STATISTICAL ANALYSIS PLAN

Study: EP0132

Product: Brivaracetam

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

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.

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TABLE OF CONTENTS

LIST OF TABLES

VERSION HISTORY

This statistical analysis plan (SAP) for study EP0132 is based on the protocol amendment 2 dated 29MAR2021.

SAP Version	Approval Date	Change	Rationale
Original	15 Oct 2021	Not Applicable	Original version
Amendment 1	25 Oct 2024	Sections 2.2.2, 3.13.2, and 3.13.4 Removed the term 'permitted' when referring to concomitant use of antiepileptic drugs (AEDs). Section 3.12.1 Section added to explain the change from protocol with regards to removing the term 'permitted' when referring to the concomitant use of AEDs.	A change from protocol. All AEDs may have an impact on the efficacy outcomes and should be considered in the analysis.
		Section 2.2.2 Added timeframe to secondary efficacy endpoints. Section 3.1 Added timeframe to secondary efficacy endpoints Section 3.12.2 Section added to explain the change from protocol with regards to truncating the efficacy data up to Month 24 for the secondary efficacy endpoints.	A change from protocol. Efficacy endpoints will be assessed up to Month 24.
		Section 2.3.1 Update to clarify Down-Titration	Down-Titration Period is not necessary if the participant has already reached a dose of

SAP Version	Approval Date	Change	Rationale
		Period attendance for participants who already reached a dose of 1mg/kg/day (50mg/day for study participants with body weight >50kg) at FV or EDV	1mg/kg/day (50mg/day for study participants with body weight >50kg) at FV or EDV
		Section 3.2 Clarification added regarding presentation of pharmacokinetic (PK) data.	To clarify that PK data is presented based on significant figures rather than decimal places.
		Section 3.3.1.3 Updated to consider an EDV as attended when the participant is not considered a completer as per Section 3.3.5	Consistency of completer definition
		Section 3.3.1.4 Section added to define the Final Visit (FV) and when this may occur.	
		Section 3.3.2 Definition of Overall Period added to the text and Table 3-2.	Overall Period is included in the planned tables but there was no definition in the SAP.
		Section 3.3.2 and 3.3.3 Text updated to use the date of the first dose in EP0132 as the start of the Evaluation Period and the start of the first 3 and 6 month periods instead of using the entry visit (EV) as the reference day.	The expectation was for the 1st dose to be taken in the evening of the EV but this may not be the case for all participants and so the use of EV and day of 1st dose, in derivations were inconsistent across the SAP.
		Section 3.3.2 Text added to clarify that the Evaluation Period may be truncated at Month 24 YEV for	To add clarity to Evaluation Period used for the absence seizure freedom analyses based on seizure diary data.

SAP Version	Approval Date	Change	Rationale
		the absence seizure freedom efficacy analyses based on seizure diary data.	
		Section 3.3.2 Text added to clarify that for participants who do not require down-titration at FV or EDV, the Overall Period includes the Evaluation Period and the Safety Period.	Down-Titration Period is not necessary if the participant has already reached a dose of 1mg/kg/day (50mg/day for study participants with body weight >50kg) at FV or EDV
		Section 3.3.2 Text added to clarify that for participants who complete the Study at FV, the Overall Period is the Evaluation Period	Down-Titration Period and Safety Period attendance is not necessary if the subject has completed the study at FV
		Section 3.3.2 Text added to Table 3-2 to clarify that for participants who do not require down-titration at FV, the Safety period starts the day after FV rather than the day after DTV	Down-Titration Period attendance is not necessary if the participant has already reached a dose of 1mg/kg/day (50mg/day for study participants with body weight >50kg) at FV
		Section 3.3.2 Text added to Table 3-2 to clarify that for participants who do not require down-titration at EDV, the Safety period starts the day after EDV rather than the day after DTV	Down-Titration Period attendance is not necessary if the participant has already reached a dose of 1mg/kg/day (50mg/day for study participants with body weight >50kg) at EDV
		Section 3.3.2 Text added to clarify attendance of the Down-Titration Period for participants	Consistency with Section 2.3.1

SAP Version	Approval Date	Change	Rationale
		who do not require down titration at FV or EDV	
		Section 3.3.3 Text added to include the type of summaries that will utilize 3 month periods versus 6 month periods. Table 3.5 and text added to clarify the difference in a study period and the timing of scheduled assessments. All tables extended past Month 24 for subjects who remain in EP0132 past 24 months. Clarified data inclusion for safety and efficacy summaries.	To acknowledge the difference in the definition of 3 and 6 monthly periods (eg, seizure diary data) and protocol defined scheduled assessments at 3 or 6 monthly intervals (electroencephalogram [EEG]). To fully describe mapping approach for visits past the expected end of study at Month 24. Efficacy is truncated at Month 24 but there is interest in safety data beyond Month 24.
		Section 3.3.4 Text added to include the date the World Health Organization (WHO) declared the end of the Coronavirus Disease 2019 (COVID-19) pandemic.	Added date when date became available (5 May 2023).
		Section 3.3.5 Text added to clarify completer definitions for participants who do not require down-titration	Down-Titration Period is not necessary if the participant has already reached a dose of 1mg/kg/day (50mg/day for study participants with body weight >50kg) at FV.

SAP Version	Approval Date	Change	Rationale
		Text added to clarify completer definitions for participants who are considered completers at FV by investigator	Complete possible scenarios for study completion.
		Section 3.3.6 For the data sources for the EP0132 EV, ethnic subgroup and physical examination have been removed from the list of variables to be obtained from the N01269 analysis database. Gender has been added to the list of data obtained from the N01269 analysis database. Added that height will be obtained from Visit 6 of N01269 if available and will otherwise be missing. Added that EV data for EpiTrack Junior and Pediatric Quality of Life Inventory (PedsQL) from the N01269 database brought across to the EP0132 EV will be listed only.	The EV of EP0132 will not obtain ethnic subgroup and physical examination from the N01269 database as these data were not collected. Height is not scheduled at Visit 7 or at an Early Discontinuation Visit (EDV) in N01269. To add clarity to use of EP0132 EV assessments in summaries.
		Section 3.3.7 Detail added on how to handle assessments performed at an EDV.	To clarify how EDVs will be handled in the analysis.
		Section 3.3.8 Section added for the mapping of assessments performed at a FV.	To clarify how FVs will be handled in the analysis.

SAP Version	Approval Date	Change	Rationale
		Section 3.3.9 Section added for the mapping of assessments performed at unscheduled visits. Text added and amended for the handling of mapping unscheduled assessments for participants who stay in the study longer than 2 years.	To clarify how unscheduled visits will be handled in the analysis.
		Section 3.3.10 Text added to describe how a participant's dose can be maintained or modified. Removed reference to using the interactive voice or web response system (IXRS) vendor data for changes in the daily dose and instead use data captured in electronic case report form (eCRF). Added the scenario in which the modal dose category will be calculated.	IXRS vendor data is not available in the required format to define changes to dose. To specify that modal dose will be calculated even if a participant doesn't complete a period.
		Section 3.11 Updated World Health Organization Drug Reference List version from SEP2017 to SEP2020.	The dictionary version for coding medications was updated during the study.
		Section 3.13.2 to 3.13.9 Replaced all references to rescue medication with any concomitant AED or benzodiazepines.	In EP0132 maintenance AEDs are allowed. From an efficacy perspective, all concomitant AED or benzodiazepines used

SAP Version	Approval Date	Change	Rationale
			as maintenance medication or as rescue medication have the potential to impact the efficacy of the study.
		Section 3.13.2 to 3.13.7 Text added and amended to clearly define how absence seizure freedom will be determined for each of the absence seizure freedom endpoints.	To add clarity to the derivation of the endpoints.
		Section 3.13.8 Text added to clarify how to use multiple assessments on the same day	To add clarity to the derivation of the endpoints.
		Section 3.13.8 and 3.1.9 Text added to clearly define consecutive absence seizures and cumulative consecutive absence seizures and provide additional information on how unscheduled assessments are handled.	To add clarity to the derivation of the endpoints.
		Section 3.13.10 Text added to clarify the source of the EpiTrack Junior scores at the EV in EP0132. Text added to clarify that the age correction is from the first time the EpiTrack Junior	 Participants aged <6 will not have completed the

SAP Version	Approval Date	Change	Rationale
		score is completed and that the Baseline is available only for those who were aged 6 and above at N01269 Baseline.	EpiTrack Junior score at Baseline.
		Section 3.13.11 Text added to clarify that participants aged 2 to 4 will not have a baseline value for the PedsQL self-report and that the change from baseline (CFB) for the parent proxy report will not be calculated when the participant turns 5.	For participants aged 2 to 4 years old, there is no self-report version available and the parent proxy report includes fewer items than the versions for the older age groups and so is not comparable.
		Section 3.13.12 Removed reference to using the IXRS vendor data for changes in the daily dose and instead use data captured in eCRF. Formula for number of days the study participant received dose from which discontinued has been updated.	IXRS vendor data is not available in the required format to define changes to dose. Amended to reflect the scenario in which last dose is prior to date of discontinuation. '+1' added to correctly calculate the number of days on dose from which discontinued.
		Section 3.13.13 Dose at Adverse Event (AE) onset added.	New section added to provide detail on the derivation of dose at AE onset.
		Section 3.13.15 The derivation of the number of days on study drug has been updated to use the	The expectation was for the 1st dose to be taken in the evening of the EV but this may not be the case for all participants.

SAP Version	Approval Date	Change	Rationale
		first dose in EP0132 instead of EV.	
		Section 4.1.3 Text added to clarify that the absence seizure is based on EEG.	Added text for completeness as sentence references EEG.
		Section 4.1.4.3 Text updated to split out the rules for handling medications with partial or missing dates when the medications are ongoing or not ongoing from N01269.	Added text for completeness.
		Section 4.1.4.4 Text updated to split out the rules for handling AEs with partial or missing dates when the AEs are ongoing or not ongoing from N01269. Added additional scenario of partial AE onset date and text for considering an AE to be treatment-emergent when the data are unclear or unavailable.	Added text for completeness.
		Section 4.1.4.5 Text updated to clarify the rules for handling study medication with partial stop dates.	Previously the text was written with the expectation that the date of last contact would be the date of death. However, the CRF Completion Guidelines state the date of last contact refers to the last contact whilst the participant was alive. If a participant dies, it is assumed that they

SAP Version	Approval Date	Change	Rationale
			continue on treatment until their death date and so no longer want to take the earliest date of last contact or death date.
		Section 5.1.1 Removed summary of screen failures and specified details on screen failures are to be listed only. For the overall summary and listing of disposition added new completer subcategory text for the number of participants who were prescribed BRV after EP0132 study. Added text for the summary and listing of scheduled study visits. Also added a summary and listing of study periods. For the listing, have added date of final contact	No screen failures data reported so far; thus it will suffice to list data that becomes available and a summary will no longer be required. This is to provide clarity for how many participants completed the study were transitioned to another program and continued to be prescribed BRV after EP0132 study. This was to clearly present the number of study visits attended by each participant and the number of 3-month study periods started and completed for each participant. Align with the shell text.
		Section 5.1.3 Removed reference to serious non-fatal AEs. Clarified that only the most severe type of AE is taken.	Text was incorrect and has been updated to align with the standards. Align with the shell text.
		Section 5.3 Removed description of COVID-19 data summaries.	No COVID-19 impact data reported so far thus it will suffice to list any data that becomes available and

SAP Version	Approval Date	Change	Rationale
			summaries will no longer be required.
		Section 6.1 Age at N01269 Visit 1 summaries removed. EudraCT and clinicaltrials.gov age categories added. Text added for countries to be summarized as part of the demographics summary.	Age at N01269 Visit 1 is not used anywhere in this study so summary of this data is not required. To align with N01269 and with reporting requirements. To align with disclosure and data transparency reporting requirements.
		Section 6.3 Summary of medical history removed.	Only the medical history not captured in N01269 are reported in EP0132 and so a listing of the data is deemed to be sufficient.
		Section 6.4 Detail regarding AED groupings for previous and concomitant medications has been updated.	The physician reviewed spreadsheet of AEDs has been updated, so this section now refers to the spreadsheet rather than listing the medications in each group.
		Section 8.1 Detail added for determination of the denominators to be used in the calculation of percentages for the summaries. Text added to explain that the secondary efficacy variables will not be summarized for visits or periods beyond scheduled Month 24 YEV for	To add clarity on how the percentages will be calculated. To add clarity that the secondary efficacy variables will not summarize the visits/periods beyond Month 24 that are only available for small

SAP Version	Approval Date	Change	Rationale
		participants who continue in the study beyond 2 years. Section 8.1.1 to 8.1.7 Text amended to clearly distinguish between scheduled MEV/FEV/YEV visits and monthly periods.	subset of participants that continued in the study beyond 2 years. To add clarity to the secondary efficacy endpoints being summarized.
		Section 8.1.1 and 8.1.3 Added text for a new sub-category to be summarized under the number participants that are not absence seizure free. These are participants who discontinued the study prior to Month 24 and are imputed as not absence seizure free.	To clarify how many discontinued participants have been imputed as not absence seizure free per each scheduled assessment or monthly period.
		Section 9.1 Removed reference to post-dose PK samples. Text added describing the details to be provided in the PK listing, including the addition of previous dose date and time and time since previous dose. Removed reference to using the IXRS vendor data for changes in the daily dose and instead use data captured in eCRF.	Per the protocol, only pre-dose PK samples are planned. To clarify that the pre-dose PK samples are to be compared to the timing of the previous dose and not the post-dose. IXRS vendor data is not available in the required format to define changes to dose.

SAP Version	Approval Date	Change	Rationale
		Section 10.1 Text added to specify the inclusion of participant years of exposure in the summary table and provide its definition. In Table 10-1 and the following text, the wording was changed from Exposure Duration Cohorts to Exposure Duration Categories. For the modal dose exposure summary, the wording for overall summary changed to all participants. Removed reference to using the IXRS vendor data for changes in the daily dose and instead use data captured in eCRF. Text added to define the prescribed starting dose and the dose at subsequent visits.	Participant years of exposure was being included in the corresponding summary table but was not defined in the SAP. To clarify the exposure durations are categories and not cohorts. To help distinguish between all participants in the Evaluation Period and the Overall Period . IXRS vendor data is not available in the required format to define changes to dose. Starting dose is not captured in the eCRF so needs to be assumed based on the protocol information.
		Section 10.2 Removed reference to using the IXRS vendor data for changes in the daily dose and instead use data captured in eCRF.	IXRS vendor data is not available in the required format.
		Section 10.2 and 10.2.1 Text added to	To add clarification on the AE plain language

SAP Version	Approval Date	Change	Rationale
		describe the AE summaries to be reported for the plain language summary.	summary reporting. This is to be reported outside of the CSR.
		Section 10.2 and 10.2.1 Text added to clarify the periods to be summarized for each AE summary.	To add clarification which AE summaries are to be produced on the Overall Period, Evaluation Period and for each 3-month period in the Evaluation period.
		Section 10.3.1 Text added to clarify the inclusion of laboratory variables from central/local laboratories for study participants with possible clinically significant treatment-emergent (PCST) values.	To add clarification regarding the presentation of PCST values.
		Section 10.5.1 Removed text regarding truncating the non-absence seizure 1-hour EEG data at Month 24.	Non-absence seizures are part of primary safety objective hence all data will be reported in the summary of non-absence seizures.
		Section 10.5.1 and 10.5.2 Text added to clarify the inclusion of assessments post Month 24 in summaries.	To add clarification for the summaries.
		Section 10.6.1 Text added to clarify that participants who turn the age of 18 before or on the first scheduled EpiTrack Junior assessment will be excluded from all summaries.	Protocol states that EpiTrack Junior in EP0132 is only required for participants <18 years of age, and original text was not clear on how to handle the participants who are 18 or turn 18 during EP0132.

SAP Version	Approval Date	Change	Rationale
		Section 10.6.2 Text added to clearly describe what data will be included for participants aged 2 to 4 years old and that participants will be included in the summaries by age group based on their age at N01269 baseline.	Original text was not clear on the handling of PedsQL scores for participant's aged 2 to 4 years old plus which summary the participant is reported in as their age enter the older age groups.
		Sections 13.1.1 (Table 13-1), 13.1.3 (Table 13-5), and 13.1.4 (Table 13-6) updated to remove any age categories not applicable to EP0132. Section 13.1.1 (Table 13-1) also updated to present the abnormality criteria in International System of Units (SI). Table 13-6 age category updated to remove > from ">12y- <17y".	To align text with the age categories relevant to EP0132. Ensure text aligns with the reporting of laboratory values in SI units. Updated following actions resulting from N01269 DEM-A review.
		Section 13.1.3 Clarification added and amended regarding the methodology to be used to determine Body Weight possibly clinically significant (PCS) criteria.	To add clarification regarding the body weight PCS criteria.

LIST OF ABBREVIATIONS

List of Abbreviations

AE	adverse event
AED	antiepileptic drug
ATC	anatomical therapeutic chemical
BLQ	below the limit of quantification
BMI	body mass index
BRV	brivaracetam
CAE	childhood absence epilepsy
CFB	change from baseline
CI	confidence interval
COVID-19	Coronavirus Disease 2019
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DEM	data evaluation meeting
DTV	Down-Titration Visit
ECG	electrocardiogram
eCRF	electronic case report form
EDV	Early Discontinuation Visit
EEG	electroencephalogram
EV	Entry Visit
FAS	Full Analysis Set
FEV	Full Evaluation Visit
FV	Final Visit
GTCS	generalized tonic-clonic seizure
HRQoL	health-related quality of life
HV	hyperventilation
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ILAE	International League Against Epilepsy
IPD	important protocol deviation

List of Abbreviations

IXRS	interactive voice or web response system
JAE	juvenile absence epilepsy
LLOQ	lower limit of quantification
LTFU	long-term follow up
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MEV	Minimal Evaluation Visit
nR	new ratio
PCS	possibly clinically significant
PCST	possibly clinically significant treatment-emergent
PDILI	potential drug-induced liver injury
PedsQL	Pediatric Quality of Life Inventory
PK	pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PLS	Plain Language Summaries
POS	partial onset seizure
PT	Preferred Term
SAE	serious adverse event
SAP	statistical analysis plan
SDTM	Study Data Tabulation Model
SBP	systolic blood pressure
SD	standard deviation
SFU	Safety Follow-up
SI	International System of Units
SOC	System Organ Class
SS	Safety Set
SV	Safety Visit
TEAE	treatment-emergent adverse event
UV	Unscheduled Visit
WHO	World Health Organization
YEV	Yearly Evaluation Visit

1 INTRODUCTION

This SAP defines the scope of the statistical analyses and provides a detailed description of the statistical methodology in order to support the final clinical study report (CSR).

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

To investigate the long-term safety and tolerability of brivaracetam (BRV) in pediatric study participants with Childhood Absence Epilepsy (CAE) or Juvenile Absence Epilepsy (JAE).

2.1.2 Secondary objective

To investigate long-term efficacy of BRV in pediatric study participants with CAE or JAE.

2.1.3 Other objectives

To investigate the long-term effect of BRV on behavior, cognition, and quality of life in pediatric study participants with CAE or JAE.

2.2 Study variables

2.2.1 Primary objective endpoints and estimands

Table 2-1: Primary objective

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 (TEAEs) **Estimand**: the estimand is defined by the following 4 attributes that will be used to define the treatment effect of interest for the primary safety analysis: 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

Table 2-1: Primary objective

Objectives	Endpoints/estimands
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• TEAEs leading to discontinuation of study drug Estimand: the estimand is defined by the following 4 attributes that will be used to define the treatment effect of interest for the primary safety analysis: 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 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	• Serious adverse events (SAEs) • Study drug-related TEAEs Estimand: the estimand is defined by the following 4 attributes that will be used to define the treatment effect of interest for the secondary safety analysis: 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.

Table 2-1: Primary objective

Objectives	Endpoints/estimands
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 adverse events (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 generalized tonic-clonic seizures (GTCS), based on diary or EEG: • Non-absence seizures based on 1-hour EEG • Non-absence seizures based on diary Estimand: the estimand is defined by the following 4 attributes that will be used to define the treatment effect of interest for the other safety analysis: 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 AE/TEAE data or seizure data (as applicable) 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.
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• CFB to each applicable visit in safety laboratory tests • CFB to each applicable visit in electrocardiogram (ECG) parameters • ECG findings at each applicable visit

Table 2-1: Primary objective

Objectives	Endpoints/estimands
	• Physical and neurological examinations findings at each applicable visit • Psychiatric and mental status at each applicable visit • CFB to each applicable visit in vital signs (blood pressure, pulse rate, body temperature) • CFB to each applicable visit in body weight and height

AE=adverse event, BRV=brivaracetam, CAE=childhood absence epilepsy, CFB=change from baseline, ECG=electrocardiogram, EEG=electroencephalogram, GTCS=generalized tonic-clonic seizure, JAE=juvenile absence epilepsy, SAE=serious adverse event, TEAE=treatment-emergent adverse event

2.2.2 Secondary objective endpoints and estimands

Table 2-2: Secondary objective

Objectives	Endpoints/estimands
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 up to Month 24 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 up to Month 24. 3. Intercurrent event handling: The intercurrent event of concomitant use of any 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 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.

Table 2-2: Secondary objective

To investigate long-term efficacy of BRV in pediatric study participants with CAE or JAE	• Absence seizure freedom based on diary over the Evaluation Period truncated at Month 24 and by each applicable 3-month time interval up to Months 22-24 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 truncated at Month 24 and by each applicable 3-month time interval up to Months 22-24. 3. Intercurrent event handling: The intercurrent event of concomitant use of any 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 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 up to Month 24 • Consecutive absence seizure freedom in 6-month periods based on diary up to Month 24

AED=antiepileptic drug, BRV=brivaracetam, CAE=childhood absence epilepsy, EEG=electroencephalogram, JAE=juvenile absence epilepsy, SAE=serious adverse event, TEAE=treatment-emergent adverse event

2.2.3 Tertiary/exploratory object endpoints

Table 2-3: Tertiary/exploratory objective

Objectives	Endpoints/estimands
To investigate the long-term effect of	• CFB to each applicable visit in the EpiTrack Junior scores (for study participants 6 to <18 years old)

Table 2-3: Tertiary/exploratory objective

Objectives	Endpoints/estimands
BRV on behavior, cognition, and quality of life in pediatric study participants with CAE or JAE	• CFB 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) • CFB 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)

BRV=brivaracetam, CAE=childhood absence epilepsy, CFB=change from baseline, JAE=juvenile absence epilepsy, PedsQL=Pediatric Quality of Life

2.3 Study design and conduct

2.3.1 Overall design

EP0132 is a Phase 3, open-label, single-arm, multicenter, long-term follow-up (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 EV is the first study visit and is equivalent to last study visit of the core study (N01269). 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 (UV) 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 FV. For study participants who prematurely discontinue the study, the Evaluation Period will last from the EV until 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 and a dose of >1mg/kg/day (>50mg/day for study participants with body weight ≥50kg) is reached at the EDV or FV respectively, 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. Otherwise, for study participants who will discontinue BRV treatment following the EDV or FV and a dose of 1mg/kg/day (50mg/day for study participants with body weight >50kg) is reached at the EDV or FV respectively, down titration will not be applicable; after 2 weeks free of study drug (Safety Period), study participants will complete the SV.

2.3.2 Study treatment

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].

2.3.3 Seizure data collected

2.3.3.1 EEG

For all study participants, data from a 1-hour EEG with hyperventilation (HV) test will be collected at FEVs, YEVs, and the EDV or FV (as applicable). Each of these EEGs will be locally read. 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. The investigator/designated EEG reader will attempt to keep the study participant awake for the duration of the 1-hour EEG, and a minimum of 30 minutes of awake time is required for the EEG to be evaluable.

2.3.3.2 Daily seizure diaries

Data from daily seizure diaries will be collected during the Evaluation Period (from the EV until the EDV or FV as applicable) and the Down-Titration Period for participants who down-titrate. Study participants will record all types of seizures that occur in their diaries and will complete the diaries after each seizure or at least once a day.

2.4 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.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Endpoints and statistical measures

Table 3-1: Study endpoints and statistical measures

Objective	Endpoint	Statistical measure(s)
Primary objective	**Primary endpoint**	
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	TEAEs	Incidence of TEAEs
	TEAEs leading to discontinuation of study drug	Incidence of TEAEs leading to discontinuation of study drug

Table 3-1: Study endpoints and statistical measures

Objective	Endpoint	Statistical measure(s)
Primary objective	**Secondary endpoints**	
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	SAEs	Incidence of serious TEAEs
	Study drug-related TEAEs	Incidence of study drug-related TEAEs
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	Incidence of TEAEs requiring a change in BRV dose
	Maximum intensity TEAE experienced (mild, moderate, and severe)	Incidence of TEAEs by maximum intensity experienced
	Drug-related serious TEAEs	Incidence of drug-related serious TEAEs
	Fatal AEs	Incidence of fatal AEs
	TEAEs by maximum relationship (related and not related to BRV)	Incidence of TEAEs by maximum relationship to study drug
	SAEs by maximum relationship (related and not related to BRV)	Incidence of serious TEAEs by maximum relationship to study drug
	Non-absence seizures based on 1-hour EEG	Incidence of non-absence seizures based on EEG
	Non-absence seizures based on diary	Incidence of non-absence seizures based on diary
	CFB to each applicable visit in safety laboratory tests	Summary statistics of individual visit values and corresponding CFB to each visit

Table 3-1: Study endpoints and statistical measures

Objective	Endpoint	Statistical measure(s)
	CFB to each applicable visit in ECG parameters	Summary statistics of individual visit values and corresponding CFB to each visit
	ECG findings at each applicable visit	Incidence of ECGs which are abnormal clinically significant and abnormal not clinically significant
	Physical and neurological examinations findings at each applicable visit	Shift from Baseline neurological examinations findings which are abnormal clinically significant and abnormal not clinically significant. Physical examinations findings will be listed only
	Psychiatric and mental status at each applicable visit	Shift from Baseline psychiatric and mental status which are abnormal clinically significant and abnormal not clinically significant
	CFB to each applicable visit in vital signs (blood pressure, pulse rate, body temperature)	Summary statistics of individual visit values and corresponding CFB to each visit
	CFB to each applicable visit in body weight and height	Summary statistics of individual visit values and corresponding CFB to each visit
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, up to Month 24	Percentage of study participants free from absence seizures while awake on 1-hour EEG with

Table 3-1: Study endpoints and statistical measures

Objective	Endpoint	Statistical measure(s)
		no concomitant use of AEDs within 4 days prior to or during the 1-hour EEG
	Absence seizure freedom based on diary over the entire Evaluation Period, truncated at Month 24, and by 3-month time intervals up to Month 24	Percentage of study participants free from absence seizures based on diary during Evaluation Period and during each 3-month interval
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 up to Month 24	Percentage of study participants free from absence seizures in consecutive 6-month periods based on EEG
	Consecutive absence seizure freedom in 6-month periods based on diary up to Month 24	Percentage of study participants free from absence seizures in consecutive 6-month periods based on seizure 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	CFB to each applicable visit in the EpiTrack Junior scores (for study participants 6 to <18 years old)	Summary statistics of individual visit values and corresponding CFB to each visit
	CFB 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)	Summary statistics of individual visit values and corresponding CFB to each visit

Table 3-1: Study endpoints and statistical measures

Objective	Endpoint	Statistical measure(s)
	CFB 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)	Summary statistics of individual visit values and corresponding CFB to each visit

AE=adverse event, AED=antiepileptic drug, BRV=brivaracetam, CAE=childhood absence epilepsy, CFB=change from baseline, ECG=electrocardiogram, EEG=electroencephalogram, JAE=juvenile absence epilepsy, PedsQL=Pediatric Quality of Life Inventory, SAE=serious adverse event, TEAE=treatment-emergent adverse event

3.2 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, study participant data listings, and statistical output will be carried out using SAS® Version 9.3 or higher. Descriptive statistics, such as the number of study participants with available measurements (*n*), mean, standard deviation (SD), median, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, will be provided. Unless otherwise noted, the denominator for percentages will be based on the set of study participants in the specified analysis set with at least 1 assessment at the time point or at least 1 assessment during the time interval being summarized.

Decimal places for descriptive statistics will always apply the following rules (with the exception of PK data):

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

The individual PK concentrations will be reported to 3 significant figures in the listing. The descriptive statistics will be rounded to 4 significant figures for the mean, geometric mean, median, SD, and confidence interval (CI), to 1 decimal place for geometric coefficient of variation and to 3 significant figures for the min, max.

Unless otherwise noted, all percentages will be displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%.

Unless otherwise specified (eg, for Baseline values), all outputs are based on data collected in EP0132 only, and do not include data collected in N01269. Data sources for the EP0132 EV are specified in Section 3.3.6.

All outputs will be produced by actual syndrome (CAE/JAE) as reported in N01269 and for all participants. Adverse event outputs will be produced for the Evaluation Period and 3-month periods within the Evaluation Period. Selected outputs may also be produced by modal dose, maximum BRV dose, exposure duration, and 3-month periods during the Evaluation 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 will be run both with and without the values. Any outliers will be reviewed during data evaluation meetings (DEM). 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.

Selected summary tables and figures may be presented over all study participants and by COVID-19 period (during pandemic and post pandemic). COVID-19 periods are defined in Section 3.3.4.

Listings will specify the study participant number, actual syndrome (CAE/JAE), and where relevant, gender, age in years at EP0132 EV, race, and weight in kg at EP0132 EV. Only observed values will be displayed unless otherwise specified. For instance, partial dates will only display the observed data.

3.3 General study level definitions

3.3.1 Analysis time points

3.3.1.1 First dose of study drug

Unless otherwise noted, all references to the first dose of study drug in this SAP refer to the first dose of study drug during EP0132.

3.3.1.2 Relative day

Relative day will be calculated as the current date minus the date of first dose of study drug for days prior to the first dose of study drug, and the current date minus the date of first dose of study drug plus 1 for days on or after the date of first dose of study drug and prior to or on the day of last study drug dose (eg, the day of first dose will be Day 1 and the day prior to first dose will be Day -1). For days after the last dose of study drug, relative day will be calculated as the current date minus the date of last dose of study drug and will include a '+' to denote post-treatment days (eg, the day after the last dose will be Day +1). Relative day will not be calculated for partial dates.

3.3.1.3 Early Discontinuation Visit

The EDV will be attended if the participant discontinues study treatment early for any reason and is not considered a completer as defined in Section 3.3.5.

3.3.1.4 Final Visit

The FV refers to the last visit for study participants for completers as defined in Section 3.3.5. All FVs will be mapped to a scheduled visit where applicable, as per Section 3.3.8, and summarized accordingly.

3.3.2 Study periods

For reporting purposes, the Evaluation Period will last from the date of first dose in EP0132 until the FV inclusive, or from the date of first dose in EP0132 until the EDV inclusive for study participants who prematurely discontinue the study. The Evaluation Period may be truncated at the Month 24 YEV for the reporting of the absence seizure freedom based on seizure data (diary and EEG). It is expected that the first dose in EP0132 will be taken in the evening of the EV. For

participants who complete the study at the FV, the Overall Period will include the Evaluation Period only. Otherwise, for participants who are not required to down-titrate as a dose of 1mg/kg/day (50mg/day for study participants with body weight >50kg) is reached at the FV or EDV, the Overall Period will include the Evaluation Period and Safety Period. Otherwise, the Overall Period will include the Evaluation Period , Down-Titration Period and Safety Period.

For study participants who discontinue BRV treatment following the EDV or FV and a dose of >1mg/kg/day (>50mg/day for study participants with body weight ≥50kg) is reached at the EDV or FV respectively, 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. Otherwise, for study participants who will discontinue BRV treatment following the EDV or FV and a dose of 1mg/kg/day (50mg/day for study participants with body weight >50kg) is reached at the EDV or FV respectively, down titration will not be applicable.

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

The definitions of the Evaluation, Down-Titration, Safety Follow-up, and Overall Periods are provided in Table 3-2. Adverse events are assigned to a study period based on the date of onset. All other measurements are assigned based on the date of assessment.

Table 3-2: Definition of study periods

Period	Definition	Algorithmic rule
Evaluation Period	From the date of first dose in EP0132 inclusive until: • FV inclusive for participants who complete the study, or • EDV inclusive for participants who discontinue the study early	Day of first dose in EP0132 eCRF date inclusive to • If the participant completed the study: day of FV eCRF date inclusive; • Else if the participant attended the EDV: day of EDV eCRF date inclusive; • Else if the participant did not attend one of these visits (eg, is lost to follow up): day of last study medication as recorded on the Study Termination eCRF inclusive; • Else if the participant died: the date of death inclusive.
Down-Titration Period	• From the day after the FV inclusive for study participants who complete the study and	• If the participant completed the study and subsequently down-titrated: day after the FV eCRF date inclusive;

Table 3-2: Definition of study periods

Period	Definition	Algorithmic rule
	subsequently discontinue BRV, or • From the day after the EDV inclusive for study participants who discontinue the study early and subsequently discontinue BRV to the DTV inclusive.	• If the participant attended the EDV: day after the EDV eCRF date inclusive to • If the participant attended the DTV: day of DTV eCRF date inclusive; • Else if the participant did not attend the DTV: day of last study medication as recorded on the Study Termination eCRF inclusive; • Else if the participant died: the date of death inclusive.
Safety Period	In study participants who entered the Down-Titration Period: From the day after the DTV until the day of the SV inclusive.	In study participants who entered the Down-Titration Period (attended the FV or the EDV and is down-titrating as indicated on the Study Drug Dispensation and Administration eCRF): From the day after the DTV eCRF date inclusive to • If the study participant attended the SV: day of the SV eCRF date inclusive; • Else if the study participant was lost to follow-up: day of the last contact date on the Study Termination eCRF inclusive; • Else if the study participant died: the date of death inclusive.
	In study participants who did not enter the Down-Titration Period as a dose of 1mg/kg/day (50mg/day for study participants with body weight >50kg) is reached at FV: from the day after	In study participants who did not enter the Down-Titration Period as a dose of 1mg/kg/day (50mg/day for study participants with body weight >50kg) is reached at FV: From the day after the FV eCRF date inclusive

Table 3-2: Definition of study periods

Period	Definition	Algorithmic rule
	the FV until the day of the SV inclusive.	to • If the study participant attended the SV: day of the SV eCRF date inclusive; • Else if the study participant was lost to follow-up: day of the last contact date on the Study Termination eCRF inclusive; • Else if the study participant died: the date of death inclusive.
	In study participants who did not enter the Down-Titration Period as a dose of 1mg/kg/day (50mg/day for study participants with body weight >50kg) is reached at EDV: from the day after the EDV until the day of the SV inclusive.	In study participants who did not enter the Down-Titration Period as a dose of 1mg/kg/day (50mg/day for study participants with body weight >50kg) is reached at EDV: From the day after the EDV eCRF date inclusive to • If the study participant attended the SV: day of the SV eCRF date inclusive; • Else if the study participant was lost to follow-up: day of the last contact date on the Study Termination eCRF inclusive; • Else if the study participant died: the date of death inclusive.
Overall Period	From the date of first dose in EP0132 inclusive until: • SV inclusive for participants who complete the Safety Period	Day of date of first dose in EP0132 eCRF date inclusive to • If the study participant attended the SV: day of the SV eCRF date inclusive;

Table 3-2: Definition of study periods

Period	Definition	Algorithmic rule
	• FV inclusive for participants who transition to another BRV study or a managed access program or who convert to commercial BRV. The latest of the DTV, FV or EDV inclusive for participants who discontinue the study and do not enter the Safety Period	• Else if the study participant did not attend the SV: maximum day of the DTV, FV or EDV eCRF date inclusive (note that for participants who transition to another BRV study or a managed access program, this is expected to be the FV); • Else if the study participant was lost to follow-up: day of the last contact date on the Study Termination eCRF inclusive; • Else if the study participant died: the date of death inclusive.

BRV=brivaracetam, eCRF=electronic case report form, DTV=Down-Titration Visit, EDV=Early Discontinuation Visit, FV=Final Visit, SV=Safety Visit

3.3.3 Three- and six-month periods

A month is defined as 30 days and time intervals based on monthly durations are defined as a multiple of 30 days. The definitions of 3- and 6-month periods are described in Table 3-3 and Table 3-4 respectively.

Table 3-3: Definition of each 3-month period

Period	Days relative to date of first dose in EP0132
Months 1 to 3	1 to 90
Months 4 to 6	91 to 180
Months 7 to 9	181 to 270
Months 10 to 12	271 to 360
Months 13 to 15	361 to 450
Months 16 to 18	451 to 540
Months 19 to 21	541 to 630
Months 22 to 24	631 to 720
Months 25 to 27*	721 to 810
Months 28 to 30*	811 to 900
Months 31 to 33*	901 to 990
Months 34 to 36*	991 to 1080

Table 3-3: Definition of each 3-month period

Period	Days relative to date of first dose in EP0132
…	…

* These 3-month periods are only applicable for a subset of participants who remain in the EP0132 study past Month 24.

Table 3-4: Definition of each 6-month period

Period	Days relative to date of first dose in EP0132
Months 1 to 6	1 to 180
Months 7 to 12	181 to 360
Months 13 to 18	361 to 540
Months 19 to 24	541 to 720
Months 25 to 30*	721 to 900
Months 31 to 36*	901 to 1080
…	…

* These 6-month periods are only applicable for a subset of participants that remain in the EP0132 study past Month 24.

Three-month periods will be utilized for summaries and analyses of efficacy based on seizure data (diary data), AEs, and other safety endpoints. Six-month periods will be utilized for efficacy analyses of seizure data based on EEG, and consecutive and cumulative consecutive absence seizure freedom based on seizure data (EEG and diary data). For the analysis of AEs, participants will be included in 3-month period summaries if the end date of their Evaluation Period is on or after the first day of the 3-month period respectively.

Assessment visits are scheduled based on months calculated as 365.25/12 and thus are not fully aligned to the 3-month or 6-month periods described above. For example, the 7 to 12 month period would end at 360 days whereas the Month 12 visit is scheduled at 365 days. Similarly, the 19 to 24 month period would end at 720 days whereas the Month 24 visit is scheduled at 731 days. Further details are provided in Table 3-5.

Table 3-5: Study periods vs scheduled assessments

Period	Days relative to date of first dose in EP0132	Scheduled assessment visit[a]	Scheduled assessment visit (days)
Months 1 to 3	1 to 90	MEV, Month 3	91
Months 4 to 6	91 to 180	FEV, Month 6	183
Months 7 to 9	181 to 270	MEV, Month 9	274
Months 10 to 12	271 to 360	YEV, Month 12	365
Months 13 to 15	361 to 450	MEV, Month 15	457
Months 16 to 18	451 to 540	FEV, Month 18	548

Table 3-5: Study periods vs scheduled assessments

Period	Days relative to date of first dose in EP0132	Scheduled assessment visit[a]	Scheduled assessment visit (days)
Months 19 to 21	541 to 630	MEV, Month 21	639
Months 22 to 24	631 to 720	YEV, Month 24	731
Months 25 to 27	721 to 810	MEV, Month 27	822
Months 28 to 30	811 to 900	FEV, Month 30	913
Months 31 to 33	901 to 990	MEV, Month 33	1004
Months 34 to 36	991 to 1080	YEV, Month 36	1096

[a] Scheduled assessments are relative to the date of EV.
EV=Entry Visit, FEV=Full Evaluation visit, MEV=minimal evaluation visit, YEV=Yearly evaluation visit.

For efficacy analyses, data collected after Months 22 to 24 or Months 19 to 24, but prior to the Month 24 YEV, will be included only within summaries presenting the Evaluation Period or Overall Period. The Evaluation Period and Overall Period are defined in Section 3.3.2. For safety analyses, data will be included from all 3-month periods both prior and post the Month 24 YEV.

3.3.4 COVID-19 Periods

Two COVID-19 periods are considered for analysis:

- During Pandemic: All study participants enrolled until the day before the date when the WHO declared that COVID-19 no longer constitutes a public health emergency of international concern.
- Post Pandemic: All study participants enrolled on or after the date when the WHO declared that COVID-19 no longer constitutes a public health emergency of international concern.

A pre-pandemic period is not considered as the first study participant was enrolled after 11 Mar 2020, the date the WHO declared the outbreak of COVID-19 pandemic. The WHO declared that COVID-19 no longer constitutes a public health emergency of international concern on 5 May 2023.

3.3.5 Completion/Early Discontinuation/Ongoing

Each study participant will be considered as completing the study or discontinuing the study early. While the study is ongoing they may also be considered as ongoing.

A study participant will meet the criteria for completion if they meet one of the following criteria:

- They attend the FV and transition to another BRV study or a managed access program or convert to commercial BRV (as indicated on the FV eCRF by answering "Yes" to the question "Will the study participant be prescribed Brivaracetam after the EP0132 study (eg participant is transitioning to another BRV study, managed access program or converting to commercial BRV)?"

- The investigator determines they have completed the study following the participant attending the FV
- For participants where a dose of >1mg/kg/day (>50mg/day for study participants with body weight ≥50kg) is reached at FV: they attend the FV and subsequently down-titrate, attending the DTV and SV. If the participant does not attend both the DTV and SV after down-titration, they are not considered a completer.
- For participants where a dose of 1mg/kg/day (50mg/day for study participants with body weight >50kg) is reached at FV: they attend the FV and attend the SV, as down-titration is not required for these participants.

A study participant will be regarded as discontinuing the study early if they do not meet the criteria for completion.

3.3.6 Data sources for EP0132 EV

The EV in EP0132 is also the last completed study visit of N01269. Information at this visit will be obtained from either the N01269 analysis database or the EP0132 eCRF dependent on the data type. The last completed visit in N01269 will be one of the following:

- Visit 6
- Visit 7
- EDV

The following will be obtained from the N01269 analysis database, if available:

- Absence seizure diagnosis (CAE/JAE)
- Race
- Ethnicity
- Gender
- Neurological examination
- Psychiatric and mental status
- Vital signs
- Body weight and height
  - Height is measured only at Visit 6 in N01269 and is not scheduled at Visit 7 or EDV. Height at the EP0132 EV will therefore be obtained from the Visit 6 assessment if available and will be otherwise missing.
- Laboratory assessments
- EpiTrack Junior
- PedsQL
- ECG

The following will be obtained from the EP0132 EV eCRF:

- Age in years and months
- AEs*
- Previous and concomitant medications*

*Adverse events and concomitant medications will be summarized as reported on the EP0132 eCRF without integration from the N01269 analysis database. Any AEs or medications that are ongoing at the time of entry into EP0132 will be entered on the EP0132 eCRF.

In the event that the date of EV in EP0132 is later than the date of the last visit in N01269 additional unscheduled assessments may be performed for those measurements indicated above. In this case the unscheduled assessments performed after the last visit in N01269 and before or on the date of the EV in EP0132, will be used in any listings and summaries instead of those performed at the last visit in N01269.

EpiTrack Junior and PedsQL values obtained from the N01269 database for the EP0132 EV will be listed only.

3.3.7 Mapping of assessments performed at EDV

Efficacy and safety assessments at an EDV will be summarized at the corresponding scheduled visit if the assessment was planned at that visit. An assessment is considered to correspond to a scheduled visit if it falls within the protocol-specified visit window. Assessments performed at an EDV that is not within the protocol-specified visit window of a scheduled visit will not be mapped to a scheduled visit. Re-mapped data will be displayed in the by visit summary tables only if the assessment was planned for that particular visit.

If any particular assessment data are already recorded at the given scheduled visit, data from the EDV visit will not be re-mapped. For example, if an EDV is performed within the same protocol-specified visit window as an existing scheduled MEV/FEV/YEV (eg Month 12) and a participant has a particular assessment (eg neurological examination) present at both Month 12 and EDV, then the neurological examination data from the EDV will not be re-mapped to Month 12.

Data will be re-mapped on a ‘per assessment’ basis where assessments are grouped as follows:

- All assessments from the neurological examination
- All assessments from the psychiatric and mental status assessments
- All vital signs assessments (systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate and temperature)
- All hematology assessments
- All clinical chemistry assessments
- All endocrinology assessments
- All urinalysis assessments
- All ECG assessments
- All EEG assessments

- Height and body weight
- All C-SSRS assessments
- All EpiTrack Junior assessments
- All PedsQL assessments

The groupings above define the measurements that will be retained together for any re-mapping. If at least one data point from a group of assessments is already available at the respective scheduled visit (eg, systolic blood pressure), the data at the EDV will not be re-mapped.

Handling of EEG assessments occurring at EDVs that are not mapped to scheduled visits is described in Section 3.13.8.

3.3.8 Mapping of assessment performed at FV

Efficacy and safety assessments at a FV will be summarized at the corresponding scheduled visit if the assessment was planned at that visit. An assessment is considered to correspond to a scheduled visit if it falls within the protocol-specified visit window. FVs will be mapped to scheduled visits using the approach outlined in Section 3.3.7.

Handling of EEG assessments occurring at FVs that are not mapped to scheduled visits is described in Section 3.13.8.

3.3.9 Mapping of assessments performed at UV

Assessments performed at unscheduled visits will not be remapped to any scheduled visit or EDV or FV, except in the following scenarios:

- Unscheduled assessments performed after the last visit in N01269 and on or before the date of the EV in EP0132 (Section 3.3.6)
- Unscheduled assessments performed for participants that remain in EP0132 study beyond 2 years (Month 24) before they complete or withdraw from the study. These unscheduled assessments will be mapped to scheduled visits using the approach outlined in Section 3.3.7. In the situation where there are two unscheduled visits mapped to the same scheduled visit, the visit nearest to the scheduled day as defined in Table 3-5 will be used. If the two unscheduled visits are the same distance away from the scheduled day, the earliest visit will take priority.
  - If an assessment is missing at the mapped visit, the missing assessment may be obtained from the alternative unscheduled visit, only if the entire group of assessments are missing (Assessments will be grouped as specified in Section 3.3.7). For example, if only systolic blood pressure is present at the mapped visit, diastolic blood pressure, respiratory rate, pulse rate and temperature will not be obtained from the alternative unscheduled visit.

Handling of unscheduled EEG assessments is described in Section 3.13.8.

3.3.10 Calculation of modal dose

Modal dose categories will be calculated across all study days on or after the day of first dose of BRV in EP0132 and up to and including the day of last dose of BRV in the Evaluation Period (excluding the Down-Titration Period). Modal dose is calculated as the most frequently taken daily dose category during this period. Modal dose will be categorized as defined in Table 3-6.

Table 3-6: Dose group definitions for calculation of modal dose

Daily dose category (mg/day)[a]	Equivalent mg/kg/day [b]	Dose group label
>0 to <100	>0.0 to <2.0	>0.0 to <2.0 mg/kg/day
≥100 to < 150	≥2.0 to <3.0	≥2.0 to <3.0 mg/kg/day
≥150 to <200	≥3.0 to <4.0	≥3.0 to <4.0 mg/kg/day
≥200	≥4.0	≥4.0 mg/kg/day

[a] Daily dose category is modified for participants weighing less than 50kg.
[b] For participants weighing ≥50kg, the dose in mg/kg/day is calculated based on a weight of 50kg. The permitted dose range for all participants is between 1 and 4 mg/kg/day.

To calculate modal dose, the following steps will be applied:

1. The total daily dose in mg/kg/day will be classified into 1 of the above categories on a daily basis
   - All participants are assigned 100 mg/day (or equivalently 2.0 mg/kg/day for study participants weighing less than 50kg) at the EV.
   - At the Telephone Call visit, the dose may be adjusted to 50 to 200mg/day (or equivalently 1.0 to 4.0 mg/kg/day for study participants weighing less than 50kg). This is documented on the Study Drug Dispensation and Administration eCRF. If 'maintain dose' is selected, the dose is continued from the EV. If 'modify dose' is selected then the new dose is documented in mg/day, and will be used to calculate the daily dose in mg/kg/day. It is assumed that any new dose is first taken the morning after it is dispensed.
   - Any subsequent changes to the daily dose in mg/day will be documented on the Study Drug Collection Dispensation and Administration eCRF. If 'maintain dose' is selected, the dose is continued from the 'daily dose at last visit' entered on the eCRF at that visit. If 'modify dose' is selected, then the new dose is documented in mg/day and will used to calculate the daily dose in mg/kg/day.
   - For participants with body weight <50kg, the total daily dose in mg/kg/day will be the total daily dose in mg divided by the most recently available body weight in kg.
   - For participants with body weight ≥50kg, the total daily dose in mg/kg/day will be the total daily dose in mg divided by 50kg.
   - Each daily dose will then be classified into 1 of the daily dose categories in mg/kg/day.

   The total daily dose will be attributed to a specific period (the Evaluation Period and additionally a 3-month period as defined in Table 3-3).
2. Once all total daily doses are converted to mg/kg/day and classified into 1 of the above categories, the modal dose is the dose category which was most frequent within the specific period. In the event of a tie, the modal dose will be set to the lower of the tied dose categories.

The modal dose category will be calculated for each 3-month period the participant enters regardless of the number of days completed in this period. A participant is considered to enter a

period if the end date of the Evaluation Period is on or after the first day of the relevant 3-month period.

3.4 Possibly clinically significant values

PCST values are any laboratory measurements, vital signs or ECG parameters which meet the criteria defined in Section 13.1 which occur any time after the first dose of BRV has been taken in EP0132. PCS criteria are based on Food and Drug Association Division of Neuropharmacological Drug Products guidelines with some UCB-defined additions. Assessment of whether a measurement fulfils age-dependent PCS criteria will be performed using the age of the participant in years at the visit. Measurements that meet PCS criteria and are treatment-emergent will be considered PCST regardless of whether or not they met the criteria for PCS previously.

3.5 Definition of Baseline values

The Baseline value derived within the N01269 analysis database will be used as the Baseline for EP0132 for the following variables:

- Demographics (including body weight and height)
- QTcB (ECG)
- Clinical laboratory assessments
- Vital signs
- Neurological examination (including psychiatric and mental status)
- EpiTrack Junior
- PedsQL

In cases where CFB is assessed, the change from N01269 Baseline will be calculated.

3.6 Protocol deviations

Important protocol deviations (IPDs) are deviations from the protocol that could potentially impact the interpretation of the study data. The criteria for identifying IPDs and the classification of IPDs will be defined separately in the Specifications for IPDs document. To the extent feasible, rules for identifying IPDs will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying IPDs will be implemented algorithmically to ensure consistency in the classification of IPDs across all study participants.

All completed COVID-19 impact eCRF pages will be discussed in IPD meetings in order to determine if any such events are to be considered and reported as IPDs.

All other IPDs will also be reviewed and discussed in IPD meetings.

3.7 Analysis sets

3.7.1 All Study Participants Screened Set

The All Study Participants Screened (ASPS) Set will consist of all screened study participants who gave informed consent (and informed assent where required).

3.7.2 Safety Set

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.

3.7.3 PK Analysis Set

The PK Analysis Set (PKAS) 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. This measurement may be quantifiable or below limit of quantification (BLQ).

Participants will be included in the PKAS only if the date and time of both dosing and PK sampling is available for at least 1 PK measurement.

3.8 Treatment assignment and treatment groups

This is an open-label study. Due to the large variation in the doses a study participant may receive throughout the study, outputs will be produced by actual syndrome (CAE/JAE) and all participants only. Selected outputs may also be produced by modal dose or maximum BRV dose.

3.9 Multicenter studies

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

3.10 Center pooling strategy

The number of study participants for most sites is expected to be low. No site pooling strategy is defined for this study.

3.11 Coding dictionaries

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. Medications will be coded using the World Health Organization Drug Reference List version SEP 2020. Medical procedures will not be coded.

3.12 Changes to protocol-defined analyses

3.12.1 Concomitant use of AEDs and the impact on secondary objectives

The secondary objectives in the protocol specify the analysis of absence seizure freedom data (based on EEG and diary data) and how to handle the concomitant use of AEDs in the analysis. Specifically, the protocol has the following text:

For ‘Absence seizure freedom within 4 days prior to or during the 1-hour EEG at each applicable visit’:

‘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).’

For ‘Absence seizure freedom based on diary over the entire evaluation period and by 3-month time intervals’:

'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 SAP has been updated to remove the word 'permitted' as all AEDs (both permitted and prohibited) may have an impact on the efficacy outcomes and should be considered in the analysis.

3.12.2 Truncation of absence seizure freedom data to Month 24 and the impact on secondary objectives

Per the protocol the secondary objectives and endpoints for absence seizure freedom and consecutive absence seizure freedom based on EEG and diary data do not specify the timeframe over which absence seizure freedom is assessed. Specifically, the protocol has the following text for these endpoints:

- 'Absence seizure freedom within 4 days prior to or during the 1-hour EEG at each applicable visit'
- 'Absence seizure freedom based on diary over the entire evaluation period and by 3-month time intervals'
- 'Consecutive absence seizure freedom in 6-month periods based on EEG'
- 'Consecutive absence seizure freedom in 6-month periods based on diary'

The SAP has been updated to include a timeframe for these endpoints. The absence seizure freedom and consecutive absence seizure freedom based on 1-hour EEG endpoint will be analyzed up to Month 24 YEV. The absence seizure freedom and consecutive absence seizure freedom based on seizure diary will be analyzed over the Evaluation Period truncated at the Month 24 YEV; the 3-month and 6-month time intervals will be analyzed up to Months 22-24 and Months 19-24, respectively.

3.12.3 EpiTrack Junior

According to the protocol, in the calculation of the EpiTrack Junior score the same age correction, using the age at EV, will be applied at all visits even if a participant changes age category during the study. However, the EpiTrack Junior author has confirmed that in a LTFU study the age correction for each participant should be consistent with the age correction used in the original study. The SAP has therefore been updated to state that the total adjusted EpiTrack Junior score will be obtained from the total unadjusted EpiTrack Junior score by applying an age correction using the participant age at N01269 Baseline for all assessments.

3.13 Definitions of study specific derived variables

3.13.1 Seizures

Each seizure code in the EEG and Seizure Classification eCRFs will be assigned to exactly 1 of the following codes based on the 1981 International League Against Epilepsy (ILAE) classification: IA+IB, IC, IIA (Absence), IIB, IIC, IID, IIE, IIF or III.

3.13.1.1 Non-absence seizures

All non-absence seizures will be categorized into 1 of 3 types:

- Partial onset seizures: "POS"
- Tonic-clonic seizures: "Tonic-clonic"
- All other type 2 or 3 seizures: "All other type 2 and 3 seizures"

The following ILAE categories will contribute to the above categories:

- POS: IA, IB, IC
- Tonic-clonic: IIE
- All other type 2 and 3 seizures: IIB, IIC, IID, IIF, III

3.13.2 Absence seizure freedom during the 1-hour EEG (including dropouts)

The endpoint of absence seizure freedom on 1-hour EEG with no concomitant use of any AEDs, including benzodiazepines, within 4 days prior to or during the EEG will be assessed at each scheduled EEG visit up to and including the Month 24 YEV (or FV, if applicable) or EDV.

At each timepoint, a study participant is defined as absence seizure free if they meet all the following criteria:

1. 1-hour EEG was conducted on the study participant
2. Quality of 1-hour EEG while awake deemed sufficient for analysis
3. No absence seizure identified while awake on 1-hour EEG
4. No concomitant use of any AEDs, including benzodiazepines, on the day of initiating and during the 1-hour EEG or the 4 study days prior to it

Specific algorithmic rules for each of the above criteria are defined as follows:

Criterion 1: A study participant is defined as receiving the 1-hour EEG if there is a record that this test was conducted in the eCRF.

Criterion 2: The EEG is deemed of sufficient quality if at least 30 minutes of readable EEG while awake is recorded, as reported on the EEG eCRF.

Criterion 3: 1-hour EEG with no absence seizures recorded on the EEG eCRF (ILAE code IIA).

Criterion 4: No records of any concomitant AED, including benzodiazepines usage on the Concomitant Medications eCRF on the day of initiating the 1-hour EEG, or the 4 days prior to it.

Note that Criteria 2, 3 and 4 can only be assessed if Criterion 1 is met.

At each timepoint, if the study participant does not meet all the criteria for absence seizure freedom they will be regarded as not absence seizure free. If a participant discontinues the study early, prior to Month 24, they will be imputed as not absence seizure free for all subsequent scheduled visits after the EDV until Month 24. If a participant has a FV prior to the Month 24 assessment visit, they will not be included in any summaries for the scheduled visits following the FV.

In the event where multiple scheduled locally read 1-hour EEGs are recorded at the same timepoint, only the first EEG will be used for analysis, regardless of the quality of this EEG. The later EEGs will be considered as exploratory and listed only.

3.13.3 Absence seizure freedom during the 1-hour EEG (excluding dropouts)

The endpoint of absence seizure freedom based on 1-hour EEG with no concomitant use of any AEDs , including benzodiazepines, within 4 days prior to or during the EEG excluding dropouts will be assessed at each scheduled EEG visit up to and including the Month 24 YEV (or FV, if applicable). If a study participant misses a scheduled EEG and does not discontinue the study within the protocol defined visit window for that EEG, they will be imputed as not absence seizure free at the visit. If a study participant discontinues the study early, they will not be included in the analysis for any subsequent visits. If a participant has a FV prior to the Month 24 assessment visit, they will not be included in any summaries for the scheduled visits following the FV.

The endpoint of absence seizure freedom will be derived in the same way as described in Section 3.13.2.

At each timepoint, if the study participant does not meet all the criteria for absence seizure freedom they will be regarded as not absence seizure free.

In the event where multiple scheduled locally read 1-hour EEGs are recorded at the same timepoint, only the first EEG will be used for analysis, regardless of the quality of this EEG. The later EEGs will be considered as exploratory and listed only.

3.13.4 Absence seizure freedom based on diary (including dropouts)

The endpoint of absence seizure freedom based on diary will be assessed at 3-month time intervals within the Evaluation Period, as defined in Table 3-3, and over the entire Evaluation Period. The Evaluation Period may include any additional diary entries collected from the end of the Months 22 to 24 period up to the Month 24 YEV where the Evaluation Period is truncated for participants who reach the Month 24 YEV.

In each 3-month period (or Evaluation Period), a study participant is defined as absence seizure free if they meet all the following criteria:

1. The study participant completed their seizure diary on at least 80% of days within the relevant period. Seizure diary is defined as completed if “Diary completed” is answered “Yes” for each applicable day in the period. If “Diary completed” is answered “No” or the diary record is missing it will be defined as not completed for that day.
2. No absence seizures are reported in the seizure diaries in the relevant period
3. No concomitant use of any AEDs, including benzodiazepines during the relevant period

Specific algorithmic rules for each of the above criteria are defined as follows:

Criterion 1: Seizure diary data is reported on the Seizure Classification eCRF for at least 80% of the days within the relevant period

Criterion 2: No diary records on the Seizure Classification eCRF within the relevant period are reported with answer “Yes” to the question “Did Any Absence Seizures occur?”

Criterion 3: No records of any concomitant AED , including benzodiazepines, usage on the Concomitant Medications eCRF within the relevant period

Note that Criterion 2 and 3 will only be assessed if Criterion 1 is met. In each 3-month period (or Evaluation Period), if the study participant does not meet all the criteria for absence seizure freedom they will be regarded as not absence seizure free.

If a study participant discontinues the study during a 3-month period then Criterion 1 will be checked based on the full 3-month period and if met, the participant will be assessed for absence seizure freedom in the period of discontinuation. If Criterion 1 is not met, absence seizure freedom status will be imputed as not absence seizure free for the period of discontinuation and all subsequent 3-month periods, ending at Months 22 to 24. Study participants who discontinue the study early will still be included in the analysis conducted on the Evaluation Period.

If a study participant has a FV during a 3-month period then Criterion 1 will be checked based on the full 3-month period and if met, the participant will be assessed for absence seizure freedom in the period of the FV. If Criterion 1 is not met, the participant will not be included in the summary for that period and all subsequent 3-month periods, ending at Months 22 to 24. Study participants who have a FV prior to the scheduled Month 24 YEV will still be included in the analysis conducted on the Evaluation Period.

3.13.5 Absence seizure freedom based on diary (excluding dropouts)

The endpoint of absence seizure freedom based on diary will be assessed at 3-month time intervals within the Evaluation Period, as defined in Table 3-3, and over the entire Evaluation Period. The Evaluation Period may include any additional diary entries collected from the end of the 3-month Months 22 to 24 period up to the Month 24 YEV where the Evaluation Period is truncated for participants who reach the Month 24 YEV.

The derivation will be the same as Section 3.13.4 apart from if a study participant discontinues or completes the study during a 3-month period then Criterion 1 will be checked and if met, the participant will be assessed for absence seizure freedom in the period of discontinuation. If they do not meet Criterion 1 during the period of study discontinuation the study participant will not be included in the analysis for that period. Additionally, they will not be included in the analysis of any period subsequent to that of study discontinuation or completion. If a study participant discontinues the study at any time before the scheduled Month 24 YEV, they will not be included in the analysis conducted on the Evaluation Period. However, if a study participant has a FV prior to the scheduled Month 24 YEV, they will be included in the analysis conducted on the Evaluation Period.

3.13.6 Absence seizure freedom based on diary with modified criterion based on seizure diary completion (including dropouts)

The endpoint of absence seizure freedom based on diary with modified criterion based on seizure diary completion (including dropouts) will be derived in the same way as the endpoint defined in Section 3.13.4, however Criterion 1 will be updated to require a minimum of 50% of days of seizure diary completion within the relevant period.

3.13.7 Absence seizure freedom based on diary with modified criterion based on seizure diary completion (excluding dropouts)

The endpoint of absence seizure freedom based on diary with modified criterion based on seizure diary completion (excluding dropouts) will be assessed at 3-month time intervals within the Evaluation Period, as defined in Table 3-3, and over the entire Evaluation Period. The Evaluation Period may include any additional diary entries collected from the end of the Months 22 to 24 period up to the Month 24 YEV where the Evaluation Period is truncated for participants who reach the Month 24 YEV.

The derivation will be the same as Section 3.13.4, however Criterion 1 will be updated to require a minimum of 50% of days of seizure diary completion within the relevant period. If a study participant discontinues or completes the study during a 3-month period then Criterion 1 will be checked and if met, the participant will be assessed for absence seizure freedom in the period of discontinuation. If they do not meet Criterion 1 during the period of study discontinuation the study participant will not be included in the analysis for that period. Additionally, they will not be included in the analysis of any period subsequent to that of study discontinuation or completion. If a study participant discontinues the study at any time before the scheduled Month 24 YEV, they will not be included in the analysis conducted on the Evaluation Period. However, if a study participant has a FV prior to the Month 24 YEV, they will be included in the analysis conducted on the Evaluation Period.

3.13.8 Consecutive absence seizure freedom based on EEG

The endpoint of consecutive absence seizure freedom based on EEG is defined per 6-month period as having no absence seizures on scheduled or unscheduled EEGs during that period.

The endpoint of cumulative consecutive absence seizure freedom based on EEG is defined per 6-month period as having no absence seizures on scheduled or unscheduled EEGs during that period and all preceding periods.

Consecutive absence seizure freedom based on 1-hour EEG will be assessed at each FEV, YEV, and FV, as applicable, individually and cumulatively at each visit, truncated at the Month 24 YEV (for participants who reach Month 24). The derivation will be the same as that outlined in Section 3.13.2, except without the consideration of concomitant AEDs or benzodiazepines usage. In addition, for this analysis, unscheduled EEGs and EEGs performed at the EDV that were not mapped to a scheduled visit will be considered.

In each 6-month period, a study participant is defined as absence seizure free if they meet all the following criteria:

1. At least one 1-hour EEG (either scheduled or unscheduled) was conducted on the study participant at any time up to and including the scheduled FEV or YEV at the end of the 6-month period
2. Quality of at least one 1-hour EEG while awake deemed sufficient for analysis
3. No absence seizure identified while awake on any 1-hour EEG (scheduled and unscheduled) performed within the specified period

Specific algorithmic rules for each of the above criteria are defined as follows:

Criterion 1: A study participant is defined as receiving the 1-hour EEG if there is a record in the eCRF that at least one 1-hour EEG was conducted (either scheduled or unscheduled) within the 6-month period.

Criterion 2: The EEG is deemed of sufficient quality if at least 30 minutes of readable EEG while awake is recorded for at least one 1-hour EEG during the specified 6-month period. Note that if a participant has more than one 1-hour EEG during a 6-month period, it is only necessary to meet this criterion for one of these assessments.

Criterion 3: 1-hour EEG with no absence seizures recorded on the EEG eCRF (ILAE code IIA). Note that Criterion 3 must be met for all EEGs performed within the specified 6-month period regardless of whether each of these EEGs fulfils Criterion 2.

Note that Criterion 2 and 3 can only be assessed if Criterion 1 is met.

In each 6-month period, if the study participant does not meet all the criteria for absence seizure freedom they will be regarded as not absence seizure free.

In the event of an unscheduled EEG or an EEG performed at an EDV or FV that has not been mapped to a scheduled visit, if this EEG is on the same day as a scheduled visit this will be attributed in the analysis to the 6-month period of the scheduled visit. Otherwise, if this is not on the same day as a scheduled visit, this will be attributed in the analysis to the 6-month period of the following scheduled visit. For example, if an unscheduled EEG is performed between the Month 6 FEV and the Month 12 YEV, this will be considered in the analysis for the Month 12 YEV. As a further example, if an unscheduled EEG is performed on the same day as the Month 24 YEV, this will be considered in the analysis for the Month 24 YEV.

In the event of a missed scheduled visit any unscheduled EEG will be attributed to the period of time between the preceding visit and the next planned scheduled assessment visit relative to the EV, as defined in Table 3-5. For example, if an unscheduled EEG is performed after the Month 9 MEV and the scheduled Month 12 YEV is missing, then the unscheduled Month 9 assessment will be considered in the analysis for the period from the day after the Month 6 FEV up to and including Day 365 (Protocol scheduled assessment day for Month 12 YEV).

If a participant discontinues early, their EEG performed at the EDV will be attributed to the 6-month periods of time following the preceding visit. For example, if an EDV is performed at Month 9 MEV, then the EDV assessment will be considered in the analyses for the periods from the day after the Month 6 FEV up to and including Day 365 (Protocol scheduled assessment day for Month 12 YEV). All subsequent 6-month periods for the participant will be regarded as not absence seizure free.

If a participant has a FV prior to the scheduled Month 24 YEV, their EEG performed at the FV will be attributed to the 6-month period of time following the preceding visit. For example, if a FV is performed at Month 9 MEV, then the FV assessment will be considered in the analyses for the period from the day after the Month 6 FEV up to and including Day 365 (Protocol scheduled assessment day for Month 12 YEV). The participant will not be included in the analyses for all subsequent 6-month periods.

If a participant is regarded as absence seizure free at the scheduled FEV or YEV assessment (or at EDV) and absence seizure free at all unscheduled assessments since the last scheduled FEV or YEV assessment, then they will be regarded as absence seizure free in that 6-month period in the

consecutive analysis. If a participant is regarded as not absence seizure free at the scheduled FEV or YEV assessment (or at EDV) or at any unscheduled assessments since the last scheduled FEV or YEV visit, then they will be regarded as not absence seizure free for that 6-month period.

For the cumulative consecutive absence seizure freedom analysis, a study participant will be categorized as absence seizure free until the 6-month period in which they are first classified as not absence seizure free. After the recurrence of absence seizures, the participant is classified as not absence seizure free regardless of whether they met the criteria for absence seizure freedom in subsequent 6-month periods.

If a participant discontinues early, all subsequent 6-month periods for the participant are considered as not absence seizure free, regardless of their cumulative absence seizure status at the time of the EDV.

If a participant performs a FV prior to the Month 24 YEV and becomes not absence seizure free at any point prior to the FV then the participant will remain in the analyses for subsequent 6-month periods as not absence seizure free. However, if the participant performs a FV prior to the Month 24 YEV and they remain absence seizure free until the FV then they will remain in the analyses until the period of the FV, and will be excluded from the analyses for all subsequent 6-month periods.

3.13.9 Consecutive absence seizure freedom based on diary

The endpoint of consecutive absence seizure freedom based on diary is defined, per 6-month period within the Evaluation Period, as having no absence seizures during that period. This will be assessed at 6-month time intervals within the Evaluation Period, as defined in Table 3-4, and over the entire Evaluation Period. Consecutive absence seizure freedom for the Evaluation Period is defined as having no absence seizures for the entire Evaluation Period which also includes any additional diary entries collected from the end of the 6-month Months 19 to 24 period up to the Month 24 YEV where this is truncated for participants who reach the Month 24 YEV.

The endpoint of cumulative consecutive absence seizure freedom is defined, per 6-month period within the Evaluation Period, as having no absence seizures during that period and all preceding periods (where applicable). This will be assessed at 6-month time intervals within the Evaluation Period, as defined in Table 3-4.

The derivation will be the same as that outlined in Section 3.13.4, except without the consideration of concomitant AEDs or benzodiazepines usage.

In each 6-month period (or Evaluation Period), a study participant is defined as absence seizure free if they meet all the following criteria:

1. The study participant completed their seizure diary on at least 80% of days within the relevant period. Seizure diary is defined as completed if “Diary completed” is answered “Yes” for each applicable day in the period. If “Diary completed” is answered “No” or the diary record is missing it will be defined as not completed for that day.
2. No absence seizures are reported in the seizure diaries in the relevant period

Specific algorithmic rules for each of the above criteria are defined as follows:

Criterion 1: Seizure diary data is reported on the Seizure Classification eCRF for at least 80% of the days within the relevant period

Criterion 2: No diary records on the Seizure Classification eCRF within the 6-month period are reported with answer "Yes" to the question "Did Any Absence Seizures occur?"

Note that Criterion 2 will only be assessed if Criterion 1 is met. In each 6-month period (or Evaluation Period), if the study participant does not meet all the criteria for absence seizure freedom they will be regarded as not absence seizure free.

If a study participant discontinues the study during a relevant period then Criterion 1 will be checked and if met, the participant will be assessed for absence seizure freedom in the period of discontinuation. If Criterion 1 is not met, then the status will be imputed as not absence seizure free for that specific period and for all subsequent 6-month periods (where applicable), ending at Months 19 to 24.

If a study participant has a FV during a relevant period then Criterion 1 will be checked and if met, the participant will be assessed for absence seizure freedom in the period of the FV. If Criterion 1 is not met, then the participant will not be included in the analyses for that specific period and for all subsequent 6-month periods (where applicable), ending at Months 19-24.

For the cumulative consecutive absence seizure freedom analysis, a study participant will be categorized as absence seizure free until the 6-month period in which they are first classified as not absence seizure free. After the recurrence of absence seizures, the participant is classified as not absence seizure free regardless of whether they met the criteria for absence seizure freedom in subsequent 6-month periods.

If a participant discontinues early, all subsequent 6-month periods for the participant are considered as not absence seizure free, regardless of their cumulative absence seizure status at the time of the EDV.

If a participant performs a FV before the end of the Month 19-24 period and becomes not absence seizure free at any point prior to or at the FV then the participant will remain in the analyses for subsequent 6-month periods as not absence seizure free. However, if the participant performs a FV before the end of the Month 19-24 period, and they remain absence seizure free until the FV, then they will remain in the analyses until the period of the FV if they met Criterion 1 during the period of the FV, or the period prior if they did not meet Criterion 1 during the period of the FV, and will be excluded from the analyses for all subsequent 6-month periods.

3.13.10 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. Additionally, Last Assessment will be derived based on the last EpiTrack Junior assessment conducted post EV, for each participant in EP0132. Study participants who become 6 years old after EV will be assessed for all visits they are aged ≥6 years.

The EpiTrack Junior at the EV in EP0132 will be taken from the last visit in the N01269 analysis database. This will be applicable only for participants who discontinue early in N01269 and have an EDV assessment, or for participants having an unscheduled assessment after the last visit in N01269 and before or on the date of the EP0132 EV.

The screening tool consists of 6 subtests: interference, numbers, numbers and dots, maze test, verbal fluency, and inverted digit span.

The EpiTrack Junior eCRF will be populated with the raw score (ie, number of seconds for subtests 1-4, number of words for subtest 5 and number of figures in highest successful sequence for subtest 6) for each of the subtests, and the borderline assessment. Results from each subtest raw score will be converted in a score from 1 to 7 points as described in Table 3-7. These conversions are taken from the EpiTrack questionnaire.

Table 3-7: Converting EpiTrack raw values to points

	Points						
Subtest	**7**	**6**	**5**	**4**	**3**	**2**	**1**
Interference (seconds)	≤12	13-22	23-32	33-42	43-52	53-62	≥63
Numbers (seconds)	≤10	11-25	26-40	41-55	56-70	71-85	≥86
Numbers and dots (seconds)	≤19	20-45	46-71	72-97	98-123	124-149	≥150
Maze Test (seconds)	≤11	12-23	24-35	36-47	48-59	60-71	≥72
Verbal Fluency (number of words)	≥25	18-24	11-17	4-10	0-3		
Inverted Digital Span (number of figures)	≥6	5	3-4	2	0		

The total unadjusted EpiTrack Junior score will be calculated as the sum of the 6 subtest scores in points. If a study participant is missing any of the raw scores, then the total unadjusted EpiTrack Junior score will be missing.

The total adjusted EpiTrack Junior score will be referred to as "EpiTrack score" and will be obtained from the total unadjusted EpiTrack Junior score by applying an age correction as presented in Table 3-8 (age correction taken from the EpiTrack form). The age correction will use the participant age at N01269 Baseline for all assessments, if the participant was aged ≥ 6 at N01269 Baseline. For participants aged <6 years at N01269 Baseline the age correction will be based on an age of 6 years from the time the first EpiTrack Junior score is completed in either N01269 or EP0132.

Table 3-8: EpiTrack age corrections

Age	Correction
6 years old	+14
7 years old	+7
8 years old	+4
9 years old	+2
10 years old	None
11-14 years old	-2
15-18 years old	-4

Additionally, if the investigator has ticked the "borderline cases" box at N01269 Baseline, or at the first visit at which the EpiTrack was assessed (investigator may add one more point for "male subjects younger than 13 years old" and for "subjects that do/did not attend any secondary school") one point will be added when deriving the EpiTrack score at this and at all subsequent time points.

Study participants will be classified into a cognitive performance category based on their EpiTrack score:

- "Good": ≥36 points
- "Average": 31-35 points
- "Mildly impaired": 29-30 points
- "Significantly impaired": ≤28 points

The CFB in the EpiTrack score will be calculated by subtracting the N01269 Baseline result from the EV/FEV/YEV/EDV/FV/SV/Last Assessment result. CFB will therefore not be calculated for participants who did not complete the EpiTrack at N01269 Baseline.

Study participants will be classified into categories of change in cognitive function as specified on the EpiTrack form:

- "Improved": change in score ≥3
- "Unchanged": change in score between -1 to 2
- "Worsened": change in score ≤-2

3.13.11 PedsQL

The PedsQL Measurement Model is a modular approach to measuring health-related quality of life (HRQOL) in healthy children and adolescents and those with acute and chronic health conditions (Varni et al, 2001). This will be conducted at FEVs, YEVs, and EDV or FV (as

applicable). Additionally, Last Assessment will be derived based on the last PedsQL assessment conducted post EV for each participant in EP0132.

The PedsQL Generic core module is a reliable and valid measure which has been used in a variety of health conditions and is responsive to change over time. It consists of 23 questions (or 21 items for the parent proxy report for ages 2 to ≤4).

Two versions are available: study participant self-report for ages 5 to ≤7, 8 to ≤12, 13 to ≤18; parent proxy report for ages 2 to ≤4, 5 to ≤7, 8 to ≤12, 13 to ≤18.

The PedsQL at the EV in EP0132 will be taken from the last visit in the N01269 analysis database. This will be applicable only for participants who discontinue early in N01269 and have an EDV assessment, or for participants having an unscheduled assessment after the last visit in N01269 and before or on the date of the EP0132 EV. The version of the PedsQL at the EV will be consistent with the version that was used at Baseline in N01269. All subsequent assessments of PedsQL in EP0132 will use the version consistent with the age of the participant at the time of assessment and will use the 1-week recall period version. Participants who turn 5 years old after the N01269 Baseline assessment will only have a parent proxy report at Baseline as there is no self-report for ages 2 to ≤4.

PedsQL generic core scale scores will be calculated for each of the four PedsQL dimensions: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items [or 3 items for the parent proxy report for ages 2 to ≤4]). The PedsQL used in this study is retrospective to the prior week (acute version), and individual items are scored using a 5-point Likert scale (0 to 4 representing responses of: “never”, “almost never”, “sometimes”, “often”, or “almost always”), with the exception of the 5 to 7 year old participant-self-report, which has a scale of 0, 2, and 4 representing responses “not at all”, “sometimes”, and “a lot” respectively. The PedsQL generic item raw scores will be recorded in the eCRF.

These raw item scores of 0 to 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 HRQoL. Each dimension score is then calculated as the mean of the transformed item scores from items of the considered dimension: items 1 to 8 for Physical Functioning, 9 to 13 for Emotional Functioning, 14 to 18 for Social Functioning and 19 to 23 for School Functioning (except for the parent proxy report for 2-4 year olds where items 19 to 21 constitute the School Functioning dimension). In the case of item-level missing data, these will be replaced by the average of non-missing item scores from the respective dimension, if at least 50% of the items from that dimension are non-missing.

Summary scores will also be generated:

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

scores (Physical, Emotional, Social, or School Functioning) would be missing, the Total score will be set to missing.

The CFB in each dimension and summary score will be calculated separately for both PedsQL versions (participant self-report and parent proxy report) by subtracting the N01269 Baseline result from the EV/FEV/YEV/EDV/FV/Last Assessment result. This is re-written as a formula below:

$$\text{CFB} = \text{Score at timepoint} - \text{Score at Baseline}$$

Note that for participants aged 2 to 4 years old at N01269 Baseline, the CFB will not be calculated for the parent proxy report for assessments after the participant turns 5 years old as the 2 to 4 years old parent proxy report includes fewer items. For all other age groups, the CFB will be calculated across the different age versions of the report as the content of the reports are comparable. For example, the CFB for a participant aged 7 at Baseline will still be calculated when the participant becomes 8 years old and the 8 to ≤12 years old self-report and parent proxy report are now completed.

A meaningful change in PedsQL scores is defined based on the Minimal Clinically Important Difference (MCID) values obtained in Varni et al, (2003) and presented in Table 3-9. Note that the meaningful change categorization will not be assessed for the 2 to 4 years old parent proxy report.

For each PedsQL score:

- Improvement is defined as: CFB ≥ MCID
- No change is defined as: -MCID < CFB < MCID
- Worsening is defined as: CFB ≤ -MCID

Table 3-9: Thresholds to define meaningful change

Score	MCID (child self-report)	MCID (parent proxy report)
Total score	4.36	4.50
Physical Health	6.66	6.92
Psychosocial Health	5.30	5.49
Emotional Functioning	8.94	7.79
Social Functioning	8.36	8.98
School Functioning	9.12	9.67

MCID=Minimal Clinically Important Difference

3.13.12 Dose from which study participant discontinued

The dose of study drug the study participant was taking the day they were discontinued from study will be derived as the most recent daily dose in mg reported in the Study Drug Collection Dispensation and Administration eCRF, prior to discontinuation for participants whose dose had been modified during the study. For participants whose dose has been maintained throughout the study, the prescribed starting dose of 100mg/day at the EV (or equivalently 2mg/kg/day for study

participants weighing less than 50kg) will be the dose from which they discontinued. The number of days the study participant received this dose will be calculated as follows:

Date of study discontinuation (or date of last dose if this is prior to date of study discontinuation) – the date of the first administration at the dose level from which they discontinued the study + 1.

The calculation assumes that any new dose is first taken the morning after it is dispensed. If a study participant discontinues from the study the day after a dose is modified, it will be assumed that they are discontinuing from the most recently modified (new) dose.

3.13.13 Dose at AE onset

The dose of study drug the study participant was taking at the onset of an AE will be derived as the most recent daily dose (in mg) reported in the Study Drug Collection Dispensation and Administration eCRF, prior to the onset date of the AE. AEs with onset date on the same day as a dose level change will be considered to have started prior to the dose change and will therefore be attributed to the preceding dose level. For AEs with an onset date on the same date as the EV, the dose at onset will be the prescribed starting dose of 100mg/day (or equivalently 2mg/kg/day for study participants weighing less than 50kg). For participants whose dose has been maintained throughout the study since the EV, the prescribed starting dose will be used as the dose at AE onset throughout the study.

The dose at AE onset will not be derived for AEs ongoing from N01269.

3.13.14 Day of last dose of study drug

The day of last dose of BRV is defined as the day of FV or EDV for participants who do not down-titrate, or the day of the DTV for participants who do down-titrate. For participants who are lost to follow up, the last dose of BRV will be the date of last dose as recorded on the Study Termination eCRF (imputed, if applicable, as described in Section 4.1.4.5).

3.13.15 Total number of days on study drug

The total number of days a study participant received the study drug in EP0132 is defined as the day of last dose of BRV – date of first dose in EP0132 +1. The day of last dose of BRV is defined in Section 3.13.14.

3.14 Plasma concentrations

For the calculation of descriptive statistics, a BRV plasma concentration below the Lower Limit of Quantification (LLOQ) is substituted by LLOQ/2. For diluted samples which are reported as <XX.X, the result will be substituted with LLOQ/2 based on the LLOQ level for the undiluted samples for the purposes of PK summaries. BRV plasma concentration results above the upper limit of quantification will not be substituted and will be regarded as missing in the PK summaries.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Handling of dropouts or missing data

4.1.1 Missing data

4.1.1.1 Seizure data

Six analyses of the proportion of study participants with absence seizure freedom will be conducted: 2 using 1-hour EEG, and 4 using seizure diaries. These analyses will be conducted as described in Sections 3.13.2, 3.13.3, 3.13.4, 3.13.5, 3.13.6, and 3.13.7 respectively; for each of EEG, seizure diary, and seizure diary with modified criterion there is one analysis with imputation of non-response truncated at 24 months for participants who discontinue the study early, and one with no imputation of non-response for participants who discontinue the study early. There will be no missing data for the imputation analysis, as a study participant who does not meet all the criteria for absence seizure freedom will be regarded as not absence seizure free.

The proportion of 1-hour EEGs without absence seizure freedom will be artificially increased if some criteria have not been completed, hence every effort should be made to follow-up on missing criteria. All 1-hour EEGs with missing criteria should be discussed at DEMs, in order to determine the current stage of data management (ie, queried, response, resolution), the reason for the missingness (if available) and if additional sensitivity analysis are required. Also, note that 1-hour EEG listings will include information on which criteria have been met, not met, and are missing.

4.1.1.2 Adverse events

Missing data for AEs will be handled as follows:

- When relationship is not specified the AE is considered as related
- When intensity is not specified, the AE will be considered to be of severe intensity

4.1.2 Laboratory data

Laboratory values that are BLQ (eg, <X.X) will be imputed with value equal to the limit of quantification (ie, X.X) for the summarization of data. Laboratory values will be listed as received, prior to the substitution of any BLQ values.

4.1.3 Potential impact of Coronavirus Disease 2019 on dropouts or missing data

The COVID-19 pandemic may cause disruption in the conduct of ongoing clinical trials including treatment and study withdrawals, study participants missing study visits, and/or visits being performed remotely instead of at site. Sites will complete a COVID-19 Impact eCRF page in case a study participant was impacted by COVID-19 during the study. The COVID-19 Impact eCRF page will include the timing and impact of COVID-19, and the relationship to COVID-19 (ie, whether the study participant has confirmed/suspected COVID-19 infection, or whether the impact was due to general circumstances around COVID-19 without infection).

A study participant will be regarded as not absence seizure free based on EEG at a given visit if either the EEG was not performed or the EEG was performed but one or more criteria for absence seizure freedom were missing, regardless of whether the missing data was due to COVID-19. The impact of the COVID-19 pandemic for all endpoints will be assessed at DEMs,

and if considered significant, then sensitivity analyses may be conducted to assess the effect of the pandemic.

To assess the impact of COVID-19 vaccination on safety, selected summaries of TEAEs that are not exclusively related to COVID-19 vaccination will be presented, as described in Section 10.2.1. In addition, a listing of COVID-19 vaccination related AEs will be produced, as described in Section 10.2.2.

4.1.4 Handling of partial or missing dates

4.1.4.1 General imputation rule for incomplete dates

In all imputations for incomplete dates, the date of first dose of BRV refers to the date of first dose in EP0132. Where necessary for the calculation of derived variables, partial dates will be completed using the earliest calendar date based on the partial date provided. This rule is valid for all partial dates with the exception of the following:

- Date of birth (only year of birth is provided, and no imputation for the missing day and month will be conducted)
- Start and stop dates of medications
- Start date of AEs
- Start date of study medication

Completely missing dates will not be replaced (unless stated otherwise) and the corresponding derived variables will be set to missing.

4.1.4.2 Handling of partial date of birth

The full date of birth will not be presented. Only the year of birth will be presented for all study participants, and the day and month will not be imputed. Age will not be calculated from date of birth in this study. Age in months and years will be collected at each scheduled visit.

4.1.4.3 Handling of medications with partial or missing date

Any medications with incomplete start and end dates will be handled according to the following rules for classification as previous, concomitant, and follow-up. Such imputations will only be performed for these classifications and calculations; in the listings all data will be shown as recorded on the eCRF.

Imputation of partial start dates:

- For medications that are not ongoing from N01269:
  - If only the month and year are specified and the month and year of the first dose of study treatment in EP0132 is not the same as the month and year of the start date, then use the 1st of the month
  - If only the month and year are specified and the month and year of first dose of study treatment in EP0132 is the same as the month and year of the start date of the medication, then use the date of first dose of study treatment in EP0132
  - If only the year is specified, and the year of first dose of study treatment in EP0132 is not the same as the year of the start date, then use January 1st of the year of the start date

  - If only the year is specified, and the year of first dose of study treatment in EP0132 is the same as the year of the start date of medication then use the date of first dose of study treatment in EP0132
  - If the start date is completely unknown then use the date of first dose of study treatment in EP0132
  - If the day and year are specified, but not the month, then treat the date as if the day and month are missing using the rules above
- For medications that are ongoing from N01269:
  - If only the year is specified, then use January 1st of the year of the start date
  - If the start date is completely unknown, then use the date of first dose of study treatment in N01269

Imputation of partial stop dates:

- If only the month and year are specified, then use the last day of the month, unless the participant has died during the month, in which case use the date of death
- If only the year is specified, then use December 31st of that year, unless the participant has died during the year, in which case use the date of death
- If the stop date is completely unknown, and the study participant has died during the study, use the date of death
- If the stop date is completely unknown, and the study participant has not died during the study, do not impute the stop date. Such medications will be considered to be ongoing and therefore concomitant unless the medication started in the Safety Period (Section 3.3.2)
- If the full date of death is unavailable, then use the last day of the month of the date of death

In the event of ambiguity or incomplete data which makes it impossible to determine whether a medication was concomitant or not, the medication will be considered as concomitant.

4.1.4.4 Handling of adverse events with partial or missing date

Any AEs with incomplete onset dates will be handled according to the following rules for classification as pre-treatment AEs and treatment-emergent AEs. Such imputations will only be performed for these classifications; in the listings all data will be shown as recorded on the eCRF.

Imputation of partial AE onset dates:

- For AEs that are not ongoing from N01269:
  - If only the month and year are specified and the month and year of the first dose of study treatment in EP0132 is not the same as the month and year of AE onset, then use the 1st of the month
  - If only the month and year are specified and the month and year of the first dose of study treatment in EP0132 is the same as the month and year of AE onset, then use the date of the first dose of study treatment in EP0132.

  - If only the year is specified and the year of the first dose of study treatment in EP0132 is not the same as the year of AE onset, then use January 1st of the year of the start date
  - If only the year is specified, and the year of the first dose of study treatment in EP0132 is the same as the year of AE onset, use the date of first dose of study treatment in EP0132
  - If the AE onset date is completely unknown then use the date of first dose of study treatment in EP0132
  - If the day and year are specified, but not the month, then treat the date as if the day and month are missing using the rules above
- For AEs that are ongoing from N01269:
  - If only the month and year are specified and the AE is marked as ongoing from N01269, then use the 1st of the month
  - If only the year is specified, then use January 1st of the known year
  - If the AE onset date is completely unknown, then use the date of first dose of study treatment in N01269

There will be no imputation of partially or completely missing AE end dates as this is not required to determine if an AE is treatment-emergent.

In the event of ambiguity or incomplete data which makes it impossible to determine whether an AE was treatment-emergent or not, the AE will be considered as treatment-emergent.

4.1.4.5 Handling of study medication with partial or missing date

No imputation should be performed for missing study medication start dates. This field on the eCRF should not be partial or missing.

The last dose of study medication for participants who down-titrate will be the last dose during the Down-Titration Period; for participants who do not down-titrate, the last dose of study medication will be the date of either the EDV or the FV (unless the participant reports stopping study medication earlier). For partial or missing date of last dose of study medication on the Study Termination eCRF, the following imputation rules will be applied for the purpose of calculating overall exposure:

- If only the month and year are specified, impute the last dose date as the earliest of the last day of the month or the date of last contact reported on the Study Termination eCRF. If the participant has died during the month use the date of death if this is earlier
- If only the year is specified, impute the last dose date as the earliest of the last day of the year or the date of last contact on the Study Termination eCRF. If the participant has died during the year use the date of death if this is earlier
- If the last dose date is completely unknown on the Study Termination eCRF and no information could be obtained from data cleaning exercises, then use the date of last contact unless the participant has died during the year, in which case use the date of death. A review of the data for study participants with completely unknown last dose dates should be performed to ensure that the imputation does not result in an unrealistic value for duration of exposure

Imputed date of last dose dates should only be used for calculation of the duration of exposure. The date as recorded on the eCRF should be presented in study participant data listings (no imputed dates should be included in study participant data listings).

4.1.5 Handling of multiple assessments at a visit

If multiple EEGs, central laboratory assessments, ECGs or vital signs are recorded at the same visit, the first non-missing result (according to time of assessment recorded on the eCRF) will be used in summaries by visit. Assessments of PCS criteria will consider all assessments (scheduled and unscheduled) recorded during the period of interest.

4.2 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.

4.3 Multiple comparisons/multiplicity

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

4.4 Examination of subgroups

All outcomes will be evaluated by actual syndrome, as reported in N01269 (JAE/CAE); in addition, selected outcomes may be evaluated by COVID-19 Period (during pandemic vs post pandemic) if deemed appropriate. The impact of COVID-19 will be discussed at DEMs (as described in Section 4.1.3) and, if applicable, additional outputs may be presented. All evaluations will be descriptive.

5 STUDY POPULATION CHARACTERISTICS

5.1 Study participant disposition

5.1.1 Overall study participant disposition

The number of study participants in each of the SS and PKAS will be summarized for the ASPS.

An overall summary of disposition for study participants will present the number and percentage of study participants for the following categories:

- The number of study participants completing the study, including a sub-category for the number of study participants that were prescribed BRV after EP0132 (ie transitioned to another BRV study or a managed access program or converting to commercial BRV.)
- The number of study participants discontinuing the study and the primary reason for discontinuation

A study completer is defined as a participant who has met the criteria for study completion as described in Section 3.3.5. Completion status will be determined from the Study Termination eCRF. All percentages will be relative to the number of study participants in the SS.

Study participant disposition will be listed on the ASPS and will include the following information: study participant status (screen failure, completed [including whether they were prescribed BRV after EP0132], or discontinued), date of informed consent/assent, date of first and last dose of study drug, date of study discontinuation, date of final contact, and primary

reason for study discontinuation (if applicable). For screen failures the date and reason for screen failure will be listed only.

Further study participant discontinuation information will be listed for participants in the SS who discontinued from the study including reason for discontinuation, the dose of study drug the study participant was on the day they were discontinued from study, the number of days for which this dose was received, and the total number of days on study medication. The derivation of these variables is detailed in Sections 3.13.12, 3.13.14, and 3.13.15.

The following listings will be provided for all study participants: study participants who did not meet study eligibility criteria which will also specify each inclusion/exclusion criteria not met, and assignment of study participants to each of the analysis sets.

Additionally, the number of participants in the SS attending each scheduled study visit will be summarized. A listing of the study visits and associated visit dates will also be presented.

A separate summary of the number of participants in the SS starting and completing each 3-month period within the Evaluation Period will be summarized. A listing of the 3-month periods and associated period start and end dates will also be presented. Note if a participant completes the study (attends an FV) or discontinues from the study (attends an EDV) prior to the end of the 90-day period they are considered as not completing the 3-month period.

5.1.2 Disposition by investigator site

An overview of the date of first study participant in (earliest EV), date of last study participant out (latest scheduled or unscheduled visit), and the number of screened study participants will be summarized for all study sites, individual study site, and country.

Additionally, the number of study participants in the SS and PKAS will be summarized for all study sites, individual study site, and country.

5.1.3 Discontinuation due to AEs

The number and percentage of study participants who discontinued the study due to an AE will be summarized for the SS. Discontinuation due to AEs will be classified as serious fatal, non-fatal, and other (non-serious fatal). If a participant has multiple AEs that lead to discontinuation, the most severe type will be summarized.

5.2 Protocol deviations

The number and percentage of study participants with at least 1 IPD will be summarized overall and by main category of protocol deviation. Specific categories of protocol deviations will be defined within IPD documentation.

In addition, IPDs will be listed.

5.3 COVID-19

All data collected from the COVID-19 Impact eCRF page will be listed.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic and Baseline characteristics will be summarized and listed for the SS unless otherwise stated.

6.1 Demographics

All demographic data collected at the EV in EP0132 will be summarized. The data sources for the EP0132 EV are detailed in Section 3.3.6. In addition, the weight, height, and BMI of the study participant at Baseline in N01269 will be summarized using data from the N01269 analysis database.

Tables with descriptive statistics will be provided for the following demographic variables:

- Continuous and categorized age at EV
  - Age categories: 2 to <4 years, 4 to <6 years, 6 to <12 years, 12 to <19 years, 19 to 25 years, <18 years
  - Categorized age in years for EudraCT and clinicaltrials.gov reporting
- Gender
- Race
- Ethnicity
  - Hispanic or Latino / Not Hispanic or Latino
- Countries
- Continuous and categorized weight at EV and at N01269 Baseline
  - Weight categories: <50kg, ≥50kg
- Height at EV and at N01269 Baseline
- Continuous and categorized BMI at EV and at N01269 Baseline
  - BMI categories: <13.5 kg/m^2, 13.5 to 30 kg/m^2, >30 kg/m^2

The summaries for demographic characteristics will be conducted on the SS.

Demographic characteristics will be listed for the ASPS Set.

No tables will be presented for childbearing potential/birth control. A study participant data listing for the ASPS Set will be produced for female participants and will include reproductive potential, whether the participant is sexually active, and method of birth control.

6.2 Other Baseline characteristics

In all sections below the date of absence seizure diagnosis is obtained from the analysis database for N01269. For participants with a partial date of absence seizure diagnosis in N01269, the imputed date of absence seizure diagnosis in N01269 will be used in EP0132. In all sections below "EV" refers to the EV in EP0132.

6.2.1 History of epileptic seizures

History of epileptic seizures will summarize absence epilepsy duration in both years and months, age at time of absence seizure diagnosis in both years and months, and percent of life with absence epilepsy for the SS. A listing reflecting absence epilepsy duration in both years and months, age at time of absence seizure diagnosis in both years and months, and percent of life with absence epilepsy relative to the date of absence seizure diagnosis will be provided for the SS.

6.2.1.1 Absence epilepsy duration

Absence epilepsy duration is the number of years and months from the date of diagnosis of absence seizures to the date of EV in EP0132. If absence epilepsy duration is greater than the study participant's age due to the application of the imputation rules for date of absence seizure diagnosis in N01269, then epilepsy duration is set equal to the study participant's age.

6.2.1.2 Age at time of absence seizure diagnosis

Age at time of absence seizure diagnosis will be calculated in both years and in months using the following formula:

Age at absence seizure diagnosis (years) =[(Age at EV in months – Number of months between EV and date of diagnosis)/12].

Age at absence seizure diagnosis (months) =(Age at EV in months – Number of months between EV and date of diagnosis).

Where number of months between EV and diagnosis = [(Date of EV – date of diagnosis)/30].

For these calculations, it is assumed there are 30 days in a month. Only complete months and years will be considered in the calculation of age at absence seizure diagnosis, ie, if age at absence seizure diagnosis is calculated as 3.2 years then this will be assumed to be 3 years.

6.2.1.3 Percent of life with absence epilepsy

Percent of life with absence epilepsy will be calculated as 100 times absence epilepsy duration (in months) divided by the study participant's age in months at EV.

6.3 Medical history, procedure history, and concomitant medical procedures

Medical history, procedure history, and concomitant medical procedures will be reported as collected on the EP0132 eCRF only – no integration of data from the N01269 analysis database will be performed. Ongoing conditions that initially occurred after the time of entry into N01269 will be recorded as an AE, not as medical history on the EP0132 eCRF. Only conditions that occurred prior to N01269, that were not captured in N01269 database, should be entered as medical history on the EP0132 eCRF.

Listings of medical history conditions and glossary for the SS will be provided.

Procedure history and concomitant medical procedures will not be summarized. Listings of procedure history and concomitant medical procedures will be provided, based on the SS.

6.4 Previous and concomitant medications

Medications will be summarized as reported on the EP0132 eCRF without integration of medications from the N01269 analysis database. Any medications that are ongoing at the time of entry into EP0132 will be entered on the EP0132 Concomitant Medications eCRF.

Medications will be classified into the following categories:

- Previous medication: includes any medications that ended prior to the first dose of study drug in EP0132
- Concomitant medication: includes any medications with at least one day in common with study treatment in EP0132 (including down-titration)
  - Includes medications that started prior to the first dose of study drug in EP0132 and continued after
  - Includes medications that started during treatment in EP0132
- Follow-up medication: includes any medications that started after the final dose of study drug in EP0132. Final dose of study drug includes down-titration medication, therefore follow-up medications are those with a start date during the Safety Period.

The number and percentage of study participants taking previous and concomitant non-AED medications will be summarized overall, and by anatomical main group (Anatomical Therapeutic Chemical [ATC] classification level 1), therapeutic subgroup (ATC classification level 2), and preferred drug name for the SS. Study participants reporting multiple medications within an ATC class are counted once per medication and class.

The number and percentage of study participants who took previous and concomitant AEDs, including benzodiazepines, will be summarized by preferred drug name for the SS.

The identification and classification of medications as AED, including benzodiazepines, will be performed by merging an external physician-reviewed spreadsheet (which includes relevant flags for selecting AED medications or benzodiazepines) with the data entered into the study database in order to categorize the medications correctly for the tables.

For summarization, similar AEDs are grouped and summarized together under the following groups:

- Valproate
- Phenobarbital
- Phenytoin

The medications to be included in each of the above groups are also flagged in the spreadsheet referred to above. Combination AEDs are not considered for grouping.

All medications will be listed for the SS.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

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

8 EFFICACY ANALYSES

Unless otherwise indicated, all efficacy summaries and listings will be performed on the SS.

Scheduled and unscheduled locally read 1-hour EEGs will be listed, including if the EEG was performed, start and stop date and time of EEG, total number of interpretable EEG minutes while the study participant was awake, whether any seizures were observed during the EEG, ILAE seizure classification of any seizures that occurred, and the number of each seizure type.

Seizure diary data will be listed, including if the diary was completed, if any absence seizures occurred, if any non-absence seizures occurred, and the ILAE classification of any non-absence seizures that occurred.

8.1 Statistical analysis of the secondary efficacy variables

For all secondary efficacy variables, participants who continue in the study beyond 2 years will have their data truncated at the scheduled Month 24 YEV. Their post-Month 24 assessments visits will not be summarized in these analyses, however their 1-hour EEG and seizure diary data for these assessments will be listed.

8.1.1 Absence seizure freedom during the 1-hour EEG at each visit (including dropouts)

The number and percentage of study participants who are absence seizure free based on 1-hour EEG at each scheduled visit up to and including the scheduled Month 24 YEV or EDV (if prior to the Month 24 YEV) will be summarized. The Month 24 YEV may be the FV for some participants. The derivation of absence seizure freedom based on EEG is specified in Section 3.13.2.

The number of study participants that discontinue the study prior to Month 24 that are imputed as not absence seizure free for all subsequent scheduled visits after the EDV will be summarized at each applicable visit. These participants will be summarized as a sub-category under not absence seizure free.

The number and percentage of study participants who met each individual criterion will also be summarized at each visit. Percentages for absence seizure free, not absence seizure free and Criterion 1 will be based on the number of participants in the SS as the denominator. Percentages for criteria 2, 3 and 4 will be based on the number of participants in the SS who met Criterion 1 at each visit.

8.1.2 Absence seizure freedom during the 1-hour EEG at each visit (excluding dropouts)

The number and percentage of study participants who are absence seizure free based on EEG at each visit up to and including the scheduled Month 24 YEV or EDV (if prior to the Month 24 YEV) will be summarized. The Month 24 YEV may be the FV for some participants. The derivation of absence seizure freedom based on EEG is specified in Section 3.13.3.

At each visit, the number and percentage of study participants who met each individual criterion will be summarized. The denominator for the percentages of absence seizure free, not absence seizure free and Criterion 1 will be based on the number of participants who are ongoing in the study at each visit; if a study participant misses a scheduled EEG and does not discontinue the

study within the protocol defined visit window for that EEG, they will be imputed as not absence seizure free at the visit. If a study participant discontinues the study early, they will not be included in the analysis for any subsequent visits. Percentages for criteria 2, 3 and 4 will be based on the number of ongoing participants in the SS who met criterion 1 at each visit.

8.1.3 Absence seizure freedom based on diary (including dropouts)

The number and percentage of study participants who are absence seizure free based on diary will be summarized at 3-month time intervals within the Evaluation Period, as defined in Table 3-3, and over the entire Evaluation Period truncated at the scheduled Month 24 YEV for participants who continue in the study beyond 2 years. The latter will additionally include any diary entries collected from the end of Months 22 to 24 up to the Month 24 YEV. The derivation of absence seizure freedom based on diary is specified in Section 3.13.4.

Study participants who discontinue during or prior to each 3-month period and do not meet Criterion 1 are imputed as not absence seizure free for the period of discontinuation and all subsequent 3-month periods, ending at Months 22 to 24. These participants will be separately summarized as a sub-category of not absence seizure free in the summaries.

Similarly, study participants who discontinue during the Evaluation Period and do not meet Criterion 1 are imputed as not absence seizure free for the Evaluation Period; these participants will be summarized in a sub-category as described above.

The number and percentage of study participants who met each individual criterion will also be summarized. Percentages for absence seizure free, not absence seizure free and Criterion 1 will be based on the number of participants in the SS as the denominator. Percentages for criteria 2 and 3 will be based on the number of participants in the SS who met Criterion 1 at each visit.

8.1.4 Absence seizure freedom based on diary (excluding dropouts)

The number and percentage of study participants who are absence seizure free based on diary will be summarized at 3-month time intervals within the Evaluation Period, as defined in Table 3-3, and over the entire Evaluation Period truncated at the scheduled Month 24 YEV for participants who continue in the study beyond 2 years. The latter will additionally include any diary entries collected from the end of the 3-month period Months 22 to 24 up to the Month 24 YEV. The derivation of absence seizure freedom based on diary is specified in Section 3.13.5. The number and percentage of study participants who met each individual criterion will be summarized, irrespective of whether the other criteria were met.

If a study participant discontinues the study during a 3-month period and does not meet Criterion 1 (as defined in Section 3.13.4) during the period of study discontinuation, the participant will be excluded from this period and all subsequent periods. If a study participant discontinues the study at any time before the Month 24 YEV, they will not be included in the analysis conducted on the Evaluation Period.

The denominator for the percentages of participants that met Criterion 1 will be based on the number of participants with data in the SS. The denominator for all other percentages for each 3-month period will be based on the number of participants who met Criterion 1 during the period. Similarly, the denominator for percentages for the analysis on the Evaluation Period (truncated at Month 24 YEV) will be the number of participants who did not discontinue the study prior to the Month 24 YEV (or FV).

8.1.5 Consecutive absence seizure freedom based on EEG

The number and percentage of study participants with consecutive absence seizure freedom based on EEG by 6-month period will be summarized up to and including the scheduled Month 24 YEV. The derivation of consecutive absence seizure freedom based on EEG is specified in Section 3.13.8. The number and percentage of study participants who met each individual criterion will be summarized at each visit, irrespective of whether the other criteria were met.

In addition, the number and percentage of participants with absence seizure freedom assessed cumulatively across all 6-month periods ending at Month 24 YEV will be summarized. A study participant will be categorized as absence seizure free until the 6-month period in which they are first classified as not absence seizure free. After the recurrence of absence seizures, the participant is classified as not absence seizure free regardless of whether they met the criteria for absence seizure freedom in subsequent 6-month periods.

In all summaries the percentages for absence seizure free, not absence seizure free and Criterion 1 will be based on the number of participants in the SS as the denominator. Percentages for criteria 2 and 3 will be based on the number of participants in the SS who met Criterion 1 at each visit.

8.1.6 Consecutive absence seizure freedom based on diary

The number and percentage of study participants with consecutive absence seizure freedom based on diary will be summarized by 6-month period within the Evaluation Period, as defined in Table 3-4 and over the entire Evaluation Period truncated at the scheduled Month 24 YEV for participants who continue in the study beyond 2 years. The latter will additionally include any diary entries collected from the end of the 6-month period Months 19 to 24 up to the Month 24 YEV.

The derivation of consecutive absence seizure freedom based on diary is specified in Section 3.13.9. The number and percentage of study participants who met each individual criterion will be summarized for each relevant period, irrespective of whether the other criteria were met.

In addition, the number and percentage of participants with absence seizure freedom will be summarized cumulatively across all relevant periods ending at Months 19 to 24 . A study participant will be categorized as absence seizure free until the 6-month period in which they are first classified as not absence seizure free. After the recurrence of absence seizures, the participant is classified as not absence seizure free regardless of whether they met the criteria for absence seizure freedom in subsequent 6-month periods.

In all summaries the percentages for absence seizure free, not absence seizure free and Criterion 1 will be based on the number of participants in the SS as the denominator. Percentages for Criterion 2 will be based on the number of participants in the SS who met Criterion 1 at each visit.

8.1.7 Sensitivity analysis of the secondary efficacy variable

8.1.7.1 Absence seizure freedom based on diary with modified criterion based on seizure diary completion (including dropouts)

The number and percentage of study participants who are absence seizure free based on diary will be summarized at 3-month time intervals within the Evaluation Period, as defined in Table 3-3, and over the entire Evaluation Period truncated at the scheduled Month 24 YEV for participants who continue in the study beyond 2 years. The derivation of absence seizure freedom based on diary with modified criterion based on seizure diary completion (including dropouts) is specified in Section 3.13.6. The number and percentage of study participants who met each individual criterion will be summarized, irrespective of whether the other criteria were met. Percentages for absence seizure free, not absence seizure free and Criterion 1 will be based on the number of participants in the SS as the denominator. Percentages for Criteria 2 and 3 will be based on the number of participants in the SS who met Criterion 1 at each visit.

8.1.7.2 Absence seizure freedom based on diary with modified criterion based on seizure diary completion (excluding dropouts)

The number and percentage of study participants who are absence seizure free based on diary will be summarized at 3-month time intervals within the Evaluation Period, as defined in Table 3-3, and over the entire Evaluation Period truncated at the scheduled Month 24 YEV for participants who continue in the study beyond 2 years. The derivation of absence seizure freedom based on diary with modified criterion based on seizure diary completion (excluding dropouts) is specified in Section 3.13.7. The number and percentage of study participants who met each individual criterion will be summarized, irrespective of whether the other criteria were met.

If a study participant discontinues the study during a 3-month period and does not meet Criterion 1 during the period of study discontinuation, the participant will be excluded from this period and all subsequent periods. If a study participant discontinues the study at any time before Month 24, they will not be included in the analysis conducted on the Evaluation Period.

The denominator for the percentages of participants that met Criterion 1 will be based on the number of participants with data in the SS. The denominator for all other percentages for each 3-month period will be based on the number of participants who met Criterion 1 during the period. Similarly, the denominator for percentages for the analysis on the Evaluation Period (truncated at Month 24 YEV) will be the number of participants who did not discontinue the study prior to the Month 24 YEV (or FV).

9 PHARMACOKINETICS AND PHARMACODYNAMICS

Unless otherwise indicated, all PK analyses and listings will be carried out for the PKAS.

9.1 Pharmacokinetics

Brivaracetam plasma concentrations will be summarized descriptively, by modal dose category in the Evaluation Period, at each FEV, YEV, and EDV or FV as applicable. Summaries will include n, geometric mean, geometric 95% CI, geometric coefficient of variation, arithmetic mean, SD, median, minimum, and maximum.

Descriptive statistics will be repeated, separately by modal dose category and categorized age group at EP0132 EV (see Section 6.1), and by modal dose category and weight at N01269 Baseline (<50kg at Baseline vs >=50kg at Baseline).

The statistics are calculated only if at least 2/3 of the individual data at a specific sampling point are above or equal to the LLOQ.

All samples should be pre-dose but in cases where the sample has been taken post-dose, the sample will be excluded from the summaries.

Plasma sample collection times and concentrations will be listed by study participant and visit including the plasma sample collection date and time, daily dose (mg), previous dose date and time, time since previous dose (hours) and plasma BRV concentration (µg/mL). The previous dose date and time refers to the most recent dose taken prior to the plasma sample collection, in most cases this will be the evening dose taken at home the day before the sample. The time since previous dose will be calculated as the difference between the plasma sampling time and the previous dose time. Daily dose refers to the most recent daily dose in mg prior to the sample as reported in the Study Drug Collection Dispensation and Administration eCRF.

9.2 Pharmacodynamics

Not applicable.

10 SAFETY ANALYSES

10.1 Extent of exposure

The study medication duration for the Evaluation Period will be calculated as the date of the final dose of BRV during the Evaluation Period - the date of the first dose of BRV in EP0132 + 1 day. The Evaluation Period is defined in Table 3-2. The overall duration of BRV for the entire study (including down-titration, if applicable) will be calculated as the date of the final dose of BRV - the date of the first dose of BRV in EP0132 + 1 day, where missing or partial date of last dose is handled as described in Section 4.1.4.5.

Table 10-1: Exposure Duration Categories

Category	Duration
>0 months	≥1 day
≥3 months	≥90 days
≥6 months	≥180 days
≥12 months	≥360 days
≥18 months	≥540 days
≥24 months	≥720 days

Study medication duration for the Evaluation Period and for the entire study will be summarized descriptively for all participants, based on the SS, where study medication duration will be presented in months (1 month is equal to 30 days). In addition, cumulative exposure duration for the Evaluation Period will be summarized (number and percentage of participants). Percentages will be relative to the number of participants in the SS.

Study medication duration during the Evaluation Period will also be summarized categorically by modal dose category (>0.0 to <2.0 mg/kg/day, ≥2.0 to <3.0 mg/kg/day, ≥3.0 to <4.0 mg/kg/day, ≥4.0 mg/kg/day) and overall, based on the SS. Percentages for the modal dose categories will be relative to the number of participants in each exposure duration category. Percentages for the all participants will be relative to the number of participants in the SS. This table will also include participant years of exposure presented for all participants and by modaldose category. The participant years of exposure presented by modaldose category will be the total participant years of exposure of participants within that modaldose category.

Participant years of exposure will be calculated by summing the exposure duration in days for all participants in the Evaluation Period or in the modal dose category, and dividing the resulting value by 365.25.

BRV dosing occurring in clinic at the EV, MEV, FEV, YEV, UV as applicable, and EDV or FV as applicable will listed, indicating the visit, whether the study drug was administered, the date and time of administration, the medication formulation, and the single dosage amount (in mg or mL as applicable).

The study medication duration during the Evaluation Period and overall will be listed on the SS including the date of first dose of study medication, the date of last dose of study medication, and the study medication duration in months.

In addition, a study participant listing on the SS will be produced displaying the prescribed dose level and the associated modal dose level for each 3 month period and over the entire Evaluation Period. This listing will also include the dose level start date within each applicable period.

10.2 Adverse events

Adverse events will be summarized as reported on the EP0132 eCRF without integration of events from the N01269 analysis database. Any AEs that are ongoing at the time of entry into EP0132 will be entered on the EP0132 AE eCRF.

All AEs in this study will be classified as pre-treatment or treatment-emergent. In the following definitions, first dose of BRV refers to the first dose in EP0132. Pre-treatment AEs are defined as AEs which had an onset date prior to the first dose of BRV. Treatment-emergent adverse events are defined as AEs that had onset on or after the day of first dose of BRV. All summaries of TEAEs will be based on the SS. Summaries of TEAEs will be produced for the Overall Period, the Evaluation Period, and for each 3-month period in the Evaluation Period (as defined in Table 3-3), more details on the requirements of each period for each summary are provided in Section 10.2.1.

For the reporting of UCB plain language summaries (PLS) additional summaries of TEAEs will be reported based on the SS. These will only be produced for the Overall Period.

For all summaries (with the exception of TEAEs leading to permanent discontinuation of study drug) the intercurrent event of treatment discontinuation is handled by using a while-on-treatment strategy where observation ends 14 days after treatment is stopped. Thus summaries will include all TEAEs with onset on or after the day of the first dose of BRV up to and including the date of last dose of BRV + 14 days, where missing or partial date of last dose is handled as described in Section 4.1.4.5.

The standard AE eCRF has the outcome of "worsened" to be used when there is an increase in the intensity of an AE. The definition of "worsened" is when the AE is still present but at a heightened intensity. The eCRF instructions dictate to complete a new AE screen with the event term of the worsened event.

Note that the outcome of "worsened" is not allowed terminology within the CDISC standards. In the SDTM.AE, the data is mapped to the outcome "Not Recovered/Not Resolved". The outcome of "Worsened" will be kept in SDTM.SUPPAE.

Treatment-emergent adverse events of interest are a selection of TEAEs identified by UCB to be of interest to BRV, and TEAEs of special interest is a selection of TEAEs 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. Treatment-emergent adverse events of special interest are defined in the protocol. Adverse events of interest will be identified based on MedDRA search criteria, which are documented outside of the SAP. All AEs which are listed in "BRV List of TEAE Topics of Interest Final 24 Aug 2018.xlsx" document (provided by UCB) and are flagged with "P" or "B" in the appropriate column of the "Key" worksheet of this excel file are AEs of interest for this study. On the "MedDRA 18.1 PTs" worksheet the PTs for each topic of interest are identifiable as those flagged with "X" or "x". Adverse events of special interest will be identified on the AE eCRF.

The duration of each AE will be calculated as follows: date of outcome – date of onset +1. The duration will not be calculated if either the date of outcome (end date) or date of onset is not fully known.

Dose level at onset will be determined as the most recent daily dose in mg/day prior to the study day of AE onset, as defined in Section 3.13.13.

10.2.1 AE summaries

An overall summary of TEAEs will provide the number and percentage of study participants with at least one: TEAE, serious TEAE, TEAE requiring dose change, drug-related TEAE, severe TEAE, TEAE leading to permanent discontinuation of study drug, AE leading to death (based on the All Participants Screened Set), and TEAE leading to death. This will be produced for the Overall Period and the Evaluation Period. Additionally, this summary will be presented by modal dose category for the Evaluation Period and for each 3-month period in the Evaluation Period.

Treatment-emergent AEs requiring a dose change will be identified from the AE eCRF where "Action Taken with Study Medication" is "Dose reduced" or "Dose increased".

All AEs will be summarized overall and by MedDRA primary system organ class (SOC) and MedDRA preferred term (PT). The number and percentage of study participants experiencing each event at least once will be summarized. All summaries will be sorted alphabetically by SOC and by incidence of AEs within PTs, starting with the highest incidence overall. Only the first occurrence of a TEAE of a particular PT will be included in incidence calculations, but all occurrences of TEAEs of the same PT will be included in counts of TEAEs. All summaries will be produced for the Overall Period, Evaluation Period and for each 3-month period in the Evaluation Period except for the incidence of TEAEs leading to permanent discontinuation of study drug which will not be produced for the Overall Period.

The following summaries will be provided:

- Incidence of TEAEs
- Incidence of TEAEs leading to permanent discontinuation of study drug
- Incidence of serious TEAEs
- Incidence of TEAEs by relationship
  - Relationship is related/not related to study drug and is decided by the study investigator.
- Incidence of TEAEs by maximum relationship.
  - Related to study drug is considered more significant than not related to study drug ie, if a study participant has experienced the same TEAE on more than one occasion, where on at least one of the occasions it was considered to be related to the study drug, the maximum relationship is related.
- Incidence of TEAEs not exclusively related to COVID-19 vaccination
  - These will be identified as TEAEs where "Is the Event Related to a COVID-19 Vaccination" is answered "No" on the AE eCRF
- Incidence of TEAEs by maximum intensity
  - Each study participant will be counted at most once per primary SOC or PT according to the maximum intensity of all AEs within that SOC or PT.
- Incidence of non-serious TEAEs above reporting threshold of 5% of participants
- Incidence of non-serious TEAEs not exclusively related to COVID-19 vaccination above reporting threshold of 5% of participants
- Incidence of non-serious TEAEs above reporting threshold of 5% of participants by relationship to study drug
- Incidence of TEAEs of interest
- Incidence of TEAEs of special interest
- Incidence of serious TEAEs by relationship to study treatment
- Incidence of fatal TEAEs by relationship to study treatment

For the PLS the overall summary of TEAEs will be repeated on a subset of TEAEs considered related to study drug per investigator assessment. This will provide the number and percentage of study participants with at least one: drug-related TEAE, serious drug-related TEAE, severe drug-related TEAE, drug-related TEAE leading to permanent discontinuation of study drug, and drug-related TEAE leading to death.

The following summaries will also be provided for the PLS, summarized by the MedDRA preferred term:

- Incidence of drug-related TEAEs by preferred term
- Incidence of serious drug-related TEAEs by preferred term

10.2.2 AE listings

All AEs reported during the study will be provided in study participant data listings for the ASPS Set.

AE listings will include AE onset date, AE outcome date, AE duration (defined in Section 10.2), dose level at onset (defined in Section 3.13.13), whether the AE was serious, AE intensity, whether the AE was treatment-emergent, whether the AE was related to COVID-19 vaccination, the pattern of the event, whether the event was ongoing from N01269, whether the AE lead to dropout, whether the AE was of special interest, whether the AE was of interest, relationship to study medication, action taken with study medication, other action taken, and AE outcome.

The following AE listings will be provided:

- Glossary for all AEs
- All AEs
- All serious AEs
- All AEs leading to study discontinuation
- All deaths
- COVID-19 vaccination related AEs

Should they occur, any uncoded AEs should be designated as "coding-pending" at all MedDRA levels, and such AEs should be included in summary tables and study participant data listings based on this classification (eg, SOC and PT set to coding-pending).

10.3 Clinical laboratory evaluations

10.3.1 Hematology, Clinical chemistry, Endocrinology and Urinalysis parameters

Hematology, clinical chemistry, and urinalysis variables are assessed at MEV, FEV, YEV, FV, and EDV, and will also be assessed at SV if abnormal at the FV or EDV. For study participants on study drug for more than 12 months, laboratory assessments at MEV can be omitted. Endocrinology variables are assessed at the YEV/FV for study participants aged <18 years.

Observed results as well as CFB will be summarized descriptively, by visit, for all laboratory variables.

The definition of PCS is described in Section 3.4. The criteria for a laboratory value to be PCS are defined in Section 13.1.1 and Section 13.1.2. All laboratory measurements will be assessed to determine if they meet PCS criteria. The number and percentage of study participants with PCST values for each laboratory variable (ie, PCST low value, PCST high value) for hematology, biochemistry, endocrinology and urinalysis will be summarized, over all visits (including unscheduled visits) and by visit separately. Percentages in the overall summary will be relative to the number of study participants with at least one assessment on or after the first dose of BRV in EP0132. Percentages in the by visit summary will be relative to the number of study participants with a measurement at the visit. Note that the urinalysis variables nitrites, pH, and specific gravity will not be assessed against PCS criteria and thus will be listed only.

For female participants of childbearing potential, a urine pregnancy test is performed at MEV, FEV, YEV, FV or EDV as applicable, and SV. A urine pregnancy test may also be performed at unscheduled visits. Serum pregnancy tests are performed for PDILI assessments and local laboratory assessments. Pregnancy test results will not be summarized.

Summaries of laboratory variables will only summarize variables planned per the protocol , however, both planned and unplanned laboratory variables will be provided in data listings. Unscheduled laboratory tests conducted by local laboratories are unplanned so will be included in the listings only.

Summaries and listings of study participants with PCST values for laboratory variables will include all planned and unplanned variables from central and local laboratories. In the unlikely event that there are both central and local laboratory measurements on the same calendar date, preference will be given to the central laboratory result. Summaries of PCST values for urinalysis will only include data from central laboratories.

A listing of additional laboratory tests will be provided including urine and serum pregnancy tests and urine drug screen tests (performed as part of the PDILI assessments described in Section 10.3.2).

10.3.2 PDILI laboratory measurements

The number and percentage of participants with elevated liver function tests (the criteria for which are defined in Table 13-7) will be summarized over all visits.

In addition, the number and percentage of study participants with potential hepatotoxicity with and without symptoms potentially associated with hepatitis or hypersensitivity, and the number and percentage of participants meeting laboratory criteria for PDILI will be summarized over all visits.

Percentages in these summaries will be relative to the number of participants with at least one assessment on or after the first dose of BRV in EP0132.

All scheduled, unscheduled, EDV, DTV and SV assessments occurring on or after the first dose in EP0132 will be included in these summaries. This includes both central and local laboratory measurements. If, however, a central and local laboratory measurement is recorded for a participant on the same calendar day, only the central laboratory measurement will be considered in the summary tables. Percentages will be relative to the number of study participants with at least one assessment on or after the first dose of BRV in EP0132.

Liver function laboratory results for participants with one or more elevated liver function tests will be listed. Criteria for elevated liver function tests can be found in Section 13.1.5. In addition, Section 13.1.5 contains the criteria for PDILI and Hy's Law. The liver function laboratory results listing will include AST, ALT, total bilirubin, and new ratio (nR). The listing will also indicate whether the participant met the criteria for Hy's Law and whether symptoms of hepatitis and hypersensitivity were present. The nR is calculated as the ratio of ALT or AST (whichever is higher) divided by ALP, where ALT, AST, and ALP are expressed as multiples of their upper limits of normal (ULN). Lifestyle for study participants with PDILI will be listed and will include alcohol and illicit drug use within the previous 6 months. Additionally, family medical history will be listed for participants with PDILI. Serum pregnancy tests and urine drug tests will be listed as described in Section 10.3.1. Finally, a listing will be presented including whether the

participant took any potentially hepato-toxic medications that may have contributed to the PDILI event, their most recent study medication administration, single dosage amount, whether the participant discontinued study medication, and the reason for discontinuation of study medication.

In addition, figures including both central and local laboratory measurements, will be provided for the following:

- Shift in liver function tests from N01269 Baseline to maximum value post-first dose in EP0132 (including those at EDV, DTV, SV, and unscheduled visits) for AST, ALT, ALP, and total bilirubin, expressed as multiples of the ULN. The figure will be presented in the form of scatter plots.
- Maximum total bilirubin value versus maximum ALT value (post-first dose in EP0132 and including EDV, DTV, SV, and unscheduled visits), expressed as multiples of the ULN. The figure will be presented in the form of a scatter plot.
- Individual time course plots for participants meeting Hy's Law criteria including ALP, ALT, AST, and total bilirubin. Figures will be presented in the form of line plots with all variables overlaid on the same plot (separate plots for each participant) with values expressed as multiples of the ULN. The N01269 Baseline will be displayed on the plot.

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

10.4.1 Vital signs

Systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, temperature, and respiratory rate are assessed at MEV, FEV, YEV, EDV, FV, DTV, and SV. Height and body weight are assessed at MEV, FEV, YEV, FV, and EDV.

Observed values and CFB for each measurement will be summarized at each scheduled visit. Body weight and height will additionally be included in the summary.

The definition of PCS is described in Section 3.4. Vital signs and body weight PCS criteria are located in Section 13.1.3. The number and percentage of study participants with PCST values for each vital sign (ie, PCST low value, PCST high value) will be summarized for each variable individually over all visits (including unscheduled visits) and by visit separately. Percentages in the overall summary will be relative to the number of study participants with at least one assessment on or after the first dose of BRV in EP0132. Percentages in the by visit summary will be relative to the number of study participants with a measurement at the visit. The number of occurrences of each unique PCST type will be tabulated within each scheduled visit.

A study participant data listing of all observed vital sign, body weight and height values will be presented. The listing will contain columns indicating which values met the criteria for PCS.

10.4.2 Electrocardiograms

ECGs are performed at YEVs, EDV or FV (as applicable), and SV.

Observed values and CFB for each measurement will be summarized at each scheduled visit.

Summaries of shift from N01269 Baseline to each visit will be provided based on the categories normal, abnormal (not clinically significant) and abnormal (clinically significant). Percentages will be relative to the number of study participants with a measurement at the visit.

The observed values and CFB values for the QTcB parameter will be presented descriptively. The definition of PCS is described in Section 3.4. ECG PCS criteria are located in Section 13.1.4. All QTcB measurements (scheduled and unscheduled) will be assessed to determine if they meet PCS criteria. The number and percentage of study participants that meet the criteria for PCST will be presented for QTcB by visit.

QTcB data and findings will be listed by study participant and visit.

10.4.3 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. No summaries or listings of physical examination findings are planned. Clinically relevant findings or worsening of previous findings will be recorded as AEs.

10.4.4 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. Each examination will be classified as one of not done, normal, abnormal not clinically significant, or abnormal clinically significant. A summary of shift from Baseline at each FEV, YEV, and FV will be provided. Percentages will be relative to the number of study participants with a measurement at the visit. Additionally, a listing of abnormal neurological examinations will be provided.

10.4.5 Psychiatric and mental status

An evaluation of Psychiatric and Mental Status is performed at each FEV, YEV, EDV or FV (as applicable), and SV. Mental status is reported by recording the presence or absence of psychiatric symptoms, mental impairment, and behavioral problems. These are recorded as not done if the assessment for the parameter was not performed. If symptoms are present, these are recorded as abnormal (yes/no), and clinically significant (yes/no). A summary of shift from Baseline at each FEV, YEV, and FV will be provided. Percentages will be relative to the number of study participants with a measurement at the visit. Additionally, a listing of only abnormal psychiatric and mental status examinations will be provided.

10.4.6 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS. This will be completed at MEVs, FEVs, YEVs, EDV or FV (as applicable), UVs, DTV, and SV.

For study participants ≥6 years of age at the time of enrollment into EP0132, this scale will be used to assess suicidal ideation and behavior that may occur during the study. All study participants who are ≥6 years of age will complete the “Since Last Visit” version at each visit unless the participant turns 6 years of age while enrolled in EP0132. If a study participant becomes 6 years of age during the study, the “Already Enrolled” version of the C-SSRS should be completed at the first visit after the study participant’s 6th birthday. Thereafter, the “Since Last Visit” version of the C-SSRS should be completed at all subsequent visits.

Suicidal ideation is defined as an event in any of the following 5 categories:

[redacted]

Suicidal behavior is defined as an event in any of the following 4 categories:

[redacted]

Suicidal ideation or behavior is defined as an event in any of the above 9 categories. A listing of all C-SSRS responses will be provided for any participant with at least one abnormal result. No summaries of these results are planned.

10.5 Non-absence seizures

Non-absence seizure types are described in Section 3.13.1.1.

10.5.1 Non-absence seizure incidence during the study based on locally read 1-hour EEGs

The incidence of each non-absence seizure type will be summarized over the entire Evaluation Period (including unscheduled visits and visits beyond Month 24) and by visit. Summaries by visit will also include scheduled assessment timepoints beyond Month 24, with scheduled assessment timepoints beyond Month 24 included if at least one participant has an assessment at the timepoint. Study participants who experience more than one non-absence seizure type during a visit (ie, POS and tonic-clonic, POS and other seizure, tonic-clonic and other seizure or all three seizure types) will be counted once for each non-absence seizure type. Percentages for the by visit summary will be relative to the number of participants with a 1-hour EEG at the visit with at least 30 minutes of readable EEG time while awake. Percentages for the Evaluation Period will be relative to the number of participants with at least one (scheduled or unscheduled) 1-hour EEG with at least 30 minutes of readable EEG time while awake occurring on or after the first dose of study treatment in EP0132.

10.5.2 Non-absence seizure incidence during the study based on seizure diary

The incidence of each non-absence seizures type observed from the seizure diary will be summarized over the entire Evaluation Period (including unscheduled visits and visits beyond Month 24) and by 3-month period, as defined in Table 3-3; 3-month periods from and beyond Months 25-27 will be included if at least one participant has started the relevant 3-month period. Study participants who experience more than one non-absence seizure type during a 3-month period (ie, POS and tonic-clonic, POS and other seizure, tonic-clonic and other seizure or all three seizure types) will be counted once for each non-absence seizure type. Percentages for the

each 3-month period will be relative to the number of participants who completed their seizure diary on at least 80% of days within the 3-month period. Percentages for the Evaluation Period will be relative to the number of participants who completed their seizure diary on at least 80% of days over the Evaluation Period.

10.6 Participant and caregiver-reported outcomes

10.6.1 EpiTrack Junior

The absolute values and CFB in the EpiTrack score will be summarized at each visit using descriptive statistics.

In addition, the number and percentage of study participants in the following categories at each visit will be provided for the SS:

- Cognitive performance categories (good, average, mildly impaired, or significantly impaired) at each scheduled visit. Percentages will be relative to the number of study participants with a measurement at the visit.
- Significant change categories of cognitive function (improved, unchanged, worsened) for each visit compared to N01269 Baseline. Percentages will be relative to the number of study participants with a non-missing CFB at the visit.

All available data related to each sub-test result and associated scores, the total unadjusted score, and the Epitrack score will be listed by visit. Study participants who turn age 6 years after N01269 Baseline will be excluded from all summaries, but their results will be included in listings. Study participants who turn age 18 prior to or on the first scheduled assessment in EP0132, which is planned at Month 6, will also be excluded from all summaries, but their results will be included in listings.

10.6.2 PedsQL

The absolute and CFB in total PedsQL score, Physical Health Summary Score, Psychosocial Health Summary Score, and Emotional, Social and School Functioning dimension score will be summarized using descriptive statistics. The Physical Functioning dimension will not be summarized as it is the same as the Physical Health Summary Score.

Summaries of the participant self-report will be reported over all age groups and separately for Young Children (ages 5 to 7), Children (ages 8 to 12) and Teens (ages 13-18), based on the participants age at N01269 Baseline. The summary over all age groups will exclude participants aged 2 to 4 years old since only a parent proxy report is available for this age group.

Similarly, summaries of the parent proxy report will be reported for all age groups and separately for Toddlers (ages 2 to 4), Young Children (ages 5 to 7), Children (ages 8 to 12) and Teens (ages 13-18). The summary over all age groups will exclude the 2 to 4 years age group as it includes fewer items. The summary for 2 to 4 years age group will include the absolute and CFB score only until the participant turns 5 years old (as CFB are not calculated for subsequent versions of the questionnaire for this age group).

The number and percentage of participants with meaningful changes in PedsQL score from N01269 Baseline will be presented at each visit. This will be presented separately for the participant self-report and the parent proxy report. Each dimension score (total scale score, physical health summary score, psychosocial health summary score, emotional functioning,

social functioning and school functioning) will be presented and the summary will be aggregated over all age groups. However, the summary will exclude the parent proxy report for participants 2-4 years' age group. The denominator for percentages will be the number of participants with a non-missing CFB score at the visit.

In addition, all available data for the PedsQL will be listed.

11 OTHER ANALYSES

Not applicable.

12 REFERENCES

Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care. 2001 Aug;39(8):800-12. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr. 2003 Nov-Dec;3(6):329-41.

13 APPENDICES

13.1 PCS criteria

13.1.1 Hematology, clinical chemistry and endocrinology parameters

Table 13-1: Hematology, clinical chemistry, and endocrinology parameter abnormality criteria

Parameter	Age Range	UNIT	Abnormality Criteria
Hematology			
Hematocrit	≥2y - <18y	%	≤29 >47
	≥18y		≤85% of LLN ≥115% of ULN
Hemoglobin	≥2y - <18y	g/L	≤95 >160
	≥18y		≤85% of LLN ≥115% of ULN
WBC/Leukocytes	<12y	G/L	<3.5 >15.0
	≥12y		<3.0 >12.0
Neutrophils Absolute	>1m	G/L	<1.5
Lymphocytes	≥6m - <6y	%	≤22.0
	≥6y - <18y		≤12.0 ≥80.0
	≥18y		≤10.0 ≥80.0
Basophils	>1m	%	≥3.0
Eosinophils	>1m	%	≥10.0
Monocytes	>1m	%	≥20.0
Platelets	>1m	G/L	≤100 >600
RBC/Erythrocytes	≥2y	T/L	<3.5
Biochemistry			
AST (SGOT)	<14y	U/L	>180

Table 13-1: Hematology, clinical chemistry, and endocrinology parameter abnormality criteria

Parameter	Age Range	UNIT	Abnormality Criteria
	≥14y		>144
ALT (SGPT)	1y - <18y	U/L	>90
	≥18y		>123
Alkaline Phosphatase	<4y	U/L	>690
	≥4y - <10y		>834
	≥10y - <18y		>1174
	≥18y		>432 (F) >933 (M)
Total Bilirubin	>1m	umol/L	≥25.656
Total Protein	≥1y	g/L	<43 >100
Blood Urea Nitrogen (BUN)	≥1y	mmol/L	>10.71
Creatinine	1y - <10y	umol/L	>79.56
	≥10y - <16y		>123.76
	≥16y		>141.44
Creatinine Clearance[a]	All	mL/s	<1.169
Calcium	1y - <18y	mmol/L	<1.85 >2.925
	≥18y		≤1.975 ≥2.775
Potassium	≥1y	mmol/L	<3.0 >5.8
Sodium	>1m	mmol/L	≤130 ≥150
Glucose	>1m	mmol/L	<2.775 >9.99
Thyroxine (T4)	≥1y	nmol/L	≤48.9098 ≥173.7585

m=month; y=year.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CrCl=creatinine clearance; dL=deciliter; eCRF=electronic case report form; L=liter; LLN lower limit of normal; µg=microgram; m=month (defined as 30 days); mg=milligram; PCS=possibly clinically significant; PCST=possibly clinically significant treatment-emergent; U=unit; ULN=upper limit of normal; y=years (defined as 365.25 days)

[a]Schwartz equation (study participants <12): CrCl ml/min=[Height (cm) * 0.55] / serum creatinine (mg/dL)

Cockroft equation (study participants ≥12): Male: CrCl ml/min=[(140-age) x body weight (kg)] / (72 x serum creatinine [mg/dL]); Female: CrCl ml/min=[(140-age) x body weight (kg)] / (72 x serum creatinine [mg/dL])] x 0.85

Note: Age is collected on the eCRF at each visit and will be used for derivations of PCS assessments.
Note: Creatinine Clearance is converted from mL/min to mL/s by dividing by 60.

13.1.2 Urinalysis parameters

Urinalysis parameters assessed in this study and their possible values are specified in Table 13-2.

Table 13-2: Urinalysis parameters and possible values

PARAMETER	Possible Values
Bilirubin	NEGATIVE, TRACE, 1+, 2+, 3+
Blood	NEGATIVE, TRACE, 1+, 2+, 3+
Glucose	NEGATIVE, TRACE, 1+, 2+, 3+
Ketones	NEGATIVE, TRACE, 1+, 2+, 3+, 4+
Leukocyte Esterase	NEGATIVE, TRACE, 1+, 2+, 3+
Nitrite	NEGATIVE, POSITIVE
pH	5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, >8.5
Protein	NEGATIVE, TRACE, 1+, 2+, 3+, 4+
Specific Gravity	Numeric
Urobilinogen	NORMAL, 1+, 2+, 3+

Qualitative urine parameters are generally reported by a descriptive score, which differs among laboratories. For data analysis purpose, a four-point scale is used. Five-point, six-point, or seven-point scales will be collapsed into a four-point scale first. A value is considered PCST if an upward shift of at least 2 points from the Baseline occurs under investigational treatment. To collapse the results in a five-point scale into a four-point scale, the lowest 2 positive results will be combined as per Table 13-3.

Table 13-3: Conversion of results in a five-point scale into a four-point scale

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

Table 13-3: Conversion of results in a five-point scale into a four-point scale

Original Five-point Scale	Four-point Scale
3+/Sev	3+/Sev

Mod=Moderate, Sev = Severe

The original scale and four-point scale for PCST of each urinalysis parameter is described in Table 13-4. Nitrites are not classified into 4-point scales, as there are only 2 values, and pH is not classified into 4-point scales as low and high pH values may be considered as good or bad.

Table 13-4: Urinalysis 4-point scales for PCS criteria

	Four-point Scale			
PARAMETER	**Negative**	**1+**	**2+**	**3+**
Bilirubin	Negative	1+	2+	3+
Blood	Negative	Trace, 1+	2+	3+
Glucose	Negative	Trace, 1+	2+	3+
Ketones	Negative	Trace, 1+	2+	3+, 4+
Leukocyte Esterase	Negative	Trace, 1+	2+	3+
Protein	Negative	Trace, 1+	2+	3+, 4+
Urobilinogen	Normal	1+	2+	3+

13.1.3 Vital signs and body weight

Table 13-5: Vital signs and body weight PCS criteria

Parameter	Age Range	PCS Criteria
Pulse Rate (beats/minute)	6m - <3y	<90 >150
	3y - <12y	<60 >130
	12y - <17y	<50 >120
	≥17y	<50 and a decrease from Baseline of ≥15 >120 and an increase from Baseline of ≥15
Systolic Blood Pressure (mmHg)	6m - <3y	<70 >120
	3y - <12y	<80

Table 13-5: Vital signs and body weight PCS criteria

Parameter	Age Range	PCS Criteria
		>140
	12y - <17y	<90 >160
	≥17y	≤ 90 and a decrease from Baseline of ≥20 ≥ 180 and an increase from Baseline of ≥20
Diastolic Blood Pressure (mmHg)	6m - <3y	<45 >75
	3y - <12y	<50 >80
	12y - <17y	<50 >105
	≥17y	<50 and a decrease from Baseline of ≥15 >105 and an increase from Baseline of ≥ 15
Respiratory Rate (breaths/minute)	6m - <3y	<20 >45
	3y - <12y	<15 >35
	≥12y	<10 >25
Temperature	>1m	>101 0F (38.3 0C)
Body Weight[a]	1m - <17y	Outside of < 3% or > 97% percentile of the normal body weight based on gender and the age of study participant on date of weight assessment[b]
	≥17y	≥ 10% CFB (an increase or a decrease)

C = Celsius, F = Fahrenheit,

[a] Study participants who turn ≥17y during the EP0132 study, will continue to be assessed in the 1m - <17y category.

[b] Assessment will be based on the growth charts from CDC https://www.cdc.gov/growthcharts/clinical_charts.htm

For the assessment of body weight PCS criteria, the participant's age at EP0132 EV will be used to determine the age category as specified in the "Age Range" column of Table 13-5 and

consequently the methodology (ie, percentage change or percentiles) to be used in the assessment of PCS measurements as specified in the "PCS Criteria" column of Table 13-5.

13.1.4 ECG

Table 13-6: QTcB interval PCS criteria

Parameter	Age	PCS criteria
QTcB interval (ms)	6m-<3y	>450, or >15% increase from Baseline
	3y-<12y	>450, or >15% increase from Baseline
	12y- <17y	>450, or >15% increase from Baseline
	≥17y	>500 or ≥60 ms increase from Baseline

13.1.5 PDILI

Table 13-7: Elevated liver function tests and Hy's Law criteria

Parameter	Criteria
ALT	>3 x ULN >5 x ULN >8 x ULN >10 x ULN >20 x ULN
AST	>3 x ULN >5 x ULN >8 x ULN >10 x ULN >20 x ULN
ALT or AST	>3 x ULN >5 x ULN >8 x ULN >10 x ULN >20 x ULN
Total bilirubin	>1.5 x ULN >2 x ULN
ALP	>1.5 x ULN
PDILI	(AST or ALT ≥ 3 x ULN) and total bilirubin ≥ 1.5 x ULN at the same visit (AST or ALT ≥ 3 x ULN) and total bilirubin ≥ 2 x ULN at the same visit
Hy's Law	(AST or ALT ≥ 3 x ULN) and total bilirubin ≥ 2 x ULN and ALP < 2 x ULN at the same visit

ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, PDILI=potential drug-induced liver injury, ULN=upper limit of normal.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Approval Signatures

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