant with study medication unless allowed per protocol and UCB approval is granted. • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study medication and continue participant in the study for any protocol specified follow up assessments.Consider the need for a toxicology screening. **MONITORING:** **<u>For bilirubin or INR criteria</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to Baseline. • A specialist or hepatology consultation is recommended. **<u>For all other criteria</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to Baseline.	• Obtain blood sample for PK analysis within 2 days after the most recent dose[f] • Serum CPK and LDH • Fractionate bilirubin, if total bilirubin ≥ 2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury (eg, fatigue, nausea, vomiting, right upper quadrant pain), or hypersensitivity, on the AE report form • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF. • Record alcohol use on the liver event alcohol intake CRF • Exclude pregnancy **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James et al, 2009]). **NOTE: Not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRFs.

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; CRF=case report form; HbcAb=hepatitis B core antibody; HbsAg=hepatitis B surface antigen; HPLC=high performance liquid chromatography; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PCR=polymerase chain reaction; PK=pharmacokinetic; SAE=serious adverse event; ULN=upper limit of normal

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study medication if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

[b] All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of**

hepatic impairment or cirrhosis). The INR measurement is not required and the stated threshold value will not apply to participants receiving anticoagulants.

[c] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).

[d] Includes: Hepatitis A IgM antibody; HbsAg and HbcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

[e] If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal et al, 2005].

[f] PK sample may not be required for participants known to be receiving placebo or noncomparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study medication prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

Phase 3-4 liver chemistry increased monitoring criteria with continued study medication

Liver Chemistry Increased Monitoring Criteria	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify UCB Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study medication • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, bilirubin) until the abnormalities resolve, stabilize, or return to Baseline. • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 7.1. • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to Baseline.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal

10.7 Appendix 7: Medical device AEs, adverse device effects, SAEs and device deficiencies: definition and procedures for recording, evaluating, follow-up, and reporting

Not applicable.

10.8 Appendix 8: Rapid alert procedures

Not applicable.

10.9 Appendix 9: Country-specific requirements

Not applicable.

10.10 Appendix 10: Abbreviations and trademarks

AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
bid	twice daily
BRV	brivaracetam
CAE	childhood absence epilepsy
COVID-19	coronavirus disease
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DTV	Down-Titration Visit
ECG	electrocardiogram
eCRF	electronic case report form
EDV	Early Discontinuation Visit
EEG	electroencephalogram
ESM	ethosuximide
EV	Entry Visit
FEV	Full Evaluation Visit
FSH	follicle-stimulating hormone
FV	Final Visit
GCP	Good Clinical Practice
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
iv	intravenous
IXRS	interactive voice or web response system

JAE	juvenile absence epilepsy
LEV	levetiracetam
LTFU	long-term follow-up
LTG	lamotrigine
MedDRA®	Medical Dictionary for Regulatory Activities
MEV	Minimal Evaluation Visit
PCST	possibly clinically significant treatment-emergent
PDILI	potential drug-induced liver injury
PedsQL	Pediatric Quality of Life
PK	pharmacokinetic(s)
POS	partial-onset seizure(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SDV	source data verification
SS	Safety Set
SV	Safety Visit
SV2A	synaptic vesicle protein 2A
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VPA	valproic acid
WOCBP	woman of childbearing potential
YEV	Yearly Evaluation Visit

10.11 Appendix 11: Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1 (08 Sep 2020)

Overall Rationale for the Amendment

EP0132 Protocol Amendment 1, dated 08 Sep 2020, was completed to remove all decentralized study components as it was decided that all participant visits will occur on site. Centrally read 24-hour electroencephalogram (EEGs) were removed; locally read 1-hour EEGs that reflect normal clinical practice will be used in this study. In addition, the Conners Continuous Performance Tests (CPT), Achenbach Childhood Behavior Checklist (CBCL), and EuroQol 5-Dimension (EQ-5D) Quality of Life Assessments have been removed from the list of participant- and caregiver-reported outcomes and the wearable EEG (SeizeIT) substudy has been removed.

Section # and Name	Description of Change	Brief Rationale
Synopsis and Section 3 (Objectives and Endpoints)	Centrally read 24-hour EEGs were removed and replaced by 1-hour locally read EEGs.	Obtaining a 1-hour EEG mimics routine clinical practice and it was determined that there will be no central reader in EP0132.
Synopsis and Section 3 (Objectives and Endpoints)	The Achenbach CBCL, Conners CPT, and EQ-5D Assessments were removed as endpoints for the exploratory objective of this study.	Removed assessments to reduce overall complexity, patient burden, and to address logistical challenges.
Synopsis and Section 3 (Objectives and Endpoints)	Removed the exploratory objective planned to investigate the use of a wearable EEG device (SeizeIT) in a subset of study participants.	Removed wearable device substudy to reduce complexity and participant/site burden.
Section 1.3 (Schedule of activities)	Removed header row from Table 1-2 designating each visit as a decentralized visit or a site visit.	The virtual visits were removed as the visit schedule of the study is close to the standard visit schedule of pediatric epilepsy patients in clinical practice; therefore, the additional burden of the patients going to the sites is minimal.
Section 1.3 (Schedule of activities)	Removed information regarding the Achenbach CBCL, Conners CPT, and EQ-5D Assessments.	Removed assessments to reduce overall complexity, patient burden, and to address logistical challenges.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 (Schedule of activities)	Removed information regarding the wearable EEG (SeizeIT) substudy.	Removed wearable device substudy to reduce complexity and participant/site burden.
Section 1.3 (Schedule of activities)	Added a new footnote to define the EDV.	Provide additional informational details.
Section 1.3 (Schedule of activities)	Added text to the footnote describing PK assessment visits to clarify that on the FEV, YEV, EDV, and FV Visits, participants should not take their morning BRV dose prior to arriving at the clinic.	Provide additional clarifying detail that for visits when PK assessments are planned, the morning BRV dose will be administered at the clinical unit.
Section 1.3 (Schedule of activities)	Added a new footnote to clarify that the investigator/designated EEG reader should attempt to keep the study participant awake for the duration of the 1-hour EEG to ensure that the minimum period of awake time (30 minutes) required for evaluability is achieved.	Provide additional clarifying details to ensure that the 1-hour EEGs achieve the minimum period of awake time (30 minutes) required for evaluability.
Section 4.1.1 (Site-based model)	Removed section and relocated text stating that all study assessments will be conducted on site to Section 4.1.	Post-approval decision that a site-based model will be used by all countries.
Section 4.1.2 (Decentralized model)	Removed section describing the decentralized model.	The virtual visits were removed as the visit schedule of the study is close to the standard visit schedule of pediatric epilepsy patients in clinical practice; therefore, the additional burden of the patients going to the sites is minimal.
Section 6.1.1 (Medical devices)	Removed section describing the wearable EEG (SeizeIT) substudy.	Removed wearable device substudy to reduce complexity and participant/site burden.
Section 6.5.3 (Rescue medication)	Removed text referencing the 24-hour EEG.	The 24-hour EEG will no longer be performed as a 1-hour EEG mimics routine clinical practice.
Section 8.1.1 (Seizure data based on EEG)	Revised text previously describing 24-hour ambulatory EEGs to describe 1-hour EEGs.	Obtaining a 1-hour EEG mimics routine clinical practice.

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1 (Seizure data based on EEG)	Removed text describing EEG procedures for countries where the decentralized model was to be used.	The virtual visits were removed as the visit schedule of the study is close to the standard visit schedule of pediatric epilepsy patients in clinical practice; therefore, the additional burden of the patients going to the sites is minimal.
Section 8.1.2 (Seizure diary)	Removed reference to an electronic diary for recording daily seizure activity.	Post approval decision to use paper diaries instead of electronic diaries in this study.
Section 8.2.4 (Electrocardiograms)	Text was added to clarify that for abnormal ECG values observed during N01269, prior to participant's entry into EP0132, or during EP0132, ECGs will be repeated until the participant's values return to normal or Baseline or are no longer considered clinically significant.	Provide clarifying details regarding the follow up of abnormal ECGs during this study.
Section 8.2.6 (Suicidal risk monitoring)	Text was added to clarify that the C-SSRS will only be conducted in participants ≥6 years of age and to provide details for procedures to follow when a participant turns 6 during the study.	Provide clarification of the participants' ages in which the C-SSRS will be used, in addition to further procedural details.
Section 8.2.7 (Participant- or caregiver-reported outcomes)	Removed the Achenbach CBCL, Conners Performance Tests, and EQ-5D Quality of Life Assessments from the tabular presentation (Table 8-1) of the participant- and caregiver-reported outcomes.	Removed assessments to reduce overall complexity, patient burden, and to address logistical challenges
Section 8.2.7.1 (Achenbach Childhood Behavior Checklist)	Removed section describing the Achenbach CBCL.	Assessment has been omitted from the protocol.
Section 8.2.7.3 (Conners Continuous Performance Test)	Removed section describing the Conners CPT.	Assessment has been omitted from the protocol.
Section 8.2.7.4 (Pediatric Quality of Life Inventory)	Revised the text to state that the 1-week recall version of the PedsQL will be used for all planned assessment timepoints.	The 1-week recall version of the PedsQL will be used for all assessment timepoints in N01269; therefore, using the same version in

Section # and Name	Description of Change	Brief Rationale
		this LTFU study will allow for consistent comparisons.
Section 8.2.7.5 (EuroQol-5-Dimension Quality of Life Assessment)	Removed section describing the EQ-5D Quality of Life Assessment.	Assessment has been omitted from the protocol.
Section 8.2.8.1 (Nonabsence seizure incidence after first BRV treatment during the study based on EEG)	Removed text describing 24-hour EEG.	Post approval decision to only conduct 1-hour locally read EEGs, which aligns with routine clinical practice.
Section 8.3.8 (Medical device – AEs and device deficiencies)	Removed section describing the SeizeIT wearable EEG device.	Not applicable to EP0132 since the SeizeIT device has been omitted from the protocol.
Section 8.6 (Pharmacokinetics)	Added text describing the PK assessment visits to note that on the FEV, YEV, EDV, and FV, participants should not take their morning BRV dose prior to arriving at the clinic.	Provide additional clarifying detail that for visits when PK assessments are planned, the morning BRV dose will be administered at the clinical unit.
Section 9.3.1 (Analysis of the secondary efficacy endpoint)	Revised text describing 24-hour ambulatory EEG to 1-hour EEG.	Post approval decision to only conduct 1-hour locally read EEGs, which aligns with routine clinical practice.
Section 9.4.3 (Other analyses)	Revised text to remove reference to the Conners CPT, Achenbach CBCL, and EQ-5D Assessments. Also removed reference to the wearable EEG device (SeizeIT).	Removed assessments and the wearable EEG substudy from the protocol to reduce overall complexity, patient burden, and to address logistical challenges.
Section 10.7 (Appendix 7: Medical device AEs , adverse device effects, SAEs and device deficiencies: definition and procedures for recording, evaluating, follow-up, and reporting)	Removed appendix text describing medical device AEs.	Not applicable to EP0132 since the SeizeIT device has been omitted from the protocol.

AE=adverse event; BRV=brivaracetam; CBCL=Childhood Behavior Checklist; CPT=Continuous Performance Test; C-SSRS=Columbia Suicide Severity Rating Scale; EDV=Early Discontinuation Visit; EEG=electroencephalogram; EQ-5D=EuroQol 5-Dimensions Quality of Life Assessment; FEV=Full Evaluation Visit; FV=Final Visit; PedsQL=Pediatric Quality of Life; PK=pharmacokinetic; SAE=serious adverse event; YEV=Yearly Evaluation Visit

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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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