Janssen Research & Development *

Clinical Protocol

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-40411813 as Adjunctive Therapy in Subjects with Focal Onset Seizures with Suboptimal Response to Levetiracetam or Brivaracetam

Short Title:
A study to investigate JNJ-40411813
in combination with levetiracetam or brivaracetam in epilepsy.

Protocol 40411813EPY2001; Amendment INT-4; Phase 2a

JNJ-40411813

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312)

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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DOCUMENT HISTORY	
Document	**Date**
Amendment INT-4	17-November-2022
Amendment INT-3	12-July- 2022
Amendment INT-2	07 April 2022
Amendment INT-1	18 January 2021
Original Protocol	13 November 2020

Amendment 4 (17-November-2022)

Overall Rationale for the Amendment: This protocol amendment has been issued in order to provide instructions for up-titration CCI [redacted] in Cohort 2 and to allow for dose increases in the Open Label Extension Part of the study and to implement several different corrections and clarifications as listed below

The changes made to the clinical protocol 40411813EPY2001 as part of Protocol Amendment 4 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 11.11 Appendix 11: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Dosage and administration Section 2.3.1 4.3 Justification for dose	Added: All patients in Cohort 2 (CCI [redacted] will start the double-blind phase with a dosage of CCI [redacted] (or matching placebo). Induced patients will be up titrated to CCI [redacted] (or matching placebo) on day 8 of the double-blind phase.	Up-titration is expected to reduce the number of early onset AE's (dizziness, incoordination, sedation, or fatigue).
Section 1.1 Dosage and Administration Section 2.3.1 Risk for Study Participation	Changed: For participants receiving dosages of CCI [redacted] will be permitted in case adverse events consisting of dizziness, incoordination, sedation, or fatigue (or similar descriptive terms) appear within the first 2 weeks of treatment and which, in the judgment of the investigator, potentially limit activities of daily living. This dosage reduction may last no longer than 2 weeks and may not be repeated. Following the return to the originally assigned dosage, recurrence of intolerable adverse events would require discontinuation of the study medication Into: CCI [redacted] will be permitted in case adverse events consisting of dizziness, incoordination, sedation, or fatigue (or similar descriptive terms) which, in the judgment of the investigator, potentially limit activities of	This option for temporary and/or permanent dose reduction will minimize the likelihood of discontinuation because of adverse events, and will provide experience to guide dosing instructions in future studies

Section Number and Name	Description of Change	Brief Rationale
	daily living. The PI is encouraged to rechallenge if the AEs resolved on the lower dose. If rechallenge is unsuccessful, i.e., the AEs recurred when the dose was increased, the dose may be reduced again and kept at that level	
Section 4.2 Optional temporary dose reduction	Deleted: 'temporary'	The option for dose reduction does not need to be temporary, i.e. if rechallenge is unsuccessful the participant may remain on the lower dose
Section 4.1 Overall design	Added to CCI [redacted] CC or placebo on day 8	Up-titration is expected to reduce the number of early onset AE's (dizziness, incoordination, sedation, or fatigue
1.1 Participant Population 4.1 Overall design 5. Study population	Changed: 60 patients Into: approximately 60 patients	Because exact number of Screen Failures is not predictable and for planning reasons (planning for the Interim Reviews), it is possible that cohorts would not have exactly 60 patients.
9.5 Data Review after each cohort	This section has been revised.	This is a correction to bring the protocol in line with Amendment 3 (no pause in recruitment between cohorts)
5.2 Exclusion Criterion Excl 7	Clarification Participants that have not had a visual field examination after vigabatrin discontinuation could have one done at any point prior to randomization.	Visual field abnormalities are common in people that have been treated with vigabatrin, and in themselves should not be exclusionary. The importance for understanding the safety of JNJ-40411813 is that, in case visual field abnormalities are discovered in any of our participants, we will have a baseline to determine if this is new (and possibly treatment-emergent), vs old and not related to JNJ-40411813. Note that current treatment with vigabatrin is still exclusionary
5.2 Exclusion Criteria Excl 15	Added to Positive test result(s) for alcohol and/or drugs of abuse: does not apply for patients using medicinal cannabis to treat a medical condition that is documented in the Medical History	Cannabis is not considered as a drug of abuse if used to treat a medical condition.
9.2.1 Primary, Population	Deleted: for at least 1 year	This is a correction to bring the protocol in line with changes in Amendment 2
6.1. Table 2	Added: If visit 7 coincides with Open Label Extension visit 1, participants should be dosed with double blind medication in the morning and with open label medication in the evening.	For clarification
8.5. Table 4	Changed: With study Visit Into	For clarification

Section Number and Name	Description of Change	Brief Rationale
	After dosing	
6.5. Concomitant Therapy	Added that on day of visit 7, other anti-epileptic drugs should be taken in the clinic	For clarification and to be in line with instructions for dosing of the AED on other visit days.
10.4.1. Overall design 10.6.1 Study interventions administered	Text on dosing has been updated to allow dose increases in patients in the OLE phase	To give patients the opportunity to be treated, in the OLE phase, with a dose that is expected to be the most efficacious.
10.4.2 Combination with levetiracetam or brivaracetam	Added: Monotherapy with JNJ-40411813 to treat epilepsy is not allowed.	For clarification.
10.10 Schedule of Activities in the OLE period	Added to footnote i: If OLE1 coincides with Visit 7 of the Double-Blind Phase: C [redacted] CI [redacted]	For clarification.
10.10 Schedule of Activities in the OLE period	Added: Visit windows in footnote 'k'	Information was missing in Amendment 3 and Amendment 4
10.8.1 Overview, 10.8.2.1 Study Procedures 10.8.3.1 Seizure count	Deleted: Paper diary may be provided	Electronic Diary is in place and should be used.

1. PROTOCOL SUMMARY

1.1. Synopsis[a]

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-40411813 as Adjunctive Therapy in Subjects with Focal Onset Seizures with Suboptimal Response to Levetiracetam or Brivaracetam

Background:

JNJ-40411813 is a positive allosteric modulator (PAM) of the metabotropic glutamate receptor-2 (mGlu2), which is abundantly expressed in the forebrain and cerebellum. The mGlu2 receptor functions as a presynaptic auto-receptor that, upon activation, decreases the release of the excitatory neurotransmitter glutamate. Positive allosteric modulation of a receptor will result in the direct enhancement of the agonist-induced signal while PAMs themselves have generally no or low intrinsic activity at the receptor. The net effect of JNJ-40411813 is hypothesized to be a normalization of hyper-glutamatergic transmission. JNJ--40411813 is being evaluated for the treatment of disorders of the central nervous systems (CNS), such as epilepsy, and has been evaluated in schizophrenia and anxious depression.

This study as per Amendment INT-2 and INT-3 will consist of a double-blind treatment period and an open-label extension (OLE) period. Details about the OLE period are described in Section 10.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective of this study is to evaluate the efficacy of up to 3 dose levels of adjunctive JNJ-40411813 compared to placebo based on the time to baseline monthly seizure count in participants with focal onset seizures who are receiving levetiracetam or brivaracetam and up to 3 other anti-epileptic drugs (AEDs).

Secondary Objectives

- To evaluate the overall safety and tolerability of adjunctive JNJ-40411813 compared to placebo in participants with focal onset seizures who are receiving levetiracetam or brivaracetam and up to 3 other AEDs.
- To evaluate the efficacy of up to 3 dose levels of adjunctive JNJ-40411813 compared to placebo based on percent reduction in the double-blind monthly seizure count, relative to the pre-randomization monthly seizure count, in participants with focal onset seizures.
- To evaluate the efficacy of JNJ-40411813 over the double-blind period using percent participants with seizure freedom and percent responders (>50% seizure rate reduction).
- To evaluate the pharmacokinetics (PK) of JNJ-40411813 and selected metabolites and levetiracetam or brivaracetam in participants with focal onset seizures who are receiving levetiracetam or brivaracetam and up to 3 other AEDs.

Exploratory Objectives

- CCI [redacted]

[a] This section has been amended by Amendment INT-1, INT-3 and INT-4

- CCI [redacted]

Hypothesis

The hypothesis of this study is that JNJ-40411813 added to treatment that includes levetiracetam or brivaracetam significantly prolongs the time to baseline monthly seizure count compared to placebo add-on treatment.

OVERVIEW OF STUDY DESIGN

This is a double-blind, randomized, parallel, placebo-controlled study with the option for an open-label extension (OLE) period. The study will consist of 1 to a maximum of 3 cohorts. In each cohort, for each participant the study consists of a screening visit, an 8-week prospective pretreatment baseline period, an up to12-week double-blind treatment period and, for those participants electing not to enter the OLE period, a follow-up telephone visit 2 weeks after the last dose of study intervention. Participants have the option to enter the OLE period, in which treatment with JNJ-40411813 may be continued until the product becomes available by prescription, or until development of JNJ-40411813 in this indication ceases. The total maximal duration of the study is approximately 22 weeks for each participant, up to the time of entry into the OLE period.

Participants from 18 to 69 years (inclusive) old with an established diagnosis of focal onset seizures will be enrolled in the study. For the first cohort, approximately 80 eligible participants will be initially enrolled to ensure that approximately 60 participants are randomly assigned in a 2:1 ratio to receive either JNJ-40411813 CCI CCI or placebo. For each following cohort, approximately 60 eligible participants will be initially enrolled to ensure that approximately 50 participants are randomly assigned in a 4:1 ratio to receive either JNJ-40411813 CC or placebo.

CCI [redacted]

After giving written informed consent, participants will be screened immediately prior to the start of the pretreatment baseline period to ascertain their eligibility for the study per the inclusion and exclusion criteria. Upon completion of all informed consent form (ICF) procedures, recording of adverse events (AEs) and concomitant medication will start.

After the screening visit, the data of the participant will be subject to an adjudication process by independent experts from the epilepsy consortium. In this adjudication process the experts decide whether the participant is correctly classified to participate in the study.

After screening, if they meet the inclusion criteria and not meet the exclusion criteria for which data are available, participants can start the 8-week prospective pretreatment baseline period pending the results of the central laboratory and the adjudication process. However, when the results of these assessments indicate that the participant does not meet the in- and exclusion criteria, the participant will terminate the baseline period and will not be randomized to treatment.

During the 8-week prospective pretreatment baseline period, participants will continue to take their prescribed AEDs (one of which must include levetiracetam or brivaracetam) without change in dosage(s);

new concomitant AEDs should not be added. During the baseline period, participants will record seizure information (type and frequency of seizures) in an e-diary. Baseline monthly seizure count will be defined as the number of observable focal onset seizures recorded during the baseline period, multiplied by 28/ X_{BL}, where X_{BL} is the number of days comprising the baseline.

Participants must be compliant with the recording of information in the e-diary throughout the study. Seizures that will be entered during baseline and throughout the study include focal aware seizures with and without motor signs, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures. Myoclonic, or other generalized seizures will not be entered.

Participants who meet study entry criteria at the end of the prospective pretreatment baseline period will be randomized to JNJ-40411813 or placebo, CCI . The dosage(s) of concomitant AEDs should not be increased, and new concomitant AEDs should not be added to the treatment regimen.

CCI . In the following cohorts, the dose(s) of JNJ-40411813 will be determined based on an ongoing assessment of tolerability, and safety results from the previous cohort. CCI participants. The highest dose selected to be administered by induced participants will be expected to not exceed the 95th percentile of the plasma maximum drug concentration (C_{max}) for JNJ-40411813, CCI CCI CCI CCI

Participants are encouraged to complete at least the first 4 weeks of treatment when there are no safety concerns. Participants who have exceeded their pre-randomization monthly seizure count at Week 4, or within any 4-week interval after Week 4 ("4-week sliding window approach") up to Week 12, will have the option to discontinue the study drug for lack of efficacy and to perform the end of study/early withdrawal visit, to continue double blind treatment, or to enter the open-label extension (OLE) period. Participants who have not exceeded the pre-randomization seizure count will continue the double-blind treatment period through Week 12 and will have the option to perform the end of study visit or to enter the OLE period.

Participants who continued treatment to the end of the double-blind treatment period (Week 12) or have completed the study as per Section 7.2 will continue to collect information on the number of seizures they experience using the e-diary until 2 weeks after the last dose of study medication. Participants entering the optional OLE will continue to record seizures by using an e-diary.

Participants will visit the study center according to the schedule in the Schedule of Activities (SoA).

After at least 55 patients in Cohort 1 and after at least 45 patients in Cohort 2 have completed at least 4 weeks of treatment, an interim unblinded review of all cumulative safety, PK and efficacy data of JNJ-40411813 available to that date will be performed to decide on whether there should be any addition or modification to the dose(s) in the following cohorts and subsequent clinical studies. If the results of the review are inconclusive with respect to the assessment of efficacy, a second interim review of the same cohort may be done after the last participant has completed the 12-week visit.

PARTICIPANT POPULATION

At least 60 and a maximum of 160 male and female participants are planned to be randomized in the study. To reach these numbers it is expected that about 200 participants will start the baseline pre-randomization period of 8 weeks.

WOCBP will use a highly effective birth control method as outlined in the in/exclusion criteria.

DOSAGE AND ADMINISTRATION

JNJ-40411813 will be supplied for this study as 25-mg and 50-mg tablets. Placebo will be supplied as matching tablets.

The tablets will be taken CC from Day 1 to Day 85 (or day of Visit 7 when before Day 85). All study intervention, apart from the study intervention taken in the clinic during Visits 2, 4 and 6 will be taken at home and intake of the intervention should be confirmed in the e-diary.

All patients in Cohort 2CCI). CCI (or matching placebo) on day 8 of the double-blind phase. CCI .

For participants receiving dosages CCI will be permitted in case adverse events consisting of dizziness, incoordination, sedation, or fatigue (or similar descriptive terms) which, in the judgment of the investigator, potentially limit activities of daily living. The PI is encouraged to rechallenge the initial dose within 2 weeks if the AEs are resolved on the lower dose. If rechallenge is unsuccessful, i.e., the AEs recurred when the dose was increased, the dose may be reduced again and kept at that level.

Patients should be advised to call the site if they experience dizziness or somnolence in the first 2 weeks of the double-blind phase.

Study intervention should be taken in fed condition CCI. The tablets must be swallowed whole with water and not chewed, divided, dissolved, or crushed.

The CCI during Visit 2 (Day 1) of the double-blind period when the participant is in the clinic in the morning. Dosing during the site visit will be witnessed by the study staff. CCI

The participants will bring the study intervention and all other AEDs currently taken with them at each study visit.

On the day of Visit 4 (Week 4) and Visit 6 (Week 8), the CCI will be taken in the study center during the study visit CCI. Dosing during the site visit will be witnessed by the study staff. CCI

The actual dose and the composition of tablets to be taken will be determined for each cohort and stratum within a cohort.

EFFICACY EVALUATIONS

The primary efficacy evaluation will be the time to baseline monthly seizure count. To assess this endpoint, the number and type of seizures during the baseline period and during the double-blind treatment period needs to be documented carefully.

The participant and/or caregiver will be provided access to an (electronic) diary to record seizures and intake of study intervention. The e-diary will be an app downloaded on the smartphone owned by the participant. Only if the participant and/or caregiver do not own a smartphone, a smartphone programmed for the study will be provided.

CCI

PHARMACOKINETIC EVALUATIONS

Venous blood samples of 2 mL each will be collected for determination of plasma concentrations of JNJ-40411813 and metabolites including but not limited to CCI, levetiracetam or brivaracetam and, when used by the participant, CCI as specified in the SoA and Table 4.

SAFETY EVALUATIONS

The collection of AEs and concomitant medications will start after the ICF has been signed and will continue until the final study visit.

Apart from this, the following safety assessments will be performed: physical and neurological examination, body weight, vital signs (including temperature), 12-lead electrocardiogram (ECG), pregnancy testing (female participants only), clinical labs (hematology, chemistry panel) and urinalysis. At screening only: serology and testing for alcohol and drugs of abuse.

Additional blood and urine samples may be taken, or vital signs and ECGs recorded at the discretion of the investigators.

Additionally, emergence of suicidal ideation will be assessed using the Colombia suicide severity rating scale (C-SSRS) at screening, and during each study visit.

STATISTICAL METHODS

Sample size determination

The calculation of the maximum sample size planned for this study was simulation-based and was estimated using a Cox's proportional hazard regression model comparing the time to baseline seizure count between JNJ-40411813 and placebo. A longitudinal model for individual daily seizure counts, taking into account between-subject variability in baseline seizure rate and response to treatment, and a residual overdispersed Poisson error was applied. The simulated daily seizure count data were then converted to time to baseline count data and analyzed using a Cox's proportional hazard regression model.

Assuming a placebo median percentage seizure rate reduction of 15% and a further reduction of 50% (respectively 30%) for JNJ-40411813, a cohort with 40 participants randomized to JNJ-40411813 and 20 to placebo would achieve a power of 99% (respectively 83%) at the α=5% one-sided significance level. In subsequent cohorts with 40:10 randomization, the power becomes 94% for a 50% reduction, with all other assumptions unchanged.

Efficacy analyses

Primary

The intent-to-treat population will be the primary efficacy population, which includes all participants who are randomly assigned to receive study drug and who have baseline and postbaseline seizure data. Data from participants on placebo in cohorts 2 and 3 will be combined with those from Cohort 1 if the Kaplan-Meier curves of the subjects treated with placebo are comparable between cohorts. The analysis for interim review may be done including both pooled and non-pooled placebo subjects.

The individualized baseline monthly seizure count is defined as the number of observable focal onset seizures occurring during the 8-week baseline period, multiplied by 28/ X_{BL}, where X_{BL} is the number of days comprising the baseline period. Observable focal onset seizures include focal aware seizures with motor signs, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures. Focal aware seizures will not be counted towards baseline monthly seizure count. The endpoint time to baseline monthly seizure count is defined, for each patient, as the number of days, until the patient experienced the number

of seizures equal to baseline monthly seizure count, up to the end of the 12-week double-blind treatment period.

Kaplan-Meier analyses will be conducted to describe the time to baseline monthly seizure count distribution (with 95% CI) for each treatment group for all observable focal-onset seizures. A formal comparison of time to monthly baseline seizure count will be made by a Cox proportional hazard regression model, including factors for treatment and any other relevant covariates (details will be provided in the statistical analysis plan). Appropriate adjustment for multiple testing, in case of subsequent cohorts, will be detailed in the SAP.

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 5 components:

- **Population:** patients with established diagnosis of focal epilepsy, for at least 1 year (ILAE 2017 criteria) with 3 to 100 seizures per 28 days; currently on 1 to 4 AEDs with inadequate response to levetiracetam or brivaracetam who have met the inclusion/exclusion criteria.
- **Variable:** the number of days, until the patient experienced the number of seizures equal to baseline monthly seizure count, up to the end of the 12-week double blind treatment period.
- **Intervention event:** the effect of the initially randomized treatment that would have been observed had all participants remained on their treatment throughout the double-blind treatment phase.
- **Intercurrent event (ICE):** treatment discontinuation will be handled according to the hypothetical strategy as if the ICE would not have occurred. Similar efficacy is assumed for subjects who had the ICE as those subjects from the same treatment group who did not have the ICE.
- **Population-level summary:** the difference in estimated hazard ratio between the treatments.

Sensitivity analyses for the primary estimand regarding missing data assumptions; and a supplementary estimand to inform subsequent trials will be specified in the SAP.

Secondary and exploratory

Secondary efficacy endpoints will be subject to an exploratory analysis including descriptive statistics by treatment arm and graphical exploration. Details of the analysis for each secondary endpoint and exploratory endpoints will be provided in the SAP. The SAP will also describe the analysis of the endpoints in the OLE period.

Seizure Freedom

Percent participants with seizure freedom over the complete double-blind period. Participants who exit the study after reaching their pre-randomization baseline seizure count can be included in this analysis without introducing bias as they were not seizure free during the study.

Secondary generalized seizures (Focal to bilateral tonic-clonic seizures)

Separate analyses (including time to baseline count and % reduction of counts) for focal to bilateral tonic-clonic seizures will be performed if a large enough number of events is observed.

Responder rate

A responder is defined as a participant having at least a 50% reduction of the monthly seizure rate. Participants who exit the study at Week 4 after reaching the baseline seizure count will be treated as non-responders in this analysis. As the number of seizures they experienced is either equal or larger than their baseline monthly seizure count, their observed % seizure rate reduction is either zero, or negative (implying an increase).

CCI [redacted]

[redacted]

Pharmacokinetic Analyses

Data for all participants who receive a dose of JNJ-40411813 and have at least one measurement of plasma concentration, will be included in the PK analysis. Plasma concentrations of JNJ-40411813 and metabolites including CCI [redacted], levetiracetam or brivaracetam and CCI [redacted] will be listed for all participants.

Descriptive statistics will be calculated for the plasma concentrations of JNJ-40411813 and metabolites including CCI [redacted], levetiracetam or brivaracetam and CCI [redacted] at each applicable time point. Statistics include sample size (n), mean, standard deviation, coefficient of variation (CV), geometric mean, median, minimum, and maximum.

Population PK and/or PBPK analyses of JNJ-40411813 and levetiracetam or brivaracetam may be performed on the data of this study in combination with data pooled from other studies. An objective of these analyses is to investigate the potential effects of covariates, such as demographics and concomitant drugs, on the pharmacokinetics of JNJ-40411813. The results of the population analyses may be reported separately.

PK and pharmacodynamic (PD) relationship will be explored, if feasible. The results of population PK/PD analyses will also be reported separately.

Safety analyses

All safety analyses will be performed based on the safety analysis set, which will include all participants who receive at least 1 dose of study intervention. Safety summaries will be provided by treatment, unless specified otherwise.

AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class, by severity and relationship to study intervention. Summaries, listings or participant narratives may be provided, as appropriate, for those participants who die, who discontinue treatment due to an AE, or who experience a severe or a serious AE.

The safety analysis will include the incidence of AEs, actual data and changes in blood pressure, pulse rate, laboratory safety data, 12-lead ECG and physical and neurological examination data from predose to all postdose assessments.

The participants with suicidal ideation and/or suicidal behavior collected from the C-SSRS will be listed.

1.2. Schedule of Activities (SoA)[a]

Periods	Screening	Baseline	Double-blind treatment						Follow-up
Study Week (end of)	-8	-8 to 0	-	2	4	6	8	12 (or Early withdrawal)[a]	14
Study Day	-57	-56 to -1[c]	1	15[b]	29[b]	43[b]	57[b]	85[b]	99[b]
Visit[d]	1		2[e]	3	4[e]	5	6[e]	7	8
Clinic visit (C)/ Telephone contact (TC)	C	TC[f]	C	TC	C	TC	C	C	TC
Screening/Administrative Procedures									
Informed consent	X								
CCI [redacted]	X								
Inclusion/exclusion criteria	X		X						
Complete the diagnostic review form	X								
Medical history and demography	X								
Review concomitant medication including antiepileptic drug(s)	X								
Study drug administration									
Randomization			X[g]						
Dispense study drug (PBO or JNJ-40411813)			X[g]		X		X		
Intake study drug CCI [redacted]			Continuous[h]						
Intake CCI [redacted] CCI			X[g]		X		X		
Take levetiracetam or brivaracetam and current AEDs that are CCI [redacted] in the clinic.			X		X		X		
Study drug accountability					X		X	X	

[a] This section has been amended by Amendment INT-1

Periods	Screening	Baseline	Double-blind treatment						Follow-up
Study Week (end of)	**-8**	**-8 to 0**	**-**	**2**	**4**	**6**	**8**	**12 (or Early withdrawal)[a]**	**14**
Study Day	**-57**	**-56 to -1[c]**	**1**	**15[b]**	**29[b]**	**43[b]**	**57[b]**	**85[b]**	**99[b]**
Visit[d]	**1**		**2[e]**	**3**	**4[e]**	**5**	**6[e]**	**7**	**8**
Clinic visit (C)/ Telephone contact (TC)	**C**	**TC[f]**	**C**	**TC**	**C**	**TC**	**C**	**C**	**TC**
Blood and urine collection									
Clinical laboratory test[i] (hematology, serum chemistry and urinalysis)	X		X		X		X	X	
Serology	X								
Blood sample for biomarkers[i]			X[j]		X			X[k]	
PK blood samples for JNJ--40411813 and metabolites, levetiracetam or brivaracetam and AEDs CCI [redacted]			X		X		X	X[m]	
Alcohol breath test and urine drug	X								
Pharmacogenomics assessment									
Pharmacogenomic blood sample collection			X[n]						
Efficacy assessments									
Seizure counts and drug intake in e-diary					X				X[o]
CCI [redacted]			X		X			X	
Safety assessments									
Physical examination	X							X	
Neurologic examination	X							X	
Brief neurological examination			X		X		X		
C-SSRS	X		X		X		X	X	
Vital signs[q]	X		X		X		X	X	
Body weight	X							X	

Periods	Screening	Baseline	Double-blind treatment						Follow-up
Study Week (end of)	**-8**	**-8 to 0**	**-**	**2**	**4**	**6**	**8**	**12 (or Early withdrawal) [a]**	**14**
Study Day	**-57**	**-56 to -1[c]**	**1**	**15[b]**	**29 [b]**	**43 [b]**	**57[b]**	**85[b]**	**99[b]**
Visit[d]	**1**		**2[e]**	**3**	**4[e]**	**5**	**6[e]**	**7**	**8**
Clinic visit (C)/ Telephone contact (TC)	**C**	**TC[f]**	**C**	**TC**	**C**	**TC**	**C**	**C**	**TC**
Height	X								
Electrocardiogram[r]	X				X			X	
Pregnancy test[s]	X		X		X		X	X	
Adverse events	←	—	—	—	—	—	—	—	→
Concomitant therapy	←	—	—	—	—	—	—	—	→

Footnotes:

a) If a participant discontinues treatment before the end of the double-blind treatment period, early withdrawal (EW) visit should be completed
b) ± 2 days
c) When required for practical reasons, the baseline period may be up to 1 week longer or shorter than 8 weeks. Baseline monthly seizure count will be defined as the number of observable focal onset seizures recorded during the baseline period, multiplied by 28/ X_{BL}, where X_{BL} is the number of days comprising the baseline.
d) Participant should come to the study visit in fasted conditions (at least 4 hours) when possible
e) Visit in the morning hours before noon.
f) Participants will be contacted by phone during the baseline period to confirm correct use of the e-diary. This contact should take place at least 4 weeks after the start of the baseline period, but multiple contacts are allowed when required.
g) After completion of all visit assessments (except post-dose PK blood sample).
h) Except in-clinic doses during visits
i) To be collected before dosing and when possible in fasting condition
j) During Visit 2, also collect a blood sample for biomarkers at 2 hours post dose (together with PK-sample)
k) Collect with clinical laboratory sample.
l) Detailed timepoints for PK sample collection are provided in Table 4: PK sampling Strategy
m) Only levetiracetam or brivaracetam and JNJ-40411813, at EW only when EW visit is after Visit 6.
n) CCI [redacted]
o) Only seizure counts. Only subjects who continued treatment to the end of the double-blind treatment period (Week 12) or have completed the study as per Section 7.2
p) CCI [redacted].
q) Systolic and diastolic blood pressure, heart rate and body temperature (oral or tympanic)
r) Triplicate ECG at screening. Single ECG at the other timepoints.
s) In women of childbearing potential only. Serum pregnancy test at screening and a urine pregnancy test at the other visits.

2. INTRODUCTION

JNJ-40411813 is a positive allosteric modulator (PAM) of the metabotropic glutamate receptor-2 (mGlu2), which is abundantly expressed in the forebrain and cerebellum. The mGlu2 receptor functions as a presynaptic auto-receptor that, upon activation, decreases the release of the excitatory neurotransmitter glutamate. Positive allosteric modulation of a receptor will result in the direct enhancement of the agonist-induced signal while PAMs themselves have generally no or low intrinsic activity at the receptor. The net effect of JNJ-40411813 is hypothesized to be a normalization of hyper-glutamatergic transmission. JNJ-40411813 is being evaluated for the treatment of disorders of the central nervous systems (CNS), such as epilepsy, and has been evaluated in schizophrenia and anxious depression.

For the most comprehensive nonclinical and clinical information regarding JNJ-40411813, refer to the latest version of the Investigator's Brochure (IB) for JNJ-40411813.

The term “study intervention” throughout the protocol, refers to JNJ-40411813 or placebo.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

Based on nonclinical data JNJ-40411813 is expected to show synergistic activity with levetiracetam or brivaracetam, which is thought to bind to and regulate Synaptic Vesicle glycoprotein 2a (SV2a), a vesicular protein in the presynaptic terminal involved in glutamate release (Metcalf 2017, 2018). In state of hyperglutamatergic activity such as in an epileptic seizure, coadministration of both compounds is thus expected to decrease the epileptic activity in participants with focal onset seizures with suboptimal response to levetiracetam or brivaracetam.

The current study will be conducted to assess the efficacy, safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of adjunctive JNJ-40411813 in participants with focal onset seizures with suboptimal response to levetiracetam or brivaracetam and to assess long term safety and efficacy in an OLE period.

2.2. Background

2.2.1. Nonclinical Studies[a]

Nonclinical pharmacology

The in vitro potency (as effective concentration [EC_{50}]) is ~100 nM on human mGlu2 based on several cellular read-outs (Lavreysen 2015).

[a] This section has been amended by Amendment INT-2

JNJ-40411813 antagonized the serotonin type 2A (5-HT_{2A}) receptor with moderate potency (K_b=1.1 μM) and showed ≥30-fold selectivity versus other targets. M47 is the major metabolite found in rat but not in human plasma and is equipotent to the parent drug for mGlu2.

EC_{50} for occupying rat mGlu2 is reached at a plasma concentration of 1,032 to 2,247 ng/mL.

JNJ-40411813 has anticonvulsant efficacy in the mouse 6 Hz model. Median effective dose (ED_{50}) after subcutaneous administration was 12.2 and 21.0 mg/kg in the 6 Hz 32 mA and 44 mA stimulus intensity model.

6 Hz 44 mA ED_{50} of levetiracetam was 345 mg/kg intraperitoneal when levetiracetam was dosed alone versus 9.6 mg/kg in combination with a subprotective dose of 10 mg/kg SC JNJ-40411813, an approximately 36-fold shift in the ED_{50}.

JNJ-40411813 was tested in the 6 Hz model in combination with another SV2A Ligand, brivaracetam. In the 6 Hz 44-mA assay, the subprotective dose of JNJ-40411813 (10 mg/kg SC) shifted the ED_{50} of brivaracetam approximately 50-fold

A PD interaction between JNJ-40411813 and levetiracetam was observed in the rat amygdala kindling model. For more details see the IB for JNJ-40411813.

In contrast, there was only limited benefit from combining JNJ-40411813 with diazepam or carbamazepine in the 6 Hz model, and as such the synergy seems specific and unique for the "mGlu2 PAM – SV2A" combination.

Toxicology

No relevant effects on cardiovascular and respiratory functioning were observed in animals. Minor CNS findings (exaggerated pharmacology) were observed.

A benign toxicological profile was seen when dosing animals with JNJ-40411813. Decreases in body weight were seen in rats and dogs.

Administration of JNJ-40411813 CCI [redacted] oral gavage in the Sprague-Dawley rat for 26 weeks was well tolerated, with transient, minimal clinical signs, lower body weight sometimes associated with lower food consumption, minimal changes in hematology and clinical chemistry parameters. Histological changes in liver and thyroid, associated with gross findings and increased organ weight, were indicative of enzyme induction. The No Observed Adverse Effect Level (NOAEL) was considered to be 1000 (male rats) or 500 (female rats) mg/kg/day.

Administration of JNJ-40411813 CCI [redacted] oral gavage for 39 weeks was well tolerated in beagle dog up to 160 mg/kg/day. Treatment induced clinical signs at a low incidence, decreased body weight gain, sometimes associated with lower food consumption, and minimal changes in clinical chemistry parameters. Histological prostate immaturity, associated with gross findings and decreased organ weight, possibly reflected delayed maturation as an indirect effect linked to the

test article-related body weight effects. The NOAEL in the 9-month dog study was considered to be 160 mg/kg/day.

There were no effects on fertility in male rats; a high dose of 200 mg/kg in female rats resulted in estrous cycle irregularities and a higher incidence of pre- and post-implantation loss, likely because of the lower food intake and body weight performance.

There were no test article-related effects on embryo-fetal development in pregnant rats and rabbits.

No genotoxic or phototoxic liabilities have been identified.

Pharmacokinetics and Metabolism in Animals

After oral dosing CCI) absorption from the gut was fast. Using nanosuspensions, the absolute bioavailability of JNJ-40411813 was variable between species and ranged between CCI general, CCI

JNJ-40411813 showed high and comparable plasma protein binding in all species. Tissue distribution experiments showed a fast and moderate distribution to the tissues. The brain/plasma area under the plasma concentration-time curve (AUC) ratio was 0.93. Elimination from tissues appeared parallel to plasma.

Clearance of JNJ-40411813 was mainly via oxidative metabolism in vitro in nonclinical species and man, and in vivo in rat and dog.

The potential of JN-40411813 CCI enzymes is considered limited.

JNJ-40411813 showed lowest CCI

JNJ-40411813 is a weak mechanism-based inhibitor of CYP3A4. Metabolites CCI did not show any potential as CCI

2.2.2. Clinical Studies

To date, 9 Phase 1 clinical studies have been completed including a total of 345 healthy subjects, a Phase 2 study of 100 subjects with schizophrenia, and a Phase 2 study of 121 subjects with Major Depressive Disorder (MDD) with anxiety symptoms.

Pharmacokinetics, Product Metabolism, and Pharmacodynamics

Single oral doses of 5 mg up to 1,000 mg are characterized by a rapid absorption and a biphasic decline. With increasing doses, maximum drug concentration (C_{max}) and AUC_{∞} increase in a less than dose-proportional manner between 5 and 225 mg. However, between the doses of 225 and 1,000 mg, C_{max} and AUC_{∞} tended to increase dose proportionally. With increasing doses, time to

achieve maximum concentration (t_{max}) was delayed and the mean terminal half-life increased from 10.6 hours at 5 mg, to ~27 hours at 1,000 mg. CCI [redacted].

Administration of JNJ-40411813 as a nanosuspension CCI [redacted] Higher exposure CCI [redacted]

Repeated dosing between 50 and 150 mg CCI [redacted] achieved steady state within 2 to 4 weeks.

CYP3A4 has a major role in the metabolic clearance of JNJ-40411813. When CYP3A4 was inhibited with ketoconazole, JNJ-40411813 showed an approximate 43% increase in C_{max} and a 7-fold increase in AUC_{last}. CCI [redacted].

Metabolites are not expected to contribute to the mGlu2 antiepileptic activity of JNJ-40411813 in humans.

Cognitive test results suggest that JNJ-40411813 slightly reduces reaction speed and precision but does not interfere with memory function at dose levels associated with a decrease in alertness.

While no effect was measured on rapid eye movement (REM) sleep latency or duration, an increase in the total time spent in deep sleep as well as a reduction in total sleeping time was observed. JNJ-40411813 500 mg also attenuated the perceptual and behavioral changes induced by a low, subanesthetic dose of ketamine.

JNJ-40411813 100 mg bid reduced craving in abstinent dependent smokers without significantly affecting the negative mood states induced by nicotine abstinence.

The 40411813SCH2001 study was designed to assess compound safety and tolerability in a schizophrenia population. The daily dose was 50 or 150 mg bid. There was no consistent pattern or trend of change observed in the Positive and Negative Syndrome Scale (PANSS) total score, Clinical Global Impression – Schizophrenia (CGI-SCH) scores, Subjective Well-being on Neuroleptics Scale (SWN) scores, and self-rating regarding appetite and attitude assessments. However, there was evidence of greater improvement on the PANSS Negative Subscale and the PANNS Negative Symptoms Marder Factor score for JNJ-40411813-treated subjects with residual negative symptoms.

The 40411813DAX2001 study was designed to evaluate the efficacy in patients with MDD with anxiety symptoms. The daily dose was between 25 and 150 mg bid. No efficacy signal was detected for JNJ-40411813 versus placebo based on change in the 6-item Hamilton Anxiety Scale

(HAM-A_6) and 14-item Hamilton Anxiety Scale (Structured Interview Guide version-SIGH-A) total score from baseline to Week 4.

However, criteria for efficacy signal detection were reached on several key secondary measures of anxiety (Hamilton Depression Rating Scale [$HDRS_{17}$] anxiety/somatization factor score, the Inventory of Depressive Symptomatology [IDS-C_{30}] anxiety subscale) and depression (Hamilton Depression Rating Scale [$HDRS_{17}$], the Hamilton Depression Rating Scale-6 [HAM-D_6, a six-item core depressive symptoms subscale of the $HDRS_{17}$], and the IDS-C_{30}). See the IB for more details.

Safety and Tolerability

JNJ-40411813 was safe and well-tolerated in healthy subjects receiving single oral doses of 5 to 1,000 mg and multiple oral doses of 50 to 225 mg bid.

The most common treatment-emergent adverse events (TEAEs) over all dose levels following single dosing with JNJ-40411813 were dizziness (25.0%), headache (12.3%), vertigo (11.9%), dizziness postural (10.2%), ataxia (8.9%), somnolence (8.1%), fatigue (5.9%), and nausea (5.1%).

The most common TEAEs over all dose levels during multiple oral dosing with JNJ-40411813 were headache (40.5%), dizziness (35.1%), fatigue (17.6%), dyspepsia (12.2%), decreased appetite (8.1%), dizziness postural (6.8%), nausea (6.8%), back pain (5.4%), and coordination abnormal (5.4%).

JNJ-40411813 was well tolerated in subjects with schizophrenia when administered as an add-on treatment to other antipsychotics with a similar TEAE profile (study 40411813SCH2001).

The 150 mg bid dose was less well-tolerated compared to placebo, with more dizziness-related adverse events (AEs) (vertigo, coordination abnormal, dizziness, and dizziness postural) and more TEAEs judged as severe by the investigator were reported in this dose group.

There were no deaths reported in the Phase 2 first-in-patient study (40411813SCH2001). Three subjects (3%) reported treatment-emergent serious adverse events (TESAEs) (including schizophrenia catatonic type, electrocardiogram abnormal, and psychotic disorder, all considered as doubtfully or not related to study drug) during the double-blind phase. Six subjects (8%) reported TESAEs (including anxiety, psychotic disorder, hyponatremia, and augmentation of schizophrenia, all considered as doubtfully or not related to study drug) in the open-label phase.

JNJ-40411813 was safe and well-tolerated in the dosing range studied in subjects with MDD with anxiety symptoms (study 40411813DAX2001), with the most common TEAEs being vertigo, nausea, and headache.

No clinically significant effects on vital signs, 12-lead electrocardiogram (ECG), or clinical laboratory parameters were observed in Phase 1 studies, or in the Phase 2 studies.

2.2.3. Brivaracetam

Brivaracetam is an antiepileptic drug indicated as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy.

Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A), a transmembrane glycoprotein found at presynaptic level in neurons and in endocrine cells. Although the exact role of this protein remains to be elucidated it has been shown to modulate exocytosis of neurotransmitters. Binding to SV2A is believed to be the primary mechanism for brivaracetam anticonvulsant activity.

The recommended starting dose in adults is either 50 mg/day or 100 mg/day based on physician's assessment of required seizure reduction versus potential side effects. Based on individual patient response and tolerability, the dose may be adjusted in the effective dose range of 50 mg/day to 200 mg/day.

The following adverse reactions have been reported as the most common. For details see the Summary of product characteristics for brivaracetam.

- Very common: may affect more than 1 in 10 people somnolence dizziness
- Common: may affect up to 1 in 10 people influenza depression, anxiety, insomnia, irritability decreased appetite convulsion, vertigo upper respiratory tract infections, cough nausea, vomiting, constipation fatigue

2.2.4. Levetiracetam

Levetiracetam is an antiepileptic drug. Its mechanism of action is modulation of synaptic neurotransmitter release through binding to the synaptic vesicle glycoprotein SV2a in the brain. Levetiracetam is a generic drug, where several different formulations are available.

The daily starting dose in adult patients is 1,000 mg/day, given as bid dosing (500 mg per intake). Additional dosing increments may be given (1,000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3,000 mg. The actual dose is titrated for each individual patient.

The following adverse reactions have been reported as the most common. For details see the Summary of product characteristics for levetiracetam.

- Very common: may affect more than 1 in 10 people nasopharyngitis sleepiness headache
- Common: may affect up to 1 in 10 people decreased appetite depression, hostility or aggression, anxiety, insomnia, nervousness or irritability convulsion, balance disorder, dizziness, lethargy (lack of energy and enthusiasm) tremor cough abdominal pain, diarrhea, dyspepsia (indigestion), vomiting, nausea rash asthenia/fatigue (tiredness).

2.3. Benefit/Risk Assessment

2.3.1. Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Unknown efficacy of JNJ-40411813 in epilepsy	JNJ-40411813 has been tested in schizophrenia and anxious depression but not in epilepsy. The synergy between JNJ-40411813 and levetiracetam has been confirmed in nonclinical studies but not in clinical studies.	By selecting the "time to baseline seizure count" as primary efficacy parameter, participants can stop treatment because of non-efficacy already after 4 weeks in the study or later as soon as this endpoint has been reached. Existing anti-epileptic drug (AED) treatment will be continued unchanged.
Non-tolerability of study treatment	Although the safety profile of JNJ-40411813, brivaracetam and levetiracetam is generally benign, no information about the safety and tolerability of the combination is available. No adverse safety effects have been identified in nonclinical studies. Also, the combination with other AEDs has not been tested before. There may be unknown safety risks.	Experience so far in the dosage range employed indicates that JNJ-40411813 is well tolerated and there is no signal for target organ damage. The start dose of JNJ-40411813 in the first cohort is relatively low. In clinical studies, CCI JNJ-40411813 was well tolerated. JNJ-40411813 has been evaluated as adjunctive treatment in a schizophrenia and anxious depression study without exacerbation of tolerability of the concomitant drugs. Participants can stop their participation any time, when the treatment is not tolerated. Amendment 4 introduces a dosage up titration to minimize the occurrence of common dose-related adverse events, and an optional dose reduction to minimize the likelihood of discontinuation in those that have adverse events: All patients in Cohort 2 CCI [redacted] will start the double-blind phase with a dosage of CCI [redacted] (or matching placebo). CCI [redacted] (or matching placebo) on day 8 of the double-blind phase. Up-titration is expected to reduce the number of early onset AE's. For participants receiving dosages of CCI [redacted]

		CCI i.e., Cohort 2 and beyond, a dosage reduction to CCI will be permitted in case adverse events consisting of dizziness, incoordination, sedation, or fatigue (or similar descriptive terms) which, in the judgment of the investigator, potentially limit activities of daily living. The PI is encouraged to rechallenge if the AEs are resolved on the lower dose. If rechallenge is unsuccessful, i.e., the AE's re-occurred when the dose was increased, the dose may be reduced again and kept at that level The safety and tolerability of JNJ-40411813 in combination with levetiracetam or brivaracetam will be reviewed after each cohort
Reduction of JNJ-40411813 CCI	CCI may be inferred but have only been studied in nonclinical models, not yet in man.	Participants will be stratified into 2 groups, with and without the concomitant use C CCI CCI , and CCI on physiologically based pharmacokinetic modeling (PBPK) of CCI . Plasma concentrations of JNJ-40411813 will be evaluated after each cohort and doses will be adapted based on observed interactions.
Increase in the concentration C CI	Based on in vitro studies, JNJ-40411813 CCI	Concomitant drugs with a narrow therapeutic margin CCI Plasma concentrations of concomitant CCI can be reduced once if the participant experiences Aes possibly related to these AEDs.

2.3.2. Benefits for Study Participation[a]

Treatment resistant epilepsy has a severe impact on quality of life and risk of mortality. JNJ-40411813 in combination with levetiracetam or brivaracetam shows promise in a nonclinical model of epilepsy and – if proven efficacious in man too – may result in a significant positive impact on this patient population.

[a] This section has been amended by Amendment INT-2 and INT-4

All participants may benefit from the safety evaluations performed during the study.

The sponsor has added an OLE period to this study (to be initiated when all required supplies are available), with eligibility for all participants who completed the double-blind study period and experienced no safety concerns.

2.3.3. Benefit-Risk Assessment for Study Participation

The risk/benefit of JNJ-40411813 is favorable and the currently available safety and efficacy data support the proposed clinical trial 40411813EPY2001 to investigate efficacy and safety of JNJ-40411813 in participants with focal onset epilepsy.

More detailed information about the known and expected benefits and risks of JNJ-40411813 may be found in the current IB for JNJ-40411813.

3. OBJECTIVES AND ENDPOINTS [a]

Objectives	Endpoints
Primary	
The primary objective of this study is to evaluate the efficacy of up to 3 dose levels of adjunctive JNJ-40411813 compared to placebo based on the time to baseline monthly seizure count in participants with focal onset seizures who are receiving levetiracetam or brivaracetam and up to 3 other AEDs	Time to baseline monthly seizure count is defined, for each patient, as the number of days until the patient experienced the number of seizures equal to baseline monthly seizure count, up to the end of the 12-week double-blind treatment period.
Secondary	
To evaluate the overall safety and tolerability of adjunctive JNJ-40411813 compared to placebo in participants with focal onset seizures who are receiving levetiracetam or brivaracetam and up to 3 other AEDs.	Adverse events, significant changes in vital signs, ECG and safety laboratory results.
To evaluate the efficacy of up to 3 dose levels of adjunctive JNJ-40411813 compared to placebo based on percent reduction in the double-blind monthly seizure count, relative to the pre-randomization monthly seizure count, in participants with focal onset seizures.	Percent reduction in the double-blind monthly seizure count is defined as the double-blind monthly seizure count minus the baseline monthly seizure count, divided by the baseline monthly seizure count. The double-blind monthly seizure count is defined as the total number of observable focal onset seizures occurring during the 12-week double blind treatment period, multiplied by $28/X_{DB}$, where is the number of days comprising the double-blind period. Observable seizures that will be counted during baseline and throughout the study

[a] This section has been amended by Amendment INT-1 and INT-3

Objectives	Endpoints
	include focal aware seizures with motor signs, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures. Focal aware seizures without motor signs, myoclonic, or other generalized seizures will not be counted.
To evaluate the efficacy of JNJ-40411813 over the double-blind period using percent participants with seizure freedom and percent responders (>50% seizure rate reduction).	The proportion of participants with no seizures during the double-blind period, and the proportion with a greater than 50% reduction in monthly seizure count relative to baseline monthly seizure count.
To evaluate the pharmacokinetics (PK) of JNJ-40411813 and selected metabolites and levetiracetam or brivaracetam in participants with focal onset seizures who are receiving levetiracetam or brivaracetam and up to 3 other AEDs.	Plasma concentrations of JNJ-40411813 and levetiracetam or brivaracetam at baseline (Day 1) and on study weeks 4, 8, and 12
Exploratory	
CCI [redacted]	

Hypothesis

The hypothesis of this study is that JNJ-40411813 added to treatment that includes levetiracetam or brivaracetam significantly prolongs the time to baseline monthly seizure count compared to placebo add-on treatment.

4. STUDY DESIGN

4.1. Overall Design[a]

This study as per Amendment INT-2 will consist of a double-blind treatment period and an open-label extension (OLE) period. Details about the OLE period are described in Section 10.

This is a double-blind, randomized, parallel, placebo-controlled study with the option for an OLE period. The study will consist of 1 to a maximum of 3 cohorts. In each cohort, for each participant the study consists of a screening visit, an 8-week prospective pretreatment baseline period, an up to 12-week double-blind treatment period and, for those participants electing not to enter the OLE period, a follow-up telephone visit 2 weeks after the last dose of study intervention. Participants have the option to enter an OLE period, in which treatment with JNJ-40411813 may be continued until the product becomes available by prescription, or until development of JNJ-40411813 in this indication ceases. The total maximal duration of the study is approximately 22 weeks for each participant, up to the time of entry into the OLE period.

Participants from 18 to 69 years (inclusive) old with an established diagnosis of focal onset seizures will be enrolled in the study. For the first cohort, approximately 80 eligible participants will be initially enrolled to ensure that approximately 60 participants are randomly assigned in a 2:1 ratio to receive either JNJ-40411813 CCI placebo. For each following cohort, approximately 60 eligible participants will be initially enrolled to ensure that approximately 50 participants are randomly assigned in a 4:1 ratio to receive either JNJ-40411813 CCI placebo.

In each cohort, participants will be CCI CCI

At least 20% of the participants must be included in each of the two groups.

After giving written informed consent, participants will be screened immediately prior to the start of the pretreatment baseline period to ascertain their eligibility for the study per the inclusion and exclusion criteria. Upon completion of all informed consent form (ICF) procedures, recording of Aes and concomitant medication will start.

After the screening visit, the data of the participant may be subject to an adjudication process by independent experts from the epilepsy consortium. In this adjudication process the experts may decide whether the participant meets eligibility criteria to participate in the study.

After screening, if they meet the in- and exclusion criteria for which data are available, participants can start the 8-week prospective pretreatment baseline period pending the results of the central laboratory and – if applicable – the adjudication process. However, when the results of these

[a] This section has been amended by Amendment INT-1 and INT-2 and INT-3

assessments indicate that the participant does not meet the in- and exclusion criteria, the participant will terminate the baseline period and will not be randomized to treatment.

During the 8-week prospective pretreatment baseline period participants will continue to take their prescribed AEDs (one of which must include levetiracetam or brivaracetam) without change in dosage(s); new concomitant AEDs should not be added. During the baseline period, participants will record seizure information (type and frequency of seizures) in an e-diary. Baseline monthly seizure count will be defined as the number of observable focal onset seizures recorded during the baseline period, multiplied by $28/X_{BL}$, where X_{BL} is the number of days comprising the baseline.

Participants must be compliant with the recording of information in the subject e-diary throughout the study. Observable seizures that will be counted during baseline and throughout the study, include focal aware seizures with motor signs, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures. Focal aware seizures without motor signs, myoclonic, or other generalized seizures will not be counted.

Participants who meet study entry criteria at the end of the prospective pretreatment baseline period will be randomized to JNJ-40411813 or placebo, CCI [redacted]. The dosage(s) of concomitant AEDs should not be increased, and new concomitant AEDs should not be added to the treatment regimen.

Dosages of JNJ-40411813 in the first cohort will be CCI [redacted] or placebo for CCI [redacted], and CCI [redacted] or placebo CCI [redacted]. Dosages of JNJ-40411813 in Cohort 2 will be CCI [redacted] or placebo for CCI [redacted] or placebo for 7 days, dose increase to CCI [redacted] or placebo on day 8) and CCI [redacted]. In the following cohorts, the dose of JNJ-40411813 will be determined based on an ongoing assessment of tolerability and safety results from the previous cohort. The highest dose in following cohorts will be CCI [redacted]. The highest dose selected to be administered by induced participants will be expected not to exceed the 95th percentile of the CCI [redacted] fter repeated administration of CCI [redacted] The minimum dose that might be considered in successive cohorts will be CCI [redacted]

Participants are encouraged to complete at least the first 4 weeks of treatment when there are no safety concerns. Participants who have exceeded their pre-randomization monthly seizure count at Week 4, or within any 4-week interval after Week 4 ("4-week sliding window approach") up to Week 12, will have the option to discontinue the study drug for lack of efficacy and to perform the end of study/early withdrawal visit, to continue double blind treatment, or to enter the OLE period. Participants who have not exceeded the pre-randomization seizure count will continue the double-blind treatment period through Week 12 and will have the option to perform the end of study visit or to enter the OLE period.

Procedures performed in the OLE period are described in Section 10.

Participants will visit the study center according to the schedule in the Schedule of Activities (SoA).

After at least 55 patients in Cohort 1 and after at least 45 patients in Cohort 2 have completed at least 4 weeks of treatment, an interim unblinded review of all cumulative safety, PK and efficacy data of JNJ-40411813 available to that date will be performed to decide on whether there should be any addition or modification to the dose(s) in the following cohorts and subsequent clinical studies. If the results of the review are inconclusive with respect to the assessment of efficacy, a second interim review of the same cohort may be done after the last participant has completed the 12-week visit.

See Figure 1 for the study flow diagram.

The study assessments will be completed as described in the SoA in Section 1.2.

Follow-up examination or early withdrawal

All participants will have a follow-up visit by telephone (Visit 8) at 2 weeks ±2 days after the last dose of study intervention. Participants who prematurely withdraw from the study should complete Visit 7. Participants who continued treatment to the end of the double-blind treatment period (Week 12) or have completed the study as per Section 7.2 will continue to collect information on the number of seizures they experience using the e-diary until 2 weeks after the last dose of study medication. The procedures to be completed during this visit are listed in the SoA.

4.2. Scientific Rationale for Study Design

Design aspects and placebo control

A 1 to 3-cohort approach has been chosen to limit the number of participants exposed to study intervention and study procedures. Starting in Cohort 1 with a dose that is well tolerated but also expected to generate clinical effect, a rational decision may be taken based on ongoing assessment of the tolerability and safety whether in successive cohorts a higher or lower dose is needed for

optimal treatment. This decision may be based on the incidence of serious adverse events, or adverse events leading to discontinuation, as a cohort approaches full enrollment. Given a low incidence of these events, decision to evaluate of a higher dosage in the following cohort can be made, without pausing screening and enrollment.

The placebo response in studies in epilepsy may be significant (Goldenholz 2016). A placebo control will be used to establish the change in seizure count and the change in safety endpoints that may occur in the absence of active treatment.

Stratification

JNJ-40411813 is metabolized mainly by CYP3A4. CCI [redacted]

Optional dosage reduction

As noted in the Investigator's brochure, dizziness, vertigo, coordination abnormal and fatigue are adverse drug reactions attributable to JNJ-40411813. Somnolence has also been reported. These are adverse events commonly seen with other AEDs; their frequency and severity may be related to dose and may be mitigated by temporary dose reduction or dose titration. Accordingly, if these adverse events occur with increasing frequency when dosages exceed CCI [redacted] CCI [redacted] e.g. Cohort 2 and beyond, the investigator will have the option to reduce dosage temporarily, followed by rechallenge. The PI is encouraged to rechallenge the initial dose within 2 weeks if the Aes are resolved on the lower dose. If rechallenge is unsuccessful, i.e., the AEs recurred when the dose was increased, the dose may be reduced again and kept at that level.

This option will minimize the likelihood of dropout because of adverse events, and will provide experience to guide dosing instructions in future studies

Time to baseline monthly seizure count as an endpoint

The most commonly used endpoint in studies in epilepsy is the reduction of number over seizures over a time period during treatment compared to a baseline reference period, operationalized as percent reduction in seizure frequency relative to baseline, or proportion of participants that have a 50% or greater reduction in seizure frequency relative to baseline. A post hoc analysis of 3 randomized, double-blind, placebo-controlled Phase III trials of perampanel in epilepsy (French 2015) concluded that the time to baseline monthly seizure count as an endpoint appears to properly differentiate efficacious and nonefficacious dosages, as defined by the traditional endpoints.

Use of time to baseline monthly seizure count as the primary trial outcome could result in a significant reduction in exposure to placebo or ineffective treatments if participants should exit as soon as that time point is reached, thereby facilitating trial recruitment and improving safety. However, participants are encouraged to remain on double-blind treatment for at least 4 weeks when safety allows this.

Seizure count will be recorded by the participant and/or the caregiver using an e-diary. A seizure diary has been used in multiple studies in epilepsy. It is known that the use of a diary may result in underreporting (Blachut 2015). The e-diary may limit underreporting by allowing entry of seizures by a caregiver, by sending daily reminders to the participant and by allowing the participant to use their own lay terms for seizure identification. This e-diary will allow for an immediate feedback when the time to baseline seizure count has been reached over a period of 4 weeks. This will allow the participant to terminate the study participation if required.

The secondary endpoints will include more commonly used clinical trial endpoints which will allow comparison against historical trials.

Combination with levetiracetam and brivaracetam.

Nonclinical models have shown a strong positive PD interaction of JNJ-40411813 with levetiracetam and brivaracetam. These models have been confirmed with multiple mGlu2PAMs (Metcalf 2017, 2018). The mechanism of action of levetiracetam and brivaracetam is through binding to SV2a in the brain resulting in a modification of glutamate release. By the positive allosteric modulation of the mGlu2-receptor, JNJ-40411813 also modifies glutamate release. However, the mechanism by which these effects synergize in presynaptic terminals has not been clarified in detail yet.

Study population

Male and female participants with focal onset epilepsy and not having primary generalized seizures will be enrolled in this study. The upper age limit will be 69 years, as participants over 70 years of age have an increasing incidence of progressive neurodegenerative diseases, which would make interpretation of longer-term changes in seizure frequency and tolerability more difficult to interpret.

Inclusion of women of childbearing potential (WOCBP) is supported by the absence of toxicity seen in Segment II reproductive toxicology studies. WOCBP will use a highly effective birth control method as outlined in the inclusion criteria (see Section 5.1).

Participants may benefit from their participation during the study. In addition, an OLE period has been added to this study to allow continued use of JNJ-40411813 in combination with levetiracetam or brivaracetam for those participants who benefit from this treatment.

Duration of study periods

Participants will be dosed with study intervention over 12 weeks. This is a common duration of evaluation of AED's in clinical studies (EMA 2018, FDA 1981). After at least 55 participants in a cohort 1 and at least 45 patients in Cohort 2 have completed 4 weeks of treatment, an interim

unblinded review of all cumulative safety, PK and efficacy data of JNJ-40411813 available to that date will be performed to decide on the dose in the following cohort. If the results of the review are inconclusive, a second interim review of the same cohort may be done after the last participant has completed the 12-week visit.

Based on an evaluation of the variability of seizure count in prior epilepsy studies completed by the sponsor (Janssen, data on file), a baseline duration of 8 weeks was considered to give a more accurate and representative estimate of monthly seizure count than shorter periods.

The double-blind study period will be followed by a follow-up period of 2 weeks if the participant does not take part in the OLE period. The dose will not be tapered after completion of the double-blind study period. Although there are no signals of a rebound effect after stopping the treatment with JNJ-40411813 from preclinical studies or previous clinical studies, the change of seizure count after stopping the treatment will be investigated in the follow-up period.

Safety assessments

Standard safety assessments including physical and neurological examination, vital signs, 12-lead ECG, clinical chemistry, hematology, and urinalysis will be performed.

Additionally, emergence of suicidal ideation will be assessed using the Columbia Suicide Severity Rating Scale (C-SSRS) (Posner 2007, See Section 11.9). The C-SSRS has been used frequently in clinical studies and is a standard measure for suicidal ideation assessment according to Food and Drug Administration (FDA) guidance (US FDA 2012).

[redacted] CCI [redacted]

CCI [redacted]

Biomarkers

Blood samples will be collected to determine the plasma concentration of CCI [redacted]

[redacted]

[a] This section has been amended by Amendment INT-1, INT-3, and INT-4

CCI [redacted]

[redacted].

Pharmacokinetics

Blood samples will be collected to determine plasma concentration of JNJ-40411813 in plasma. The sampling days and times were selected so that population PK and/or PBPK analyses analysis could be conducted for the parent drug. The concentrations of metabolite CCI the most prominent metabolite in human plasma after repeated administration of JNJ-40411813, CCI which is equipotent to the parent drug for mGlu2, and CCI will be measured.

The plasma concentration of levetiracetam or brivaracetam will be measured so that safety, in the presence and absence of JNJ-40411813 may be assessed (i.e., confirm that circulating levels of levetiracetam or brivaracetam are not altered). CCI [redacted] since they were the most frequently used AEDs in the Phase 3 program of perampanel, an AED approved for the adjunctive treatment of partial-onset and primary tonic-clonic seizures in patients ≥12 years of age CCI [redacted] (Majid 2016). In CCI [redacted]

Pharmacogenomics

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. CCI [redacted]

[redacted]

[redacted]

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue

participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The primary ethical concern is the use of an JNJ-40411813 as an experimental treatment in epilepsy. Although nonclinical evidence of potential efficacy is available, no studies in humans with epilepsy have been done before; therefore, the efficacy of JNJ-40411813 is unknown. However, the time-to-event design may reduce the time in the study for those participants that have not experienced a reduction of seizure rate.

The compound has been used in several clinical studies in healthy subjects and patient populations (see IB) and was generally well tolerated. In addition, participants in whom the combination of levetiracetam or brivaracetam and JNJ-40411813 is not efficacious by reaching the time to baseline seizure count before the end of the study may terminate the study.

Some of the participants will receive only placebo on top of the existing AEDs. By using the time to baseline seizure count endpoint, participants may terminate their participation as soon as the study treatment has shown to be nonefficacious. Also, the maximum study duration of 12 weeks sets further limits on the exposure to placebo.

The total blood volume to be collected (< 450 mL) is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of a Red Cross blood donation.

4.3. Justification for dose

The dose of the first cohort will be CCI or placebo for CCI participants and CCI or placebo for CCI participants. This is considered a relative low dose compared to the 150-mg dose given in completed studies in schizophrenia and anxious depression. The number of AEs documented in clinical studies is dose dependent (see IB) and a dose of CCI was well tolerated. Although no negative safety findings were observed in the nonclinical studies combining levetiracetam or brivaracetam and JNJ-40411813, there is currently no clinical experience on the safety and tolerability of this combination. For this reason, it is preferred to start at a lower dose level. Dosages of JNJ-40411813 in Cohort 2 will be CCI or placebo CCI participants and CCI participants. All patients in Cohort 2 CCI) will start the double-blind phase with a dosage of CCI (or matching placebo). CCI CCI) on day 8 of the double-blind phase. CCI CCI

In the following cohorts, the dose of JNJ-40411813 will be determined based on the preliminary efficacy and safety data from the previous cohort. The highest dose in following cohorts will be CCI . The highest dose selected to be administered by CCI participants will be expected not to exceed the 95th percentile of the plasma C_{max} for JNJ-40411813, based on a population PK and/or a PBPK model, after repeated administration of CCI in

CCI . The balance of the dose between CCI in Cohorts 3 and 4 may change based on the observed plasma concentrations in a previous cohort.

4.4. End of Study Definition[a]

End of Study Definition for the double-blind period.

The end of study for the double-blind period is considered as the last visit for Visit 7 for the last participant in the study. The final data for the double-blind period from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement. The double-blind study period will be analyzed separately from the OLE period.

5. STUDY POPULATION

For the first cohort, approximately 80 eligible participants will be initially included to ensure that approximately 60 participants are randomly assigned in a 2:1 ratio to receive either JNJ-40411813 CCI or placebo. For each following cohort, approximately 60 eligible participants will be initially enrolled to ensure that approximately 50 participants are randomly assigned in a 4:1 ratio to receive either JNJ-40411813 CC or placebo. If 3 cohorts are studied, the total number randomized would be 160 participants. The inclusion and exclusion criteria for enrolling participants in this study are described in the following sections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the study responsible physician (SRP) before entering the participant into the study. Exceptional and limited re-testing of abnormal screening values, including laboratory values, that lead to exclusion are allowed only once to reassess eligibility. This should only be considered if there is no anticipated impact on participant safety.

Participants will be enrolled after reading the participant information sheet and signing the ICF indicating that they understand the purpose of, and procedures required for the study and are willing to participate in the study and comply with the study procedures.

5.1. Inclusion Criteria[b]

Each potential participant must satisfy all the following criteria to be enrolled in the study.

Epilepsy related inclusion criteria

1. Participants must be men or women, 18 to 69 years of age, inclusive.

   Note: Participants should be at least 18 years of age or older as per the legal age of consent in the jurisdiction in which the study is taking place.
2. Body Mass Index (BMI) between 18 and 35 kg/m^2 inclusive (BMI=weight/height^2). Minimum body weight should be 40 kg.
3. Criterion modified by Amendment INT-1

[a] This section has been amended by Amendment INT-2

[b] This section has been amended by Amendment INT-2 and 3

3.1 Criterion modified by Amendment INT-2

3.2 Established diagnosis of focal epilepsy, using the International League Against Epilepsy (ILAE) criteria (Fisher 2017). Participants should not be enrolled if they are known to have had fewer than 3 or more than 100 seizures in any monthly period in the past 6 months. It is preferred that participants have experience in maintaining a seizure e-diary.

4. Criterion modified by Amendment INT-1

4.1 Must have had a neuroimaging procedure within 10 years, including a computed tomography (CT) scan or magnetic resonance imaging (MRI), that excluded a progressive neurologic disorder; these procedures may be performed within the 8-week baseline period.

5. Criterion modified by Amendment INT-2

5.1. Criterion Modified by Amendment INT-3

5.2.

5.2.1. Cohort 1: Current treatment with at least 1 and up to 4 AEDs (including levetiracetam), administered at the appropriate dosage(s) and for a sufficient treatment period before screening. These AEDs must remain unchanged throughout the pretreatment and double-blind treatment periods (with the exception of dosage reductions of concomitant AEDs because of suspected elevated AED levels or side effects).

5.2.2. Cohort 2 and beyond: Current treatment with at least 1 and up to 4 AEDs (including levetiracetam or brivaracetam), administered at the appropriate dosage(s) and for a sufficient treatment period before screening. These AEDs must remain unchanged throughout the pretreatment and double-blind treatment periods (with the exception of dosage reductions of concomitant AEDs because of suspected elevated AED levels or side effects). **Important note: screening of patients receiving Brivaracetam will start when enrolling for Cohort 2.**

- Note: One-time changes in AED dosages do not represent a change in the daily AED regimen. For example, if the participant took an extra dose of an AED on one day, this would not represent a change in the daily AED regimen. Benzodiazepines and barbiturates received on a continuing basis at stable dosages for 1 month before screening should be considered as concomitant AEDs, except if they are taken to treat anxiety.

6. This criterion has been removed per Amendment INT-2.

7. Participants who continue to meet entry criteria at the end of the baseline period must also meet the following criteria to be randomly assigned to treatment in the double-blind treatment period of the study:

- Have had ≥3 and ≤100 seizures* per 28 days within the first 4 weeks and also within the second 4 weeks of the baseline period.
- No seizure-free interval for more than 21 days

* Baseline seizure count includes: focal aware seizures with motor signs, focal impaired awareness seizures, and focal to bilateral tonic-clonic seizures.

Do not count: Focal aware seizures without motor signs, myoclonic, or other generalized seizures will not be counted.

Other inclusion criteria

8. Healthy on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the investigator.
9. Healthy on the basis of physical examination, medical history, vital signs, and 12-lead ECG [means of triplicate ECG, incl. QTcF ≤ 450 msec for males and ≤ 470 msec for females; PR interval <220 msec] performed at screening. Minor abnormalities in ECG, which are not considered to be of clinical significance by the investigator, are acceptable. The presence of Left Bundle Branch Block (LBBB), atrioventricular (AV) Block (second degree or higher), or a permanent pacemaker or implantable cardioverter defibrillator [ICD] will lead to exclusion.
10. **Men** who are sexually active with a woman of childbearing potential and have not had a vasectomy must agree to use a barrier method of birth control i.e., a condom with spermicidal foam/gel/film/cream/suppository for the duration of the study plus 3 months after receiving the last dose of study drug, and all men must not donate sperm during the study and for 3 months after receiving the last dose of study drug. In addition, male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.
11. Before first dosing, a **woman** must be either:
    a. Not of childbearing potential. This may include:
        i. Postmenopausal: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient). If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
        ii. Permanently sterilized. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.
        iii. Otherwise be incapable of pregnancy.
    b. Of childbearing potential and practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) consistent with local regulations regarding the use of birth control methods for participants participating in clinical studies and agrees to remain on a highly effective method while receiving study intervention and until 3 months after last dose - the end of relevant systemic exposure. Examples of highly effective methods of contraception

are located in Section 11.6, Appendix 6. Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Note: If a woman of childbearing potential who is not heterosexually active becomes active after the start of the study, she must begin a highly effective method of birth control, as described in Section 11.6, Appendix 6. Contraceptive and Barrier Guidance and Collection of Pregnancy Information.

12. A **woman** of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose.
13. A **woman** must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 3 months after receiving the last dose of study intervention.
14. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.
15. Sign an ICF indicating that they understand the purpose of, and procedures required for the study and are willing to participate in the study.
16. To participate in the optional pharmacogenomic component of this study, participants (or their legally acceptable representatives) must have signed the ICF for pharmacogenomic research indicating willingness to participate in the pharmacogenomic component of the study (where local regulations permit). Refusal to consent for this component does not exclude a participant from participation in the study.

5.2. Exclusion Criteria[a]

Epilepsy related exclusion criteria

1. Have a generalized epileptic syndrome.
2. Diagnosis of Lennox-Gastaut Syndrome.
3. Currently experiencing seizures that cannot be counted accurately, for example, because of the following reasons:
   - Extreme frequency or clustering.
   - Lack of clear onset and cessation between seizures.
   - Lack of informant to provide a seizure count when the participant is unable to independently recall.
4. History of any current or past nonepileptic seizures, including psychogenic seizures.
5. Criterion modified by Amendment INT-2

   5.1 Recently initiated vagus nerve stimulation, deep brain and cortical stimulation (i.e. in the last 12 months before screening).
6. Planned epilepsy surgery within the next 6 months or completed epilepsy surgery < 6 months ago.
7. Criterion modified by Amendment INT-4

[a] This section has been amended by Amendment INT-2, INT-3 and INT-4

7.1. Current treatment with vigabatrin. In the case of history of previous use of vigabatrin, a visual field examination must have been performed in the past after vigabatrin discontinuation. This examination should have been reliable and performed by an ophthalmologist or neuro-ophthalmologist. The visual field examination does not have to be normal but must be stable. Participants that have not had the visual field examination after vigabatrin discontinuation could have one done at any point prior to randomization.

Other exclusion criteria

8. History of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with minimal risk of recurrence).
9. Current or past (within the past year) major psychotic disorder, such as schizophrenia, bipolar disorder, or other psychotic conditions, recent (within the past 6 months) interictal psychosis, and MDD with psychotic features.
10. Exacerbation of MDD within the past 6 months; antidepressant use is allowed.
11. Positive test for hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) at Screening, or other clinically active liver disease (in SoA).
12. History of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at Screening.
13. Has a current or recent history of clinically significant suicidal ideation within the past 6 months, corresponding to a score of 4 (active suicidal ideation with some intent to act, without specific plan) or 5 (active suicidal ideation with specific plan and intent) for ideation on the C-SSRS, or a history of suicidal behavior within the past 1 year, as validated by the C-SSRS at screening. Participants with a prior suicide attempt of any sort, or prior serious suicidal ideation/plan > 6 months ago, should be carefully screened for current suicidal ideation and only included at the discretion of the investigator.
14. Participant has a history of at least mild drug or alcohol use disorder according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) criteria within 1 year before Screening.
15. Criterion modified by Amendment INT-3

    15.1 Criterion modified by Amendment INT-4

    15.2 Positive test result(s) for alcohol and/or drugs of abuse (opiates [including methadone], cocaine, amphetamines, methamphetamines, cannabinoids [does not apply for subjects using cannabidiol as AED or subjects using medical cannabis to treat a medical condition that is part of the medical history], barbiturates, ecstasy and benzodiazepines [does not apply for subjects using benzodiazepines or barbiturates as AED , rescue medication in epilepsy or treatment of anxiety]) at screening.

    Subjects with a positive alcohol or drug screen may have the test repeated once, based on the investigator's discretion. This determination, and the reason for permitting a repeat test, must be recorded in the subject's source documents and initialed by the investigator. A positive, repeat alcohol or drug screen is exclusionary.
16. Clinically significant acute illness within 7 days prior to study intervention administration.

17. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 90 days before the planned first dose of study intervention or is currently enrolled in an investigational interventional study.
18. Known allergies, hypersensitivity, or intolerance to placebo, JNJ-40411813 or its excipients (See IB).
19. Taking any disallowed therapies as noted in Section 6.5, Concomitant Therapy before the planned first dose of study intervention.
20. Inability to swallow the study intervention whole with the aid of water.
21. Donation of 1 or more units (approximately 450 mL) of blood or acute loss of an equivalent amount of blood within 90 days prior to study intervention administration.
22. Pregnant, or breast-feeding, while enrolled in this study.
23. Had major surgery, (e.g., requiring general anesthesia) within 8 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study or within 4 weeks after the last dose of study intervention administration

    Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate
24. Psychological and/or emotional problems, which would render the informed consent invalid, or limit the ability of the participant to comply with the study requirements.
25. Any condition that in the opinion of the investigator would complicate or compromise the study, or the wellbeing of the participant.
26. Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.
27. Vulnerable participants (e.g., a person kept in detention).
28. Participants unable to read and understand the consent forms and patient reported outcomes, complete study-related procedures, and/or communicate with the study staff. Participants with mild intellectual or cognitive disability are allowed in the study when they have the capacity to provide consent, or at least assent with consent provided by a legally authorized person.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's status changes (including laboratory results) after screening but before first dose of study intervention is given such that they now meet an exclusion criterion, they should be excluded from participation in the study.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.5, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (e.g., contraceptive requirements).

5.3.1. Meals and Dietary Restrictions

1. Participants may not consume any food or beverages containing, grapefruit juice, Seville oranges (including any orange marmalade), or quinine (e.g., tonic water) from 48 hours (72 hours in the case of grapefruit juice and Seville oranges) before the first dose of study intervention until the last dose of study intervention.
2. Participants may not consume food containing poppy seeds from 72 hours before to completion of the screening visit.

5.3.2. Caffeine, Alcohol, and Tobacco

1. Participants should abstain from using excessive alcohol or any illegal drugs within 3 days prior to Day 1 and at any time during the study. Current low to moderate use of alcohol as approved by the investigator may be continued unchanged.
2. The participant will be advised not to change the current use of caffeine and current smoking behavior.

5.3.3. Activity

1. Should avoid driving or operating complex machinery until the participant knows whether the drug adversely affects reaction time or impairs judgment.
2. Participants must avoid donating blood for at least 90 days after completion (i.e., final follow-up visit) of the study.

5.4. Screen Failures[a]

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Exceptional and limited re-testing of abnormal screening values, including laboratory values, that lead to exclusion are allowed only once to reassess eligibility. However, if the participant is a screen failure based on the adjudication process by independent experts from the epilepsy consortium at screening, re-testing will not be allowed.

[a] This section has been amended by Amendment INT-1 and INT-3

If the adjudication process is not possible e.g., because of technical limitations of protected data transfer, the participant will not be a screen failure.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time after discussion with the sponsor representative. Rescreened participants will be assigned a new participant number, undergo the informed consent process, and then start a new screening and baseline phases. Rescreened individuals must meet all criteria before entering the double-blind phase.

6. STUDY INTERVENTIONS

For description of the study intervention in the OLE period, see Section 10.6.

6.1. Study interventions Administered[a]

JNJ-40411813 will be supplied for this study as 25-mg and 50-mg tablets. Placebo will be supplied as matching tablets.

The tablets will be taken CCI from Day 1 to Day 85 (or day of Visit 7 when before Day 85). All study intervention, apart from the study intervention taken in the clinic during Visits 2, 4, and 6 will be taken at home and intake of the intervention should be confirmed in the e-diary.

Study intervention should be taken in fed condition during or immediately CCI CCI. The tablets must be swallowed whole with water and not chewed, divided, dissolved or crushed.

The CCI dose will be ingested immediately CCI Visit 2 (Day 1) of the double-blind period when the participant is in the clinic CCI. Dosing during the site visit will be witnessed by the study staff. CCI

The participants will bring the study intervention and all other AEDs currently taken with them at each study visit.

On the day of Visit 4 (Week 4) and Visit 6 (Week 8), CCI will be ingested in the study center during or CCI uring the study visit and not at home. Dosing during the site visit will be witnessed by the study staff. CCI For Visit 7,CCI

The actual dose and the composition of tablets to be taken will be determined for each cohort and stratum within a cohort. In Table 1 below the most likely examples are presented. However, these examples may change based on actual dose decisions.

[a] This section has been amended by Amendment INT-1

CCI [redacted]

A description of the study interventions is presented in Table 2:

Table 2: Description of Interventions

Arm Name	JNJ-40411813	Placebo
Intervention Name	JNJ-40411813	Placebo
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	25 or 50 mg JNJ-40411813	Placebo
CCI [redacted]	[redacted]	[redacted]
Route of Administration	oral	oral
Use	experimental	Placebo-comparator
Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP)	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Provided in child-resistant packaging, labeled to meet applicable regulatory requirements.	Provided in child-resistant packaging, labeled to meet applicable regulatory requirements.
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

6.2. Preparation, Handling, and Storage

All study intervention will be manufactured and provided under the responsibility of the sponsor. All study intervention will be provided in child-resistant high-density polyethylene bottles. All study intervention will be stored in a secure area with restricted access. Tablets must be stored at controlled room temperatures as indicated on the product specific labeling.

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of study intervention to the

participant, and the return of study intervention from the participant, must be documented in the interactive web response system (IWRS) system. Participants must be instructed to return all original study intervention kits, whether empty or containing study intervention.

Study intervention must be handled in strict accordance with the protocol and the label. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the study intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the medication return form.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding[a]

Procedures for Randomization

Central randomization will be implemented in this study. Participants will be randomly assigned to one of two treatment groups based on computer-generated randomization schedules prepared before the study by, or under the supervision of the sponsor.

The randomization will be balanced by using randomly permuted blocks CCI [redacted]

The IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kits for the participant. The requestor must use his or her own user identification and personal identification number each time when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

For programming of the IWRS-system, the following cohort numbers will be applied:

- Cohort 1: first cohort with CCI [redacted] dose level (approximately 40 participants receiving JNJ-40411813 and approximately 20 receiving placebo)
- Cohort 2: second cohort with a dose level of CCI [redacted] (approximately 40 participants receiving JNJ-40411813 and approximately 10 receiving placebo)
- Cohort 3: third cohort with a higher dose if the efficacy of the higher dose used in Cohort 2 is still insufficient (approximately 40 JNJ/ approximately 10 placebo)

[a] This section has been amended by Amendment INT-1

- Cohort 4: this cohort includes both a lower dose and a higher dose. This cohort will randomize 100 subjects in a ratio 40:40:20 (high dose/low dose/placebo). This cohort may follow Cohort 2.

Blinding

Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Participants and investigators will be blinded for treatment (JNJ-40411813 or placebo) but not for dose.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the treatment assignment (e.g., study intervention plasma concentrations, plasma biomarkers) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding. Also, the site staff should not discuss insights on unblinding of randomization with the participants.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. The investigator may in an emergency determine the identity of the treatment by contacting the IWRS. While the responsibility to break the treatment code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the particular situation before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the appropriate section of the electronic case report form (eCRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner. Participants who have had their treatment assignment unblinded should continue to return for required follow-up evaluations.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, for the interim review in each cohort (see Section 9.5) and for unblinded review by the data review committee (DRC, see Section 7.1), the randomization codes and the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those participants included in the interim review.

6.4. Study Intervention Compliance[a]

Study intervention will be taken by the participant at home or during a study visit in the clinic. The first dose will be taken by the participant at Visit 2 (Day 1) of the study in the clinic. The participant will be instructed to take their study intervention to the clinic at each study visit.

When in the clinic during visits 2 and 4, study intervention will be self-administered on site as outlined in Section 6.1. The administration of study intervention will be witnessed by the investigator or a properly trained designee. The exact date and time of study intervention administration will be recorded in the eCRF.

The participant will receive an e-diary to record – apart from seizures – the intake of the study intervention.

For study visits 2, 4 and 6, participants are requested to record the time of last dosing of levetiracetam or brivaracetam, their CCI [redacted] and the study drug on the day before the study visit. Participants will also record the time of last dosing of levetiracetam or brivaracetam and study drug taken at home prior to visit 7. An appointment-card will be provided for documentation.

The investigator or designated study personnel will maintain a log in IWRS of all study intervention dispensed and returned. Study intervention supplies will be inventoried and accounted for throughout the study.

If appropriate, additional details may be provided in a pharmacy manual/study site investigational product manual that is provided separately and noted in Section 8.1, Study-Specific Materials.

6.5. Concomitant Therapy[b]

All prestudy therapies administered up to 30 days before screening must be recorded at screening (and confirmed by treating physician).

During the 8-week prospective pretreatment baseline period and during the 12-week double-blind treatment period, participants will continue to take their prescribed AEDs (one of which must include levetiracetam or brivaracetam) without change in dosage(s); new concomitant AEDs should not be added. For the concomitant AEDs including levetiracetam or brivaracetam, all doses within the limits of current clinical practice will be allowed. Concomitant AEDs will not be provided by the study sponsor.

Two exceptions to this rule will be allowed:

[a] This section has been amended by Amendment INT-1

[b] This section has been amended by Amendment INT-1

- Based upon clinical judgment, a one-time dosage adjustment of concomitant AEDs is permitted to mitigate adverse events attributable to those AEDs. Collection of blood for plasma concentration of these AEDs is allowed, at the discretion of the investigator.
- One-time changes in AED dosages do not represent a change in the daily AED regimen. For example, if the participant took an extra dose of an AED on one day, this would not represent a change in the daily AED regimen.

Rescue medication may be used as needed (PRN). Each administration of rescue medication must be documented in the seizure e-diary. However, benzodiazepines or barbiturates received on a continuing basis at stable dosages for 1 month before screening should be considered as concomitant AEDs. Benzodiazepines or barbiturates used as sleep aid or to treat anxiety will be allowed but should be documented in the eCRF.

For levetiracetam or brivaracetam drug intake on the days of study visits, the same rule applies as for JNJ-40411813: On the day of Visits 2, 4, 6 and 7 CCI will be taken in the study center during the study visit and CCI. Dosing during the site visit will be witnessed by the study staff. CCI. Participants taking levetiracetam XR should preferably take their medication in the morning and take this medication in the clinic during Visits 2, 4, 6 and 7. If the participant takes levetiracetam XR in the evening, this should not be changed for the study.

For study visits 2, 4, 6 and 7 participants are requested to record the time of last dosing of levetiracetam on the day before the study visit. Participants will also record the time that levetiracetam is taken at home prior to visit 7. An appointment-card will be provided for documentation.

CCI Dosing during the site visit will be witnessed by the study staff. CCI. CCI

For the study visits 2, 4 and 6, participants are requested to record the date and time of last dosing of CCI when applicable on the day before the study visit. An appointment-card will be provided for documentation.

JNJ-40411813 is primarily metabolized by CYP3A4. CCI

Section 11.5 includes examples of disallowed CYP3A4 inhibitors (prohibited from 14 days or at least 5 times the drug's half-life, whichever is longer prior to study drug administration until the follow-up visit) and inducers (prohibited from at least 1 month prior to study drug administration until the follow-up visit).

Similarly, participants should avoid consumption of grapefruit, grapefruit juice and Seville oranges (including orange marmalade) and herbal products containing St. John's wort, ephedra, ginkgo, ginseng, or kava.

JNJ-40411813 itself is also an inhibitor of CYP3A4 and CCI [redacted] or CYP3A4 metabolism and have a narrow therapeutic index with caution.

Examples of drug classes that include sensitive substrates to CYP3A4 and have a narrow therapeutic index include opioid analgesics, chemotherapy/oncologic agents, and immunosuppressive agents. Additional sensitive substrates that have a narrow therapeutic index include amiodarone, clindamycin, dihydroergotamine, dofetilide, ergotamine, and theophylline.

CCI [redacted]

CCI [redacted]

See Section 11.5 for an overview of drugs to be avoided.

If the administration of any concomitant therapy becomes necessary, it must be reported in the appropriate section of the eCRF.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.6. Recording of drug intake; overview

The participant will receive an e-diary to record the intake of the study intervention. In the e-diary, only confirmation of intake of study medication and rescue medication are recorded. The time of intake will not be recorded in the e-diary. Intake of rescue medication should also be recorded in the eCRF.

For reasons of proper PK analysis of study medication, levetiracetam or brivaracetam and currently used AEDs that are substrate of CYP3A4, at some occasions the date and time of the drug intake needs to be recorded by the participant (using the subject participation card) or the investigator/site staff (using the eCRF) outside the scope of the e-diary.

An overview of this specific recordings of date and time of intake of AEDs is given in Table 3.

Table 3: Recording of date and time of last drug intake outside the scope of the e-diary.

Study visit	When to record.	Study drug	Levetiracetam/ brivaracetam	CCI [redacted]
2	Day before	Not applicable	By participant	By participant
	During visit	By investigator	By investigator	By investigator
4	Day before	By participant	By participant	By participant
	During visit	By investigator	By investigator	By investigator
6	Day before	By participant	By participant	By participant
	During visit	By investigator	By investigator	By investigator
7	Same day, prior to the visit	By participant	By participant	Not applicable
	During visit	Not applicable	Not applicable	Not applicable

* CCI [redacted]

6.7. Intervention After the End of the Study[a]

Investigators may re-contact the participant to obtain follow-up information regarding the participants' safety if there are any safety concerns at the last study visit.

Participants should continue taking the AEDs they were using during the study until such time as changes in their treatment are recommended by their treating physician. Changes in their treatment for epilepsy will be allowed when required during the follow-up period.

The sponsor has added an OLE period to this study (to be initiated when all required supplies are available), with eligibility for all participants who completed the double-blind study period and experienced no safety concerns.

[a] This section has been amended by Amendment INT-2

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

If a participant discontinues study intervention or withdraws from the study before the end of the double-blind period, the early withdrawal assessments (Visit 7) should be obtained.

7.1. Safety Data Review

Continuous or periodic blinded safety reviews will be done by the SRP. An unblinded review of the data (on the individual participant level) will be conducted if there are safety concerns from this blinded review as a result of severe, serious or unexpected AEs that are at least possibly related to the study intervention or if the frequency of discontinuations due to TEAEs exceeds 10% of the participants (see Section 7.4).

This unblinded review will be done by a DRC. A DRC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in a separate charter.

In addition to the above, an interim unblinded review of safety, PK and efficacy data will be performed by an internal unblinded review committee as described in Section 9.5.

7.2. Completion

A participant will be considered to have completed the double-blind period of the study if he or she has completed the double-blind period up to Week 12 or has elected to exit after reaching the baseline monthly seizure count by Day 28 or exceeding the monthly baseline seizure count during a moving 28-day interval after Day 28. Participants who prematurely discontinue the study intervention for any other reason before completion of the double-blind period will not be considered to have completed double-blind period of the study.

Any participant who discontinues the study before Week 12 after receiving the study intervention will have an early withdrawal evaluation as described in Section 8.2.4.

Participants who discontinued the double-blind period for reason other than safety concerns, are allowed to enter the open-label extension period. See Section 10.

Participants who prematurely discontinue the study will not be replaced.

7.3. Participant Discontinuation/Withdrawal from the Study[a]

A participant will be withdrawn from the study for any of the following reasons. The participant must discontinue the study intervention and, whenever possible, the early withdrawal visit must be completed.

- Lost to follow-up

[a] This section has been amended by Amendment INT-2

- Death
- Withdrawal of consent. When a participant withdraws consent, effort should be made to determine if the cause of withdrawal was due to tolerability or lack of efficacy.
- Noncompliance to take the study intervention. Noncompliance will be decided on a case-by-case basis depending on the number of missed tablets and the interval between missed doses.
- Experiences a severe adverse event or serious adverse event (SAE) while receiving treatment, that is considered at least possibly related to study drug.
- The investigator or sponsor believes (e.g., that for safety or tolerability reasons such as a SAE at least possibly related to the study intervention) it is in the best interest of the participant to discontinue the study intervention.
- A participant who shows signals of clinically meaningful acute suicidal ideation at any time during the study should be withdrawn from the study and promptly referred for appropriate medical/psychiatric care.
- The participant becomes pregnant.
- If the QTcF interval is higher than 500 msec or is prolonged >60 msec from the baseline (Screening) value. If the QTcF is not readily available, the QTcB may be used instead. The participant will continue to be monitored (maximum 12 hours) by repeated 12-lead ECGs (at least every 60 minutes) until the ECG normalizes.
- If the liver function tests exceed the values as presented in Section 11.7.

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study intervention assigned to the withdrawn participant may not be assigned to another participant.

7.4. Protocol Stopping Criteria

Blinded medical monitoring by the sponsor will occur on a continuous basis including AEs, laboratory and ECG data. When there is any concern about the safety of the participants as a result of severe or serious AEs that are at least possibly related to JNJ-40411813 or if the frequency of discontinuations due to TEAEs exceeds 10% of participants, an unblinded review of the safety data will take place (see Section 7.1). The cohort will be stopped at any time if significant safety concerns are related to JNJ-40411813 as per the reviewers' decision. However, if the safety observations allow, a new cohort with a lower dose of JNJ-40411813 may be started. If safety concerns continue, or when safety concerns are not expected to be solved by a dose reduction, the study will be stopped. The principal investigator (PI) may decide to stop study participation at any time when he/she estimates there is an acute risk for participants in study.

7.5. Withdrawal from the Use of Research Samples

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 11.3). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF.

7.6. Lost to Follow-up

If a participant is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the participant and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented. Refer to Section 7.3, Participant Discontinuation/Withdrawal from the Study.

8. STUDY ASSESSMENTS AND PROCEDURES

For study assessments and procedures in the OLE period, see Section 10.8

8.1. Overview[a]

The SoA summarizes the frequency and timing of all assessments applicable to this study.

Repeat or unscheduled blood samples may be taken for safety reasons, additional PK samples or for technical issues with the samples.

Additional serum (by local laboratory) or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

The total blood volume to be collected from each participant will be approximately 76 mL.

For each participant, the maximum amount of blood drawn from each participant in this study will not exceed 200 mL.

Volume of Blood to be Collected from Each Participant

Type of Sample	Volume per Sample (mL)	No. of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Hematology	2	5	10
Serum chemistry	2.5	5	12.5
Serology (HIV, hepatitis)	7.5	1	7.5
Serum β-HCG pregnancy test	1.5	1	1.5
Pharmacokinetic samples[b]	2	14	28
Biomarker Sample Collection	2	4	8
Pharmacogenomics	8	1	8
Approximate Total[c]			75.5

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Includes the samples for JNJ-40411813 and metabolites, levetiracetam/ brivaracetam and CCI [redacted].
c. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

Note: An indwelling intravenous cannula may be used for blood sample collection.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded on the laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of

[a] This section has been amended by Amendment INT-1

serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected.

Refer to the SoA for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual(s) that will be provided before the start of the study. The exact dates and times of blood sampling must be recorded in the CRF.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB for JNJ-40411813.
- Pharmacy manual/study site investigational product manual or equivalent document e.g., Investigational Product Preparation Instructions.
- Laboratory manual.
- (Electronic) diary for participants and/or caregivers
- Electronic systems or paper documents for the completion of CCI and C-SSRS.
- Only if available for this study: Electronic devices and manuals for remote seizure monitoring.
- Sample ICF.

8.2. Study procedures

8.2.1. Screening[a]

Participants will report to the clinical study center for the eligibility screening assessment just prior to the start of the 8-week baseline period. Participants will be asked to bring their current AEDs with them. Before any study specific procedures are conducted and following an explanation of the purpose and risks of the study, participants will sign an ICF and optionally the pharmacogenomics ICF. Recording of AEs/concomitant medication will start following consent and will continue until the final study visit. The screening assessments may be performed over multiple visits if deemed necessary for logistical reasons.

The eligibility screening examination will consist of the following:

- Complete medical history and demography
- Review of concomitant medication including AEDs
- Physical and neurological examination (including height and body weight)

[a] This section has been amended by Amendment INT-1

- Supine vital signs (systolic and diastolic blood pressure, oral or tympanic temperature)
- 12-lead ECG
- Clinical safety laboratory assessments under fasted conditions (at least 4 hours), when feasible (including serology, hematology, serum chemistry and urinalysis)
- Urine drug screen and alcohol breath test
- Serum pregnancy test for WOCBP
- The C-SSRS (baseline) is completed by the investigator or qualified delegate.
- Complete the diagnostic review form to initiate the adjudication process
- Record AEs
- Review inclusion/exclusion criteria

Exceptional and limited re-testing of abnormal screening values, including laboratory values, that lead to exclusion are allowed only once to reassess eligibility.

After the screening visit, the completed diagnostic review form of the participant will be sent to the epilepsy consortium for an adjudication process by independent experts. In this adjudication process the experts decide whether the participant meets eligibility criteria to participate in the study. If the adjudication process is not possible e.g., because of technical limitations of protected data transfer, the participant will not be a screen failure.

8.2.2. Baseline period[a]

After screening, if they meet the in- and exclusion criteria for which data are available, participants can start the 8-week prospective pretreatment baseline period pending the results of the central laboratory and the adjudication process. However, when the results of these assessments indicate that the participant does not meet the in- and exclusion criteria, the participant will terminate the baseline period and will not be randomized to treatment.

When required for practical reasons, the baseline period may be up to 1 week longer or shorter than 8 weeks.

The participant and/or caregiver will be provided access to an (electronic) diary to record seizures. The e-diary will be an app downloaded on the smartphone owned by the participant. Only if the participant and/or caregiver do not own a smartphone, a smartphone programmed for the study will be provided.

During the baseline period, the participant will be contacted by phone by the investigator or study nurse to confirm correct use of the e-diary. This contact should take place at least 4 weeks after the start of the baseline period, but multiple contacts are allowed when required.

[a] This section has been amended by Amendment INT-1

Participants must be compliant with the recording of information in the diary throughout the study. Seizures that will be entered during baseline and throughout the study include focal aware seizures with and without motor signs, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures. Myoclonic, or other generalized seizures will not be entered.

8.2.3. Treatment Period[a]

Participants who complete the baseline period will be asked to come to the study center for Visit 2. Visit 2 should be planned in the morning hours, before noon (12.00 pm). Participants must report seizures in the e-diary from Day 1 through the following double-blind treatment period. When possible, participants have to come to the study center in fasting condition and will have a meal after the blood collection for clinical laboratory testing and biomarkers.

Participants who continue to meet entry criteria at the end of the baseline period must also meet the following criteria to be randomly assigned to treatment in the double-blind treatment period of the study:

- Have had between 3 and 100 seizures per 28 days within the first 4 weeks and also within the second 4 weeks of the baseline period.
- No seizure-free interval for more than 21 days

At Visit 2, before randomization and the first dose administration, all assessments (except post-dose PK blood collection) must have been completed.

The participant will visit the study center after 4, 8 and 12 weeks. After 2 and 6 weeks, the investigator will have a telephone call with the participant to discuss adverse events, use of the e-diary and concomitant medication. Visits 2 (Day 1), 4 (4 weeks), and 6 (8 weeks) should be planned in the morning hours, before noon (12.00 pm). During the study visits, all assessments will be completed per the SoA. At each study visit, the participant should come to the study center in fasted condition (at least 4 hours) when possible and – during visits 2, 4, 6 and 7- will be dosed during or immediately after a meal at the study center after predose blood collections. Dosing should be witnessed by the study staff. At each study visit, participants should take their study intervention with them, and return used and partly used bottles.

During each study visit the following sequence of activities is preferred (not all activities at all visits. See the SoA for details):

- Collection of blood samples (clinical labs, pre-dose PK, biomarkers and pharmacogenomics)
- Pregnancy test
- Meal
- Scales (C-SSRS, CCI [redacted] CCI [redacted]
- Vital signs, 12-lead ECG

[a] This section has been amended by Amendment INT-1

- Physical/neurological examination
- Dose of study intervention, levetiracetam or brivaracetam and other AEDs when applicable
- Review of e-diary, AEs and concomitant medication
- Post dose PK blood sample when applicable.

Participants and caregivers should continue to report seizures, new or extra concomitant medication and AEs during the full 12 weeks of the study when possible.

Participants are encouraged to complete at least the first 4 weeks of treatment when there are no safety concerns. Participants who have exceeded their pre-randomization monthly seizure count at Week 4, or within any 4-week interval after Week 4 ("4-week sliding window approach") up to Week 12, will have the option to discontinue the study drug for lack of efficacy and to perform the end of study/early withdrawal visit, or to continue double-blind treatment. Participants who have not exceeded the pre-randomization seizure count will continue the double-blind treatment period through Week 12.

8.2.4. Follow-up/Early Withdrawal Visit

For participants who will participate in the OLE period, no follow-up visit will be performed. For details see Section 10.4.

All participants who discontinue the study before Week 12 are encouraged to complete the early withdrawal visit (Visit 7, Week 12/Early Withdrawal). The procedures to be completed during this visit are listed in the SoA. Participants who complete all study visits (including Visit 7) will have a follow-up telephone call with the investigator to review AEs and health status.

Participants who continued treatment to the end of the double-blind treatment period (Week 12) or have completed the study as per Section 7.2 will continue to collect information on the number of seizures they experience using the e-diary until 2 weeks after the last dose of study medication. Participants can start treatment with a new AED when required during the follow-up period.

8.3. Efficacy Assessments

8.3.1. Seizure count[a]

The primary efficacy evaluation will be the time to baseline monthly seizure count. To assess this endpoint, the number and type of seizures during the baseline period and during the double-blind treatment period needs to be documented carefully.

The participant and/or caregiver will be provided access to an (electronic) diary to record seizures and intake of study intervention. The e-diary will be an app downloaded on the smartphone owned by the participant. Only if the participant and/or caregiver do not own a smartphone, a smartphone programmed for the study will be provided.

[a] This section has been amended by Amendment INT-1

Participants must be compliant with the recording of information in the e-diary throughout the study. Seizures that will be entered during baseline and throughout the study include focal aware seizures with and without motor signs, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures. Myoclonic, or other generalized seizures will not be entered.

Optionally, when the systems are available for the study, during some days of the baseline and treatment period and in a limited number of study centers, wearable devices may be used for remote registration of seizures. This is an exploratory technique and when required, details will be described in an addendum to the protocol.

8.3.2. Secondary Evaluations[a]

8.3.2.1. CCI

[redacted]

CCI

[redacted]

8.4. Safety Assessments

The collection of AEs and concomitant medications will start after the ICF has been signed and will continue until the final study visit. All safety assessments listed below will be performed as specified in the SoA.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the SoA.

8.4.1. Physical Examination

The study investigator, or other authorized and appropriately qualified designee, will perform the physical and neurological examinations. On Visits 2 through 6, a brief neurological examination should be performed, including assessment of eye movements, gait, and other findings relevant to evaluation of AEs.

Body weight will be measured as per the SoA. Body weight will be measured using a calibrated scale. Participants will be weighed at approximately the same time of day on the same scale, wearing underwear and a gown and without shoes; they will be instructed to empty their bladders

[a] This section has been amended by Amendment INT-1

before being weighed. (Note: if disrobing for weighing is logistically impossible, the participant should be dressed as lightly as possible, with consistency from visit to visit).

8.4.2. Vital Signs

Blood pressure measurements will be assessed in supine positions with a completely automated device. Manual techniques will be used only if an automated device is not available.

Supine blood pressure measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (e.g., television, cell phones).

In addition, oral or tympanic temperature will be measured.

Vital signs should be measured in nonfasting conditions whenever possible.

8.4.3. Electrocardiogram (ECG)[a]

At screening, a triplicate ECG recording is required, i.e., 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

At the other visits indicated in the SoA, single twelve-lead ECGs, intended for safety monitoring, will be recorded supine (following 5 minutes rest) so that the different ECG intervals (RR, PR, QRS, QT) can be measured at multiple time points at screening and during the study (see SoA). The ECG will be recorded until 4 regular consecutive complexes are available in good readable quality.

Hot and cold drinks and food should be avoided 30 minutes before an ECG measurement whenever possible.

Clinically relevant abnormalities occurring during the study should be recorded in the Adverse Event section of the eCRF/eSource. During the collection of ECGs, participants should be in a quiet setting without distractions (e.g., television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG, vital signs, blood draw. Please note that fasting blood draw may precede the ECG and vital signs in this study.

8.4.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected as noted in Section 11.2, Clinical Laboratory Tests. A central laboratory will be used for testing. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF.

[a] The section has been amended by Amendment INT-2

8.4.5. Suicidal Risk Monitoring

JNJ-40411813 is considered to be a CNS-active compound. The sponsor considers it important to monitor for such events before and during this clinical study.

Columbia Suicide Severity Rating Scale (C-SSRS)

An interview to assess the risk of suicidal ideation and behavior will be conducted at screening, through the double-blind treatment period and at follow-up/early withdrawal. The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment (Posner 2007). The C-SSRS is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the occurrence and intensity of suicidal thoughts and suicidal behaviors. It can also be used during treatment to monitor for clinical worsening. See Section 11.9 for details.

8.5. Pharmacokinetics[a]

Blood samples (2 mL each) for the determination of plasma concentrations of JNJ40411813 and metabolites including but not limited to CCI [redacted], levetiracetam or brivaracetam and, when used by the participant, CCI [redacted] will be collected according to Table 4 below.

[a] This section has been amended by Amendment INT-1 and INT-3

Table 4: Schedule of collection of 2-mL PK blood samples

Study visit	Study Day	JNJ-40411813 and metabolites Relative to in-clinic dose	Brivaracetam or Levetiracetam Relative to in-clinic dose*	CCI [redacted]
2	1	• 2 hours after dosing	• predose • 2 hours after dosing	• predose
4	29	• predose • 1 hour after dosing	• predose • 1 hour after dosing	• predose
6	57	• predose	• predose	• predose
7***	85***	• after dosing (combine with other blood collection when feasible)	• At the same time as sample for JNJ-40411813	-

*If the subject is taking levetiracetam XR once daily in the evening, then one PK sample for levetiracetam will be collected on Visits 2 and 4 (at the same time as the postdose sample for JNJ-40411813) and Visit 6 (at the same time as the predose sample for JNJ-40411813)

C [redacted]

*** Also, at early withdrawal when after Visit 6.

Plasma samples will be analyzed to determine concentrations of JNJ-40411813, levetiracetam or brivaracetam, and CCI [redacted] using validated, specific and sensitive liquid chromatography mass spectrometry/mass spectrometry (LC-MS/MS) methods. Some plasma samples will be analyzed to document the presence of JNJ-40411813 metabolites CCI [redacted] and perhaps other metabolites, or may be used to determine protein binding using qualified research methods or validated methods. If deemed necessary, the concentrations of other co-administered AEDs may also be measured. In addition, plasma PK samples may be stored for future analysis of protein binding, biomarkers and the metabolite profile

The exact dates and times of blood sampling must be recorded in the laboratory requisition form. In addition, the exact dates and times of the last administration of drug (administered at home or at the clinic) prior to collection of each pharmacokinetic sample should be documented.

Data will be listed for all participants with available plasma concentrations per treatment and study day. All concentrations below the limit of quantification (LOQ) or missing data will be labeled as such in the concentration data listings. Concentrations below the LOQ will be treated as zero in the summary statistics.

8.6. Genetics

Blood samples (8 mL) will be collected CCI [redacted]

CCI [redacted]s

CCI [redacted] Participation in the genetic/pharmacogenomic part of this study is optional.

8.7. Biomarkers

During the study, blood will be collected for the assessment of the biomarkers CCI [redacted] time points indicated in the SoA (see also Section 4.2.) Additional instructions for collection of biomarker samples:

- Blood biomarkers will be collected under fasting conditions – at least 4 hours, water permitted with the exception of the postdose collection during Visit 2.
- Participants should be informed not to do strenuous sports or exercises within 24 hours before blood sample collection.

Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased. CCI [redacted]

Participant data

To evaluate the biomarker results, the following information needs to be documented on each day of collection of blood samples for biomarker analysis.

- Diet (extremes during the previous week)
- Any sickness or allergy in the previous 2 weeks

8.8. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

As with any CNS-active medication, investigators should monitor carefully and document any CNS-related AE including tremor, ataxia, abnormal sensation, confusion, or possibility of seizure.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints

(PQCs), refer to Section 11.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Adverse Events of Interest

AEs of interest have not yet been defined in this study. If observations of new AEs of interest during the study require this, a protocol amendment will be issued.

8.8.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study visit, which may include contact for follow-up of safety. SAEs, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately, without undue delay, under no circumstances later than 24 hours after their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and the eCRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a SAE should be transmitted electronically or by facsimile (fax).

8.8.2. Follow-up of Adverse Events and Serious Adverse Events

AEs, including pregnancy, will be followed by the investigator as specified in Section 11.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.8.3. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

An anticipated event is an adverse event that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study the following SAEs will be considered anticipated events:

- Sudden Unexpected Death in Epilepsy (SUDEP)
- Seizures leading to injuries or hospitalizations
- Anxiety
- Depression

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the intervention group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries in which the studies are conducted.

8.8.4. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious AEs and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.9. Treatment of Overdose

For this study, any single dose of JNJ-40411813 greater than CCI [redacted] a 24-hour time period will be considered an overdose. The sponsor does not recommend specific intervention for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until JNJ-40411813 can no longer be detected systemically (at least 2 days).

- Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

9. STATISTICAL CONSIDERATIONS

The double-blind study period will be analyzed separately from the OLE period after completion of the double-blind period for each cohort.

9.1. Sample Size Determination

The calculation of the maximum sample size planned for this study was simulation-based and was estimated using a Cox's proportional hazard regression model comparing the time to baseline seizure count between JNJ-40411813 and placebo. A longitudinal model for individual daily seizure counts, taking into account between-subject variability in baseline seizure rate and response to treatment, and a residual overdispersed Poisson error was applied. The simulated daily seizure count data were then converted to time to baseline count data and analyzed using a Cox's proportional hazard regression model.

Assuming a placebo median percentage seizure rate reduction of 15% and a further reduction of 50% (respectively 30%) for JNJ-40411813, a cohort with 40 participants randomized to JNJ-40411813 and 20 to placebo would achieve a power of 99% (respectively 83%) at the α=5% one-sided significance level. In subsequent cohorts with 40:10 randomization, the power becomes 94% for a 50% reduction, with all other assumptions unchanged.

9.2. Efficacy analyses

9.2.1. Primary[a]

The intent-to-treat population will be the primary efficacy population, which includes all participants who are randomly assigned to receive study drug and who have baseline and postbaseline seizure data. Data from participants on placebo in cohorts 2 and 3 will be combined with those from Cohort 1 if the Kaplan-Meier curves of the subjects treated with placebo are comparable between cohorts. The analysis for interim review may be done including both pooled and non-pooled placebo subjects.

The individualized baseline monthly seizure count is defined as the number of observable focal onset seizures occurring during the 8-week baseline period, multiplied by 28/ X_{BL}, where X_{BL} is the number of days comprising the baseline period. Observable focal onset seizures include focal aware seizures with motor signs, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures. Focal aware seizures will not be counted towards baseline monthly seizure count.

[a] This section has been amended by Amendment INT-1

The endpoint time to baseline monthly seizure count is defined, for each patient, as the number of days, until the patient experienced the number of seizures equal to baseline monthly seizure count, up to the end of the 12-week double-blind treatment period.

Although focal aware seizures with and without motor signs are entered in the e-diary, focal aware seizures without motor signs will not be counted in the analysis.

Kaplan-Meier analyses will be conducted to describe the time to baseline monthly seizure count distribution (with 95% CI) for each treatment group for all observable focal-onset seizures. A formal comparison of time to monthly baseline seizure count will be made by a Cox proportional hazard regression model, including factors for treatment and any other relevant covariates (details will be provided in the statistical analysis plan). Appropriate adjustment for multiple testing, in case of subsequent cohorts, will be detailed in the SAP.

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 5 components:

- **Population:** patients with established diagnosis of focal epilepsy (ILAE 2017 criteria) with 3 to 100 seizures per 28 days; currently on 1 to 4 AEDs with inadequate response to levetiracetam/brivaracetam who have met the inclusion/exclusion criteria.
- **Variable:** the number of days, until the patient experienced the number of seizures equal to baseline monthly seizure count, up to the end of the 12-week double blind treatment period.
- **Intervention event:** the effect of the initially randomized treatment that would have been observed had all participants remained on their treatment throughout the double-blind treatment phase.
- **Intercurrent event (ICE):** treatment discontinuation will be handled according to the hypothetical strategy as if the ICE would not have occurred. Similar efficacy is assumed for subjects who had the ICE as those subjects from the same treatment group who did not have the ICE.
- **Population-level summary:** the difference in estimated hazard ratio between the treatments.

Sensitivity analyses for the primary estimand regarding missing data assumptions; and a supplementary estimand to inform subsequent trials will be specified in the SAP.

9.2.2. Secondary and exploratory[a]

Secondary efficacy endpoints will be subject to an exploratory analysis including descriptive statistics by treatment arm and graphical exploration. Details of the analysis for each secondary endpoint and exploratory endpoints will be provided in the SAP.

[a] This section has been amended by Amendment INT-1

Seizure Freedom

Percent participants with seizure freedom over the complete double-blind period. Participants who exit the study after reaching their pre-randomization baseline seizure count can be included in this analysis as they were not seizure free during the study.

Secondary generalized seizures

Separate analyses (including time to baseline count and % reduction of counts) for focal to bilateral tonic-clonic seizures will be performed if a large enough number of events is observed.

Responder rate

A responder is defined as a participant having at least a 50% reduction of the monthly seizure rate. Participants who exit the study at Week 4 after reaching the baseline seizure count will be treated as nonresponders in this analysis. As the number of seizures they experienced is either equal or larger than their baseline monthly seizure count, their observed % seizure rate reduction is either zero, or negative (implying an increase).

CCI [redacted]

[redacted].

9.3. PK and PK/PD analyses[a]

Data for all participants who receive a dose of JNJ-40411813 and have at least one measurement of plasma concentration, will be included in the PK analysis. Plasma concentrations of JNJ-40411813 and metabolites including CCI [redacted] levetiracetam/ brivaracetam and CCI [redacted] will be listed for all participants who received this active medication.

Descriptive statistics will be calculated for the plasma concentrations of JNJ-40411813 and metabolites including CCI [redacted] levetiracetam/ brivaracetam and CCI [redacted] at each applicable time point. Statistics include sample size (n), mean, standard deviation, coefficient of variation (CV), geometric mean, median, minimum, and maximum.

Population PK and/or PBPK analyses of JNJ-40411813 and levetiracetam/brivaracetam may be performed on the data of this study in combination with data pooled from other studies. An objective of these analyses is to investigate the potential effects of covariates, such as demographics and concomitant drugs, on the PK of JNJ-40411813. The results of the population analyses may be reported separately.

PK and PD relationship will be explored, if feasible. The results of population PK/PD analyses will also be reported separately.

[a] This section has been amended by Amendment INT-1

9.4. Safety Analyses[a]

Statistical analysis of the safety data will be done by the sponsor or under the authority of the sponsor. Specific details will be provided in the Statistical Analysis Plan.

All safety analyses will be performed based on the safety analysis set, which will include all included participants who receive at least 1 dose of JNJ-40411813 or placebo. Safety summaries will be provided by treatment and by cohort, unless specified otherwise.

AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class, by severity and relationship to study intervention and will be presented by treatment. SAEs will be summarized separately.

The safety analysis will include the incidence of AEs, actual data and changes in blood pressure, pulse rate, laboratory safety data, 12-lead ECG and physical/neurological examination data from predose to all postdose assessments.

The participants with suicidal ideation and/or suicidal behavior collected from the C-SSRS will be listed.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the MedDRA. All reported AEs with onset during the double-blind treatment period (i.e., TEAEs, and AEs that have worsened since baseline [Day 1]) will be included in the analysis. For each AE, the percentage of participants who experience at least one occurrence of the given event will be summarized by treatment group. Summaries will be provided for all participants receiving at least one dose of study intervention in this study and will include AEs from this study.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who withdraw due to an AE, or who experience a severe AE or a SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline (Day 1) and at each scheduled time point, and for changes from baseline.

The number and percentage of participants experiencing a laboratory result below or above normal reference ranges will be provided for each laboratory analyte by treatment group. Summaries will be provided for all participants receiving at least one dose of study intervention in this study.

A listing of participants with any laboratory result outside the reference ranges will be provided.

[a] This section has been amended by Amendment INT-2

ECG

Heart rate and ECG intervals (RR, PR, QRS and QT) as well as corrected QT intervals according to Bazett's formula (QTcB) and Fridericia's formula (QTcF) (Bazett 1920, Sagie 1992, Hodges 1983, International Conference on Harmonization [ICH] 2005) from the 12-lead ECG will be summarized at baseline (Screening) and at each scheduled time point and for changes from baseline using descriptive statistics.

The number and percentage of participants with at least one occurrence of a treatment-emergent potentially clinically important QTc measurement (QTc value >450, >480, or >500 msec) or with a change from baseline in QTc>30 msec or 60 msec, will be summarized by treatment group.

Data listings of participants with any potentially clinically important values or with a change from baseline in QTc will be provided.

Vital Signs

Descriptive statistics of temperature, pulse, and blood pressure (systolic and diastolic) values and changes from baseline (Day 1) will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

Physical and Neurological Examinations

Participants with abnormal findings will be presented in a data listing.

Other Safety Measures

C-SSRS
The suicidal ideation and behavior data collected from the C-SSRS will be summarized descriptively at each scheduled timepoint by treatment group. Data from the participants with suicidal ideation and behavior will be presented in data listing.

9.5. Data Review after each cohort[a]

After at least 55 patients in Cohort 1 and after at least 45 patients in Cohort 2 have completed at least 4 weeks of treatment, an interim unblinded review of all cumulative safety, PK, and efficacy data of JNJ-40411813 available to that date will be performed to decide on whether there should be any addition or modification to the dose(s) in the following cohorts and subsequent clinical studies. If the results of the review are inconclusive with respect to the assessment of efficacy, a second interim review of the same cohort may be done after the last participant has completed the 12-week visit. If safety concerns have been observed that are not expected to be solved by a dose reduction, the study will be stopped. This decision will be taken by an internal unblinded review committee. As a standard, data will be unblinded at the individual level (JNJ-40411813 vs placebo).

Completed cohorts may be unblinded for review by the sponsor members, if deemed necessary.

[a] This section has been amended by Amendment INT-1, INT-3 and INT-4

The procedures for the internal interim review for Cohorts 1 and 2 will be documented in a separate charter.

10. ADDENDUM FOR OPEN-LABEL EXTENSION (OLE) PERIOD[a]

10.1. Rationale

This is an OLE period to investigate the long-term safety and efficacy of JNJ-40411813 in subjects who completed their participation in the double-blind study period. This study period will allow study participants to continue treatment and evaluate long-term safety and efficacy of JNJ-40411813 in epilepsy. Also study participants that have been treated with placebo may be included in the OLE period.

Because epilepsy is a chronic condition, often requiring treatment for years, long-term data should be generated by conducting OLE studies in order to assess for maintenance of efficacy and safety. Treatment retention rate is recommended as a global indicator of clinical effectiveness. A one-year study duration is considered the minimum (EMA 2018).

10.2. Benefit/Risk Assessment of the OLE period

10.2.1. Risks for Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Limited information about the long-term tolerability of study treatment.	Experience from former studies so far in the dosage range employed indicates that JNJ--40411813 is well tolerated and there is no signal for target organ damage. During the double-blind treatment period, the combination of levetiracetam and JNJ-40411813 was well tolerated. The data from chronic toxicology studies in rat and dog do not show adverse effects. However, this is the first study in which exposure to JNJ-40411813 will exceed 3 months. There may be unknown safety risks.	The start dose of JNJ-40411813 in open-label extension period is the same as used during the double-blind treatment period. The safety and tolerability of JNJ-40411813 will be reviewed continuously and every 3 months, the participant will visit the study center for additional safety assessments. Participants can stop their participation any time when the treatment is not tolerated.
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[a] This section has been added for Amendment INT-2

		CCI [redacted]

10.2.2. Benefits for Participation

Treatment-resistant epilepsy has a severe impact on quality of life and risk of mortality. JNJ-40411813 in combination with levetiracetam shows promise in a nonclinical model of epilepsy and – if proven efficacious in man too – may result in a significant positive impact on this patient population.

For the individual participant who benefits from the participation in the double-blind treatment phase of study 40411813EPY2001, the extended open-label treatment will be made available as long as the participant continues to benefit during this OLE study period.

10.2.3. Benefit-Risk Assessment

The risk/benefit of JNJ-40411813 is favorable and the currently available safety and efficacy data support the proposed open-label study period to investigate the long-term efficacy and safety of JNJ-40411813 in participants with focal onset epilepsy.

More detailed information about the known and expected benefits and risks of JNJ-40411813 may be found in the current IB for JNJ-40411813.

10.3. Objectives and endpoints of OLE period

Objectives	Endpoints
Primary	
The primary objective of this open-label period is to evaluate the long-term efficacy and safety of adjunctive therapy with JNJ-40411813 in subjects with epilepsy.	Seizure count by using an (e-)diary, adverse events, significant changes in vital signs, and safety laboratory results.
Secondary	
To evaluate, during long-term treatment, the pharmacokinetics (PK) of JNJ-40411813, levetiracetam/ brivaracetam, and AEDs CCI [redacted]	Plasma concentrations of JNJ-40411813, levetiracetam/ brivaracetam, and AED CCI [redacted]

Hypothesis

This is an open-label observational study period. Therefore, no formal statistical hypothesis testing has been planned.

10.4. Design of the OLE period

10.4.1. Overall Design

Overview of the open-label period:
For each participant, the open-label period will start immediately after the last study drug intake by the participant in the double-blind period. Participants participating in this open-label period will not have the follow-up visit (Visit 8) as mentioned in the SoA in Section 1.2.

Participants from Cohort 1 will start with intake of JNJ-40411813 at CCI) or CCI). The dose can be increased stepwise CCI in the next visit to CCI

Participants from Cohort 2 will start with CCI . CCI CI

For participants receiving dosages of CCI), a dosage reduction to CCI will be permitted in case adverse events consisting of dizziness, incoordination, sedation, or fatigue (or similar descriptive terms) which, in the judgment of the investigator, potentially limit activities of daily living. The PI is encouraged to rechallenge if the AEs resolved on the lower dose. If rechallenge is unsuccessful, i.e., the AEs recurred when the dose was increased, the dose may be reduced again and kept at that level

The participants will continue to take the same concomitant AEDs as used during the double-blind period of the study. During the open-label extension period, dosages of the concomitant AEDs may be changed when needed. A concomitant AED may be added or stopped during the open-label extension period. However, if JNJ-40411813 is no longer of benefit when used in the new combination of AEDs, the participant should stop participating in the study.

Participants will continue to enter their seizures and adverse events in an (e-)diary. After 1 and 2 months and thereafter every 3 months, the subject will visit the study center for review of seizures and safety assessments including vital signs and safety laboratory.

The study assessments will be completed as described in the SoA in Section 10.10.

Withdrawal

Participants may withdraw from participation any time on their request or, at the discretion of the investigator, when JNJ-40411813 is no longer of benefit to them. Participants who withdraw from the study should complete the withdrawal visit (OLE12). Data from all subjects who withdraw from the OLE period will be used for the final analysis.

10.4.2. Scientific Rationale for Study Design

Combination with levetiracetam or brivaracetam

When possible, participants will continue the concomitant use of levetiracetam or brivaracetam. However, no data are available on the ongoing efficacy of JNJ-40411813 when treatment with levetiracetam or brivaracetam should be stopped. If treatment with levetiracetam or brivaracetam should be stopped, the participant may continue the treatment with JNJ-40411813 as long as there is a benefit for the participant. Monotherapy with JNJ-40411813 to treat epilepsy is not allowed.

Study population

Male and female participants who completed the double-blind treatment period may participate in the OLE period. Participants who did not have the OLE period available when they completed the double-blind period may start the OLE period even when there is a gap between completion of the

double-blind period and the start of the open-label period. They should enter the OLE period as soon as it becomes available in their country

Inclusion of women of childbearing potential (WOCBP) is supported by the absence of toxicity seen in Segment II reproductive toxicology studies. WOCBP will use a highly effective birth control method as outlined in the inclusion criteria (see Section 5.1).

Duration of the study

Participants will participate in the open-label period for a period of up to 2 years. If they still benefit from treatment with JNJ-40411813, they will be transferred to a new central OLE study when available, in which also participants from other (late phase) studies with JNJ-40411813 will participate.

The participants in that central OLE study can continue their participation as long as needed with a maximum until commercial availability of the compound in the country where the participant is living.

The OLE extension period may be stopped when the development of the compound is stopped by a decision of the sponsor or because of insufficient efficacy or safety concerns.

Pharmacokinetics

Data on the long term (> 3 months) pharmacokinetics of JNJ-40411813 in humans are still lacking. For this reason, plasma concentrations of JNJ-40411813 and metabolites will be measured during study visits up to 1 year after the start of the OLE period.

PK samples for levetiracetam/brivaracetam and, when used by the participant, CCI [redacted]) will be collected only during the visits after 1 month and after 2 months to evaluate the PK profiles.

10.4.3. Study-Specific Ethical Design Considerations

For the open-label period: The primary ethical concern is the long-term use of JNJ-40411813 as an experimental treatment in epilepsy. The compound has been used in several clinical studies in healthy subjects and patient populations (see IB) and was generally well tolerated. In addition, chronic toxicology studies have been completed in rat (6 months) and dog (9 months). These studies did not indicate adverse toxicological effects after chronic oral administration.

Although the current data from this ongoing study 40411813EPY2001 and studies in other indications do not indicate any serious safety risk, no studies in humans have been done before with a duration longer than 3 months.

About 11 mL of blood will be collected during the visits after 1 and 2 months and 5 mL of blood will be collected during the visits every 3 months thereafter for PK, clinical chemistry and hematology. This is considered to be a limited and acceptable amount of blood.

10.4.4. Justification for dose

No fixed dose schedule will be presented for this study. All participants will start with intake of JNJ-40411813 at the same dose they used in the double-blind study period. See also Section 4.1.

10.4.5. End of Study Definition

End of Study Definition for the OLE period.

The end of study for the OLE period is considered as the last visit for Visit OLE 11 or OLE12 for the last participant in the study. The final data for the OLE period from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement. The OLE period will be analyzed separately from the double-blind period.

10.5. Study population for the OLE period

No fixed number of participants has been defined for this OLE period.

The inclusion and exclusion criteria for enrolling participants in this open-label study period are described in the following sections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the study responsible physician (SRP) before entering the participant into the study.

Participants will be enrolled after reading the participant information sheet and signing the ICF indicating that they understand the purpose of, and procedures required for the study and are willing to participate in the study and comply with the study procedures.

An updated ICF including a description of the OLE period will be made available for those participants who were already enrolled in the study before the OLE period became available.

10.5.1. Inclusion Criteria

Each potential participant must satisfy all the following criteria to be enrolled in the open-label study period.

101. The participant must have participated in the double-blind treatment period. This also includes participants who stopped during the double-blind treatment period because they reached the time to baseline seizure count study endpoint or completed the double-blind period before the OLE period is available.
102. The participant is expected to benefit from participation in the open-label study period in the opinion of the Investigator.
103. When a woman of childbearing potential:
    - Continues to practice a highly effective method of contraception as described in the inclusion criteria of the double-blind period (Section 5.1) until at least 3 months after the last dose of study medication

- Must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 3 months after receiving the last dose of study intervention.

104. Men who are sexually active with a woman of childbearing potential and have not had a vasectomy must continue to use a barrier method of birth control i.e., a condom with spermicidal foam/gel/film/cream/suppository for the duration of the study plus 3 months after receiving the last dose of study drug, and all men must not donate sperm during the study and for 3 months after receiving the last dose of study drug. In addition, male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.
105. The participant has signed an ICF indicating that he/she understands the purpose of, and procedures required for the study and are willing to participate in the OLE period.

10.5.2. Exclusion Criteria

106. Participant meets any of the withdrawal criteria during the double-blind period or is experiencing an ongoing severe or serious adverse event considered related to study medication by the investigator.
107. Participant is receiving any investigational drug or using any experimental device in addition to JNJ-40411813 for treatment of epilepsy or any other medical condition.
108. Participant has any other condition that would prevent compliance with the study procedures or proper reporting of adverse events.

10.5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

109. Refer to the Section 6.5 on Concomitant Therapy for details regarding prohibited and restricted therapy during the study.
110. Participants may not consume any food or beverages containing, grapefruit juice, Seville oranges (including any orange marmalade), or quinine (e.g., tonic water) until the last dose of study intervention.

10.6. Study interventions

10.6.1. Study interventions Administered

JNJ-40411813 will be supplied for this OLE period as 25-mg and 50-mg tablets. CCI [redacted]. Only on the days of study visits, participants will not take the study drug at home, but will take the study drug with them to the clinic and take the study medication in the clinic after the collection of the PK-blood sample and/or the collection of blood for safety laboratory test. The clinic will be asked to provide a meal before intake of study medication.

Study intervention should be taken in fed condition CCI [redacted] The tablets must be swallowed whole with water and not chewed, divided, dissolved or crushed.

Participants from Cohort 1 will start with intake of JNJ-40411813 at CCI [redacted] or CCI [redacted] The dose can be increased stepwise (CCI [redacted] the next visit to a maximum of CCI [redacted]

Participants from Cohort 2 will start with CCI [redacted]

For participants receiving dosages of CCI [redacted] a dosage reduction to CCI [redacted]) will be permitted in case adverse events consisting of dizziness, incoordination, sedation, or fatigue (or similar descriptive terms) which, in the judgment of the investigator, potentially limit activities of daily living. The PI is encouraged to rechallenge the initial dose within 2 weeks if the AEs resolved on the lower dose. If rechallenge is unsuccessful, i.e., the AEs recurred when the dose was increased, the dose may be reduced again and kept at that level.

The actual dose and the composition of tablets to be taken will be determined for each cohort and stratum within a cohort. In Table 5 the most likely examples are presented. However, these examples may change based on actual dose decisions.

CCI [redacted]

A description of the study interventions is presented in Table 6:

Table 6: Description of Interventions

Arm Name	JNJ-40411813
Intervention Name	JNJ-40411813
Type	Drug
Dose Formulation	Uncoated tablet
Unit Dose Strength(s)	25 or 50 mg JNJ-40411813. CCI [redacted]
[redacted]	[redacted]
Route of Administration	Oral
Use	Experimental
Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP)	IMP
Sourcing	Provided centrally by the Sponsor
Packaging and Labeling	Provided in child-resistant packaging, labeled to meet applicable regulatory requirements.

Table 6: Description of Interventions

Arm Name	JNJ-40411813
CCI CCI	[redacted]

10.6.2. Preparation, Handling, and Storage

See Section 6.2.

10.6.3. Measures to Minimize Bias: Randomization and Blinding

No randomization procedure will be applied in the open-label period.

Participants completing the double-blind period and starting the open-label period will not be unblinded. Participants who had been receiving placebo will start with the JNJ-40411813 dose that was used in the applicable cohort of the double-blind period; in case more than one dose was tested in the applicable cohort, participants will start with the lower one.

10.6.4. Study Intervention Compliance

Study intervention will be taken by the participant at home (except for the days of the study visits) (See Section 10.6.1). When feasible, the participant should start the treatment following the double-blind period with no interruption or try to keep the interruption as short as possible.

Participants will not need to record their drug intake in the e-diary during the open-label period.

The investigator or designated study personnel will maintain a log in IWRS of all study intervention dispensed and returned. Study intervention supplies will be inventoried and accounted for throughout the study.

If appropriate, additional details may be provided in a pharmacy manual/study site investigational product manual that is provided separately and noted in Section 10.8.1.

10.6.5. Concomitant Therapy

See Section 6.5.

10.6.6. Recording of drug intake; overview

For reasons of proper PK analysis of study medication, levetiracetam/ brivaracetam and currently used CCI [redacted] some occasions the date and time of the drug intake needs to be recorded by the participant (using the subject participation card) or the investigator/site staff (using the eCRF).

An overview of this specific recordings of date and time of intake of AEDs is given in Table 7.

Table 7: Recording of date and time of last drug intake during the OLE period.

Study visit	When to record.	Study drug	Levetiracetam/brivaracetam	CCI [redacted]
OLE2	Day before	By participant	By participant	By participant
	During visit	By investigator	By investigator	By investigator
OLE3	Day before	By participant	By participant	By participant
	During visit	By investigator	By investigator	By investigator
OLE4 to7	Day before	By participant	na	na
	During visit	By investigator	na	na

CC [redacted]

10.7. Discontinuation of study intervention and participant discontinuation/withdrawal

Participants may withdraw from participation from the OLE period any time on their request or, at the discretion of the investigator, when JNJ-40411813 is no longer of benefit to them.

A participant will be considered to have completed the OLE period when the participant is still in the study 2 year after the start of the OLE period or when the OLE is stopped by the sponsor. Any subject who withdraws before the end of the OLE has withdrawn and is not a completer.

See also Sections 7.3, 7.5 and 7.6

10.8. Study assessments and procedures for the OLE period

10.8.1. Overview

The SoA of the OLE period (See Section 10.10) summarizes the frequency and timing of all assessments applicable to this study.

Repeat or unscheduled blood samples may be taken for safety reasons, or for technical issues with the samples.

Additional serum (by local laboratory) or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

The total blood volume to be collected from each participant during each visit will be approximately 10.5 mL in Visits OLE 2 and 3, 6.5 mL in Visits OLE4 to OLE7 and 4.5 mL in Visits 8 to 11.

For each participant, the maximum amount of blood drawn from each participant during each visit will not exceed 20 mL.

Volume of Blood to be Collected from Each Participant in each study visit.

Type of Sample	Volume per Sample (mL)	No. of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Hematology	2	1	2
Serum chemistry	2.5	1	2.5
Pharmacokinetic samples[b]	2	3	6
Pharmacokinetic samples[c]	2	1	2

a. Calculated as number of samples multiplied by amount of blood per sample.
b. After 1 and 2 months only (for JNJ-40411813 and metabolites, levetiracetam/ brivaracetam, and CCI
c. From 3 to 12 months only (for JNJ-40411813 and metabolites)
d. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded on the laboratory requisition form.

Refer to the SoA for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual(s) that will be provided before the start of the study.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB for JNJ-40411813.
- Pharmacy manual/study site investigational product manual or equivalent document e.g., Investigational Product Preparation Instructions.
- Laboratory manual.
- (Electronic) diary for participants and/or caregivers.
- Electronic systems or paper documents for the completion of C-SSRS.
- Sample ICF.

10.8.2. Study procedures

10.8.2.1. Baseline visit

For participants who continue with an interruption of ≤4 weeks from the double-blind period:

- The study will start immediately after the last study drug intake by the participant in the double-blind period.
- Participants will have to complete the last visit in the double-blind treatment period but will not have the follow-up visit.

- The last visit in the double-blind period will be considered the baseline visit of open-label period. Assessments required for the last visit in the double-blind period and for the baseline of the open-label-period, do not have to be completed twice.

For participants who start the open-label period with an interruption of >4 weeks after completing the double-blind period:

- Complete the follow-up visit when the open-label period has not been started yet.
- The baseline visit for the open-label period should be a new visit when visit 7 of double-blind study period was more than 4 weeks ago.

The baseline examination will consist of the following:

- Review inclusion/exclusion criteria for the open-label period
- Physical and neurological examination (including body weight)
- Supine vital signs (systolic and diastolic blood pressure, heart rate and oral or tympanic temperature)
- Clinical safety laboratory assessments under fasted conditions (at least 4 hours), when feasible (including hematology, serum chemistry and urinalysis)
- Urine pregnancy test for WOCBP
- The C-SSRS (since last visit) is completed by the investigator or qualified delegate.
- Review of concomitant medication including AEDs
- Record AEs
- Dispense study medication

The participant and/or caregiver will be provided access to an (electronic) diary to record seizures. The (e-)diary will be an app downloaded on the smartphone owned by the participant.

Participants must be compliant with the recording of information in the diary throughout the study. Seizures that will be entered throughout the study include focal aware seizures with and without motor signs, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures. Myoclonic, or other generalized seizures will not be entered.

10.8.2.2. Treatment Period

During the open-label treatment period, participants must report seizures in the (e-)diary. After 1 and 2 months and every 3 months thereafter, the participant will visit the study center. The participants take the study medication at home with a meal. However, during the study visits, the subjects will come to the study center in the morning hours in fasting condition (at least 4 hours) and take the study medication with them. After collection of blood for PK (Visits OLE1 to OLE7 only) and clinical chemistry and hematology, the subject takes the study medication after a meal.

Each study visit will consist of the following:

- Review of (e-)diary

- Physical and neurological examination (including body weight)
- Supine vital signs (systolic and diastolic blood pressure, heart rate and oral or tympanic temperature)
- Clinical safety laboratory assessments under fasted conditions (at least 4 hours), when feasible (including hematology, serum chemistry and urinalysis)
- Blood collection for PK (Visits OLE2 to OLE7 only)
- urine pregnancy test for WOCBP
- The C-SSRS is completed by the investigator or qualified delegate.
- Review of concomitant medication including AEDs
- Record AEs
- Dispense study medication

10.8.2.3. Withdrawal Visit

All participants who discontinue the study at any time are encouraged to complete the withdrawal visit, OLE12. The procedures to be completed during this visit are the same as during the treatment period but no new study medication will be dispensed.

10.8.3. Efficacy Assessments in the OLE period

10.8.3.1. Seizure count

The key efficacy evaluation is seizure count; #seizures per 28 days calculated as (28/the number of days between visits)*(seizures counted between the visits).

The participant and/or caregiver will be provided access to an (electronic) diary to record seizures. The e-diary will be an app downloaded on the smartphone owned by the participant. Only if the participant and/or caregiver do not own a smartphone, a smartphone programmed for the study will be provided.

Participants must be compliant with the recording of information in the e-diary throughout the study. Seizures that will be entered during baseline and throughout the study include focal aware seizures with and without motor signs, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures. Myoclonic, or other generalized seizures will not be entered.

10.8.3.2. Retention on JNJ-40411813 therapy

Retention of JNJ-40411813 therapy will be assessed by the time difference between the date of first dose taken in the open-label period and the date of the last dose taken. As daily dosing will not be recorded in the (e-)diary, a log in IWRS of all study intervention dispensed and returned will be maintained.

10.8.4. Safety Assessments

See Section 8.4 of the protocol.

10.8.5. Pharmacokinetics

During the open-label phase, blood samples (2 mL each) for the determination of trough plasma concentrations of JNJ-40411813 and metabolites (including but not limited to CCI C(CCI, levetiracetam/ brivaracetam and, when used by the participant, CCI will be collected during the visits after 1 month and after 2 months. Participants will be instructed to ingest the morning doses of JNJ-40411813, levetiracetam/brivaracetam, and the other CCI in the clinic after a meal and after the predose PK samples are collected.

During visits OLE4 to OLE7(i.e., up to 1 year after the start of the OLE period), blood samples (2 mL each) for the determination of trough plasma concentrations of JNJ40411813 and metabolites (including but not limited toCCI) will be collected. CCI

The exact dates and times of the last study intervention administrations (at home) prior to collection of each PK sample and dates and times of PK sampling for these visits will be recorded in the eCRF.

See Section 8.5 for details about the analytical procedures.

10.9. Statistical considerations for the OLE period

The OLE extension period will be analyzed separately from the double-blind period.

10.9.1. Sample Size Determination

There is no specific sample size for this study. The study will include subjects who completed the double-blind study phase.

10.9.2. Efficacy analyses

No formal hypothesis testing will be conducted. Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, CV, median, range and graphical methods as appropriate. The SAP will also describe the analysis of the endpoints in the OLE period.

10.9.3. PK and PK/PD analyses

See Section 9.3

10.9.4. Safety Analyses

See Section 9.4

10.10. Schedule of Activities (SoA) of the OLE period

Periods	Open-label treatment				
Study Month	baseline[a]	Mo 1[b,k]	Mo 2[b,k]	Mo 3 and every 3 months thereafter[b,c,k]	Withdrawal
Visit number	OLE1	OLE2	OLE3	OLE4 to 11	OLE12
Administrative procedures					
Informed consent (including OLE period)	X				
Inclusion/exclusion criteria for OLE period	X				
Study drug administration					
Dispense study drug	X	X	X	X	
CCI	Continuous[i]				
Intake concomitant AEDs.	Continuous				
Efficacy assessments					
Seizure counts in (e-)diary	Continuous				
pharmacokinetic assessment					
PK blood sample[d]		X	X	X[e]	
Safety assessments					
Clinical laboratory test[f] (hematology, serum chemistry and urinalysis)	X	X	X	X	X
Urine pregnancy test[g]	X	X	X	X	X
Physical and neurological examination and body weight	X	X	X	X	X
Electrocardiogram (single)	X	X		X[j]	
Vital signs[h]	X	X	X	X	X
C-SSRS	X	X	X	X	X
Concomitant therapy	Continuous				
Adverse events	Continuous				

Footnotes:

a) Same visit as last visit in the double- blind treatment period of the parent study when the participant continues into the open-label treatment period without interruption (assessments should be done once only). The baseline visit for the open-label treatment period should be a new visit when the last visit of the double-blind period was more than 4 weeks ago.
b) For Visits OLE2 to OLE7: Visit to be planned in the morning hours. Participants to take the study medication and concomitant AEDs with them to be dosed after PK-blood collection and a meal.
c) Up to 2 years after the start of the OLE period.
d) For JNJ-40411813 and metabolites, levetiracetam or brivaracetam and CCI [redacted] Record date and time of last drug intake before the visit and during the visit. See Section 10.6.6.
e) For JNJ-40411813 only up to 1 year in the OLE period (visits OLE 4 to 7). Record date and time of last drug intake before the visit and during the visit. See Section 10.6.6.
f) When possible, in fasting condition
g) In women of childbearing potential only
h) Systolic and diastolic blood pressure, heart rate and body temperature (oral or tympanic)
i) CCI [redacted] CCI [redacted] If OLE1 coincides with visit 7 of the double-blind phase, the participant will be dosed on that day with the last dose of the double-blind

medication [redacted].

j) This should only be performed at the Month 3 visit (OLE4).
k) Visit windows are as follows: +/- 5 days for OLE2, OLE3 and OLE4 and +/- 7 days for OLE5 and beyond (always to be calculated from OLE1); duration of 1 month is default 31 days until OLE4', duration of 3 months is default 90 days from OLE5 onwards.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Appendix 1: Abbreviations

AE	Adverse Event
AED	Anti-Epileptic Drug
ALT	alanine aminotransferase
AMA	Anti-mitochondrial antibody
ANA	Antinuclear antibody
Anti-HAV (IgM)	Anti-hepatitis A virus (Immunoglobulin M)
Anti-HEV (IgM)	Anti-hepatitis E virus (Immunoglobulin M)
AP	Alkaline phosphatase
ASMA	anti-smooth muscle antibodies
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve (time period specified by subscript).
AV	atrioventricular
CCI	[redacted]
[redacted]	[redacted]
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CHF	Congestive heart failure
CI	Confidence interval
Cmax	maximum drug concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CPK	Creatine phosphokinase
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P450
DILI	Drug induced liver injury
DNA	desoxyribonucleic acid
DRC	Data Review Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
EBV	Epstein-Barr virus
EC	Effective concentration (% responders specified by subscript).
ED	Effective dose (% responders specified by subscript).
CCI	[redacted]
EU	European Union

ECG	Electrocardiogram
(e)CRF	(electronic) case report form
eDC	Electronic data capture
ERCP	endoscopic retrograde cholangiopancreatography
ESR	Erythrocyte sedimentation rate
EW	Early Withdrawal
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
CGI-SCH	Clinical Global Impression – Schizophrenia
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
HAM-$A_{(6)}$	(6-item) Hamilton Anxiety Scale
HAM-$D_{(6)}$	(6-item) Hamilton Depression Scale
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C antibodies
$HDRS_{17}$	Hamilton Depression Rating Scale
HIV	Human immunodeficiency virus
HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
IC	inhibitory concentration (% inhibition specified by subscript).
ICD	implantable cardioverter defibrillator
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Conference on Harmonization
IDS-C30	Inventory of Depressive Symptomatology
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
IMP	Investigational Medical Product
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
IWRS	Interactive web response system
LBBB	Left Bundle Branch Block
LC-MS/MS	Liquid chromatography/mass spectrometry/mass spectrometry
LDH	Lactic acid dehydrogenase
LFT	liver function test
LKM	Liver kidney microsomal antibody
LKM1	Liver kidney microsomal antibody type 1
LOQ	Limit of quantification
LT	Liver test
MDD	Major Depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities

mGlu2	metabotropic glutamate receptor-2
MRCP	magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
NIMP	Non-Investigational Medicinal Product
NOAEL	no-observed-adverse-effect-level
NSAID	non-steroidal anti-inflammatory drug
OLE	Open-label extension
OTC	Over the counter
PAM	positive allosteric modulator
PANSS	Positive and Negative Syndrome Scale
pANCA	Anti-neutrophil cytoplasmic antibody
PBPK	physiologically based pharmacokinetic modeling
PD	Pharmacodynamic(s)
PgP	P-glycoprotein
PI	principal investigator
PK	Pharmacokinetic(s)
PQC	Product Quality Complaint
PRN	pro re nata (as needed)
PRO	Patient reported outcome
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood cell
REM	Rapid eye movement
RNA	ribonucleic acid
SAE	Serious adverse event
CCI	[redacted]
SoA	Schedule of Activities
SRP	Study responsible physician
SUDEP	Sudden Unexpected Death in Epilepsy
SUSAR	suspected unexpected serious adverse reaction
SV2a	Synaptic Vesicle glycoprotein 2a
SIGH-A	Structured Interview Guide for the Hamilton Anxiety Scale
SWN	Subjective Well-being on Neuroleptics
Tbili	Total bilirubin
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse events
TIBC	Total iron binding capacity
CCI	[redacted]
ULN	Upper Limit of Normal
US	United States
WBC	White blood cell
WOCBP	women of childbearing potential

11.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the SoA by a central laboratory.

Protocol-Required Safety Laboratory Assessments:

Laboratory Assessments	Parameters	
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Urea/Blood urea nitrogen (BUN) Creatinine Glucose (in fasting condition when possible) Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic Gamma-glutamyltransferase (GGT) Total bilirubin (Tbili) and Direct bilirubin	Alkaline phosphatase (AP) Creatine phosphokinase (CPK) Lactic acid dehydrogenase (LDH) Uric acid Calcium Phosphate Albumin Total protein Magnesium Total cholesterol LDL-cholesterol HDL-cholesterol Triglycerides
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Sediment (if dipstick result is abnormal) RBC WBC Epithelial cells Crystals Casts Bacteria
	If dipstick result is abnormal, flow cytometry or microscopy will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.	
Other Screening Tests	• For WOCBP only: Serum pregnancy test at screening and urine pregnancy test during the treatment phase. • Serology (HIV antibody, HBsAg, and HCV antibody)	

	• Urine drug screen (opiates [including methadone], ecstasy, cocaine, (meth)amphetamines, cannabinoids, barbiturates, and benzodiazepines). • Alcohol breath test.

The following biomarkers will be tested in this study. Biomarkers may be added or deleted based on the latest scientific insights without amending the protocol if the total volume of blood to be collected will not increase as a result of adding biomarkers.

sample	**analytes**
CCI [redacted]	[redacted]
[redacted]	[redacted]

11.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

Regulatory Ethics Compliance

Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants).
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study, the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor

- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the investigational drug
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Annual Safety Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or trial conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this clinical study. The re-approval should be documented in writing (excluding the ones that are purely administrative, with no consequences for participants, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

Informed Consent

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF must be signed before performance of any study-related activity. The ICF that is used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential participants the aims, methods, and potential hazards of the study, and any discomfort that participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care that they will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health

authorities and authorized sponsor staff without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF, form the participant is authorizing such access, and agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request, through the investigator, access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory PK research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or less, according to local regulations) for additional research. CCI [redacted] The research may begin at any time during the study or the poststudy storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.5, Withdrawal from the Use of Research Samples).

Country Selection

CCI [redacted] unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Administrative requirements

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for nonacceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Documentation

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the PI.

- A copy of the dated and signed, written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (e.g., Form FDA 1572), if applicable
- Documentation of investigator qualifications (e.g., curriculum vitae)
- Completed investigator financial disclosure form from the PI, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all clinical subinvestigators
- Documentation of subinvestigator qualifications (e.g., curriculum vitae)
- Name and address of any local or central laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local or central laboratory documentation demonstrating competence and test reliability (e.g., accreditation/license), if applicable

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by assigned number.

The investigator must also complete a participant screening log, which reports on all participants who were seen to determine eligibility for inclusion in the study.

Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF or database: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a participant should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Following the ICH/GCP guidelines, direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data.

Case Report Form Completion

Electronic data capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Study site personnel must complete the eCRF within 5 days after a participant visit, and the forms should be available for review at the next scheduled monitoring visit.

The responsible study monitor will check data at the monitoring visits to the clinical study site. The Investigator will ensure that the data collected are accurate, complete and legible.

All clinical work conducted under this protocol is subject to GCP regulations. This includes an inspection by the Sponsor and Competent Authority representatives at any time. The Investigator will agree to the inspection of study-related records by Competent Authority representatives and the audits of the Sponsor or third parties, named by the Sponsor.

Every effort should be made to ensure that all subjective measurements (e.g., pain scale information or other questionnaires) to be recorded in the CRF are completed by the same individual who made the initial baseline determinations. The investigator must verify that all data entries in the eDC system are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the eCRF (if applicable) and complete the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Site manager can generate a query for resolution by the investigational staff
- Clinical data manager can generate a query for resolution by the investigational staff

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, preparation, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study personnel before the start of the study.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database, they will be verified for accuracy and consistency with the data sources.

Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the site. The first post initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Study Completion/Termination

Study Completion

The study is considered completed with the last study visit for the last participant participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final participant visit at that site, in the time frame specified in the Clinical Trial Agreement.

Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon study

completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

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

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

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

On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Participant privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

Use of Information and Publication

All information, including but not limited to information regarding JNJ-40411813 or the sponsor's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of JNJ-40411813, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a clinical study report (CSR) generated by the sponsor and will contain eCRF data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of exploratory biomarker analyses performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR. Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of, and the results of, clinical studies as required by law.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

Financial disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) and contracts for details on financial disclosure.

11.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All AEs under Section 8.8.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

Serious Adverse Event

A SAE based on ICH and European Union (EU) Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

(The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis), the event must be reported as a SUSAR even if it is a component of the study endpoint (e.g., all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-40411813, the expectedness of an AE will be determined by whether or not it is listed in the IB.

Adverse Event Associated with the Use of the Intervention

An AE is considered associated with the use of the intervention if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

An AE may also be associated with one or more of the baseline AEDs. If the investigator is suspecting such an association, the attribution will be documented separately for these AEDs.

ATTRIBUTION DEFINITIONS

Assessment of Causality

The causal relationship to study intervention is determined by the Investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

SEVERITY CRITERIA

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (e.g., laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study intervention that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error involving a sponsor product (with or without participant exposure to the sponsor study intervention, e.g., name confusion)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the Serious Adverse Event page of the CRF.

PROCEDURES

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). [Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.]

The cause of death of a participant in a study within 30 days of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered a SAE.

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, e.g., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.8.1, Time Period and Frequency for Collecting Adverse Event and serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

11.5. Appendix 5: Drugs to be avoided

Examples of Concomitant Drugs to be Avoided (Moderate or Strong Inhibitor/Inducer of CYP3A4)

inhibitors		inducers	
Strong inhibitors	**Moderate inhibitors**	**Strong inducers**	**Moderate inducers**
cobicistat	amprenavir	apalutamide	bosentan
conivaptan	aprepitant	avasimibe	efavirenz
boceprevir	atazanavir	enzalutamide mitotane	etravirine
nelfinavir	cimetidine	rifampin	modafinil
ritonavir	ciprofloxacin	St. John's wort	nafcillin
telaprevir	clotrimazole		
danoprevir and ritonavir	crizotinib		
elvitegravir and ritonavir	cyclosporine		
indinavir and ritonavir	darunavir and ritonavir		
lopinavir and ritonavir	diltiazem		
paritaprevir and ritonavir	dronedarone		
saquinavir and ritonavir	erythromycin		
tipranavir and ritonavir	fluconazole		
ombitasvir and/or dasabuvir	fluvoxamine		
itraconazole, ketoconazole,	imatinib		
voriconazole, posaconazole	tofisopam		
troleandomyin clarithromycin	verapamil		
telithromycin			
mibefradil			
idelalisib			
nefazodone			

Source: FDA, https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

Examples of CYP3A4 substrates producing potentially serious toxicity when combined with CYP3A4 inhibitors

- opioid analgesics
- chemotherapy/oncologic agents
- immunosuppressive agents
- amiodarone
- clindamycin
- dihydroergotamine
- dofetilide
- ergotamine
- theophylline

Examples of CCI substrates

- CCI
- [redacted]

Example of CCI substrate

- CCI

Example of PgP substrate

- digoxin

Note: This is not an exhaustive list.

11.6. Appendix 6: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. In addition to the procedures described in Section 5.1, male participants must also use a condom if their female partner becomes pregnant to avoid exposure to the unborn child.

Pregnancy information will be collected and reported as noted in Section 8.8.4, Pregnancy and Section 11.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Specific considerations for the current study

- CCI [redacted] is part of the existing therapy, and an oral contraceptive is used, a product containing at least 30- to 35-mcg estrogen is advised. Also, an approved barrier method must be used in combination with each hormonal contraceptive.
- CCI [redacted] are use, JNJ-40411813 may inhibit CYP3A4 which may result in increased exposure of estrogen and/or progestogen. This is not expected to result in additional safety risk (Zhang 2018).

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (e.g., a premenarchal woman experiences menarche) or the risk of pregnancy changes (e.g., a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

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

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] in **combination with approved barrier methods**. – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] **in combination with approved barrier methods.** – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
ALLOWED BARRIER METHODS **Please note that a barrier method on its own is not sufficient** • condom with spermicidal foam/gel/film/cream/suppository • occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

If a participant becomes pregnant during the study and pregnancy is specified as an exclusion criterion, consider adding criteria for continuation of study intervention, eg:

Continuation of study intervention will only be included if either of the following apply:

- The study intervention has an approved label that indicates it can be used safely in pregnant females OR
- When all of the following apply:
  - The participant has a high mortality disease
  - The investigator determines the participant is benefitting from study participation and there is no reasonable intervention for her
  - The sponsor and the relevant IEC/IRB give written approval
  - The participant gives signed informed consent
  - The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring

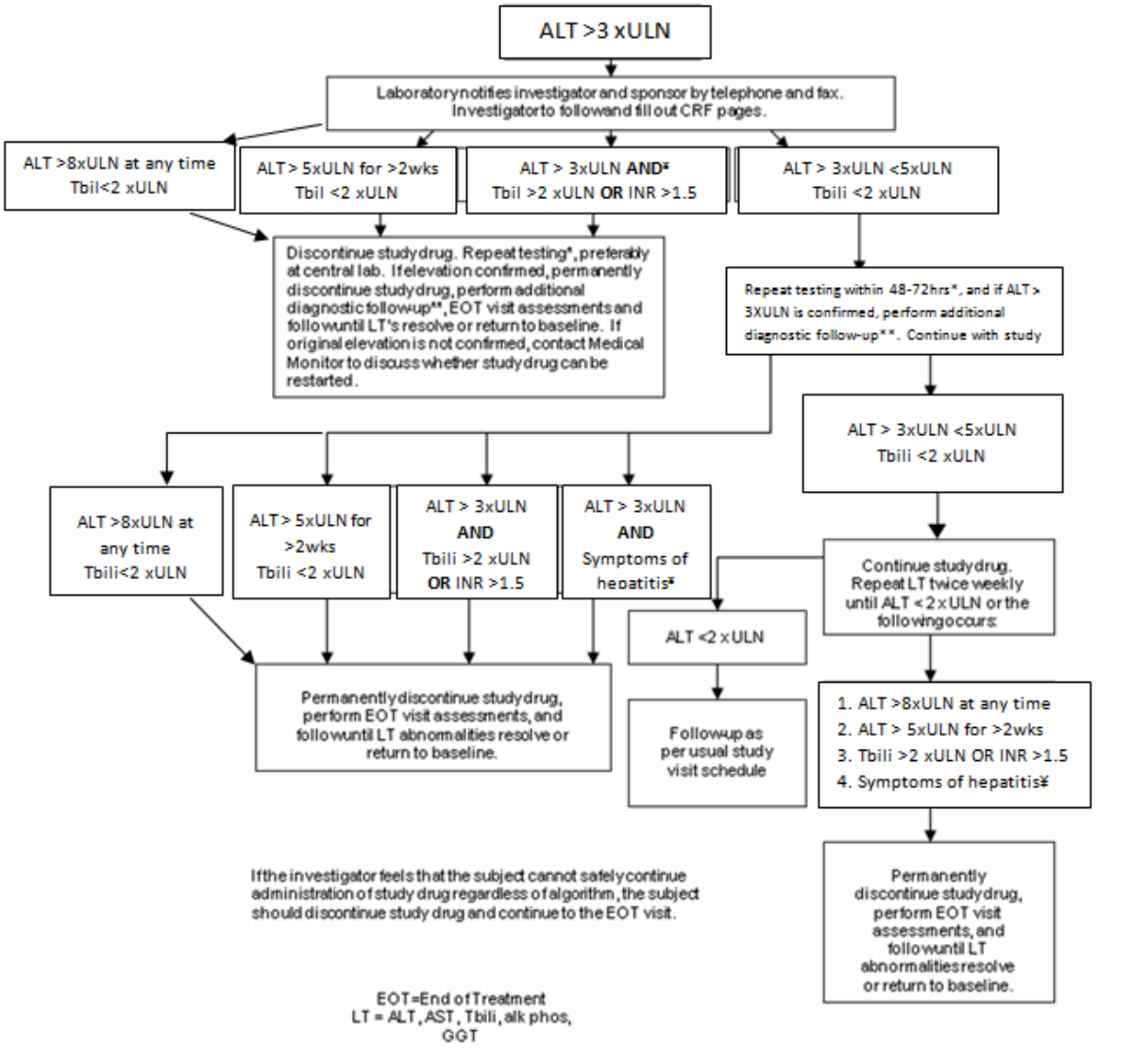
The protocol should be amended to allow such participation on a case-by-case basis, if such participation is not already addressed in the protocol.

11.7. Appendix 7: Liver Safety: Suggested Actions and Follow-up Assessments

Guideline Algorithm for Monitoring, Assessment & Evaluation of Abnormal Liver Tests in Participants with no Underlying Liver Disease and normal baseline ALT, AST, Alkaline Phosphatase and Bilirubin

Although this algorithm is still applicable across all populations, it has been developed assuming normal liver function at baseline. For populations with pre-existing liver disease and/or AST/ALT increases at baseline, product teams are strongly encouraged to consult with Hepatic Safety Group for further guidance particularly for discontinuation criteria.

NOTE: "Liver tests" or "LT's" is the proper name for what are often called "liver function tests" or "LFT's"



*Repeat testing within 48-72 hours in patients with initial ALT elevations, particularly if these are not events reported previously with the drug. If ALT transient elevations have been already established as part of the safety profile, the required frequency of retesting can be decreased

¥ OR ALT >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

****SEE NEXT PAGE FOR TESTS AND EVALUATIONS TO BE OBTAINED**

THE COMPLETE WORK-UP BELOW (ITEMS 1-5) SHOULD BE PERFORMED IN EVERY SITUATION WHERE "" APPEARS ABOVE. ITEMS 6-7 ARE OPTIONAL, TO BE CONSIDERED ON CASE BY CASE BASIS. ALL STUDIES SHOULD BE REPORTED WITH APPROPRIATE SOURCE DOCUMENTATION.**
THE STUDY MEDICAL MONITOR SHOULD BE NOTIFIED WHEN THE ABNORMALITIES ARE DETECTED AND PROVIDED WITH AN UPDATE OF THE RESULTS OF THE DIAGNOSTIC WORK-UP

The following definition of patterns of Drug Induced Liver Injury (DILI) is used when directing the work-up for potential DILI based on elevations of common liver tests (LT):

Histopathology	LT	Ratio (ALT/ULN)/(Alk Phos/ULN)
Hepatocellular	**ALT ≥ 3 × ULN**	**≥ 5**
Cholestatic	**ALT ≥ 3 × ULN**	**≤ 2**
Mixed	**ALT ≥ 3 × ULN and AP ≥ 2 × ULN**	**> 2 to < 5**

1. Obtain detailed history of present illness (abnormal LT's) including (if not already obtained at baseline) height, weight, BMI. Assess for abdominal pain, nausea, vomiting, scleral icterus, jaundice, dark urine, pruritus, rash, fever, and lymphadenopathy. Assess for history of prior abnormal liver tests, liver disease including viral hepatitis, obesity, metabolic syndrome, congestive heart failure (CHF), occupational exposure to hepatotoxins, diabetes mellitus (DM), gallstone disease or family history of gallstone or liver disease. Specifically record history of alcohol use, other meds including acetaminophen, non-steroidal anti-inflammatory drug (NSAID), over the counter (OTC) herbal supplements, vitamins, nutritional supplements, traditional Chinese medicines, and street drugs; and document whether or not there has been any recent change in any other prescription drugs and start-stop dates. Obtain travel history to endemic areas for hepatitis A, hepatitis E. Ask for history of any prior blood transfusions and when they were performed. Perform physical exam, obtain vital signs and BMI, and document presence or absence of scleral icterus, palpable liver including size, degree of firmness or tenderness, palpable spleen including size, ascites, and stigmata of chronic liver disease (spider angiomata, gynecomastia, palmar erythema, testicular atrophy). Allow free text in eCRF for other relevant history and physical information.
2. Mandatory liver ultrasound with consideration of further imaging (e.g., CT, MRI, magnetic resonance cholangiopancreatography [MRCP], endoscopic retrograde cholangiopancreatography [ERCP], Doppler studies of hepatic vessels, etc., if indicated based on ultrasound findings or clinical situation).

3. If Tbili is >2x upper limit of normal (ULN), request fractionation to document the fraction that is direct bilirubin and to rule out indirect hyperbilirubinemia indicative of Gilbert's syndrome, hemolysis or other causes of indirect hyperbilirubinemia. Complete blood count (CBC) with WBC and eosinophil count platelet count, international normalized ratio (INR), and total protein and albumin (compute globulin fraction) should also be documented. If INR is abnormal, prothrombin time (PT), partial thromboplastin time (PTT) should be obtained and these values should be followed until normal, along with documentation of whether parenteral vitamin K was given along with the effect of such treatment on INR.
4. If initial liver function tests (LFTs) and ultrasound do not suggest Gilbert's syndrome, biliary tract disease or obstruction, viral hepatitis serology should be obtained including anti-hepatitis A virus immunoglobin M (anti-HAV IgM), anti-HAV total, HBsAg, anti-HBs, anti-HB core total, anti-HB core IgM, anti-HCV, anti-hepatitis E virus IgM (anti-HEV IgM) (even if has not traveled to an endemic area for hepatitis E), Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) screen.

If participant is immunosuppressed, test for HCV ribonucleic acid (RNA) and HEV RNA.

If HBsAg or anti-HB core IgM or anti-HB core IgG positive, also get HBV DNA to detect active HepB, especially in participants who are immunosuppressed.

If all other hepatitis B serologic tests are negative and anti-HBc total is the only positive test, HBV DNA should be obtained to detect reactivation of hepatitis B.

5. Assuming that the history, physical, and initial imaging and laboratory has not revealed a cause of elevated LTs, screen for other causes of liver disease including: Total protein and albumin (estimate globulin fraction and obtain quantitative immunoglobulins if elevated), antinuclear antibody (ANA), anti-liver kidney microsomal antibody type 1 (anti-LKM1), anti-liver-kidney microsomal antibodies (anti-LKM antibodies), anti-smooth muscle antibodies (ASMA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions in table above), then GGT, anti-mitochondrial antibody (AMA) and anti-neutrophil cytoplasmic antibody (pANCA) should also be tested. If there is an indication by history or elevated baseline LTs that there may be an underlying chronic liver disease possibly exacerbated by exposure to the study intervention in the clinical trial or making the participant more susceptible to DILI, test iron/Total iron binding capacity (TIBC) and ferritin (hemochromatosis), and alpha-1-antitrypsin level. If participant is <50 years of age, ceruloplasmin should also be tested to screen for Wilson's disease. If participant is sick enough to be hospitalized and is under age 50, a slit lamp examination to detect Kayser-Fleischer rings and a 24-hour urine collection for copper should be measured. Consider serum ethanol and/or acetaminophen level and urine drug screen as clinically appropriate.
6. A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated.

   A liver biopsy may be considered:

if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent.

if peak ALT level has not fallen by >50% at 30-60 days after onset in cases of hepatocellular DILI, or if peak Alk Phosphatase has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent.

in cases of DILI where continued use or re-exposure to the implicated agent is expected.

if liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases and chronic DILI.

7. If pertinent, copies of hospital discharge summary, radiology, pathology and autopsy reports should be obtained.

11.8. Appendix 8: The Seizure-Related Disability Assessment Scale (SERDAS)

CCI

[redacted]

CCI

[redacted]

11.9. Appendix 9: Columbia Suicide Severity Rating Scale.

Appendix 10a: Columbia Suicide Severity Rating Scale – Baseline-screening

(Past x months = Past 6 months)

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past__ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

(Past x years = Past 1 year)

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Appendix 9b: Columbia Suicide Severity Rating Scale (Since Last Visit)

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). *Most Severe Ideation:* _____ _____ *Type # (1-5)* *Description of Ideation*	Most Severe
Frequency *How many times have you had these thoughts?* (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___
Duration *When you have the thoughts, how long do they last?* (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___
Controllability *Could /can you stop thinking about killing yourself or wanting to die if you want to?* (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___
Deterrents *Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?* (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply; wish to die only	___
Reasons for Ideation *What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?* (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).	___

Version 7/19/08

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. *Have you made a suicide attempt?* *Have you done anything to harm yourself?* *Have you done anything dangerous where you could have died?* *What did you do?* *Did you_____ as a way to end your life?* *Did you want to die (even a little) when you_____?* *Were you trying to end your life when you _____?* *Or did you think it was possible you could have died from_____?* *Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?* (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. *Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?* If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). *Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?* If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

11.10. Appendix 10: Guidance on Study Conduct during the COVID-19 Pandemic[a]

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If at any time a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed remotely/virtually or delayed until such time that on-site visits can be resumed. Study visits may also be performed at home by the investigator or an appropriately trained nurse. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the participant and investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes (e.g., delay or discontinuation in recruitment, site monitoring and audits) will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

[a] This section has been amended by Amendment INT-1

GUIDANCE SPECIFIC TO THIS PROTOCOL:

The local study center may decide, based on local regulation, to test participants for SARS-CoV-2 at time points indicated by the study center. Any results of such a test will be documented in the eCRF.

If for any reason related to COVID-19 a site visit has to be postponed, the following guidance should be followed:

- According to the protocol, visit 2 (Day 1) may be postponed for 1 week without inducing a protocol deviation. Participants must continue to record their (baseline) seizures in the e-diary.
- Visits 3 and 5 will be done by telephone limiting the number of site visits.
- Visits 4, 6 and 7 may be delayed up to 2 days without inducing a protocol deviation. Participants must continue to record their seizures in the e-diary. Participants have spare intervention.
- Visits 4, 6 and 7 may be delayed up to 4 days. This will be recorded as a COVID-19 related minor protocol deviation. Participants must continue to record their seizures in the e-diary. Participants have spare intervention for up to 4 days.
- Only when required in the context of COVID-19, the visits 4, 6 or 7 may be cancelled and done by telephone instead. For Visits 4 and 6, this is only allowed when the study center can dispense the study intervention at home within 4 days after the planned visit and after temperature-controlled transport. This missing visit will be documented in the eCRF and recorded as a COVID-19 related major protocol deviation. Participants must continue to record their seizures in the e-diary.

11.11. Appendix 11: Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Amendment INT-3	12 July 2022
Amendment INT-2	07 April 2022
Amendment INT-1	18 January 2021
Original Protocol	13 November 2020

Amendment INT 3 (12-July-2022)

Overall Rationale for the Amendment:

To allow for starting enrolment in the double-blind treatment phase of the second cohort as soon as enrolment of approxilately 60 in the first cohort has been completed so that there is no pause in recruitment, provided that no safety concerns are observed during the continuous safety monitoring of ongoing patients. Sections 1.1 (Overview and Study Design), 3 (Objectives), 4.1 (Overall Design), 4.3 (Justification for Dose), 6.3 (Procedures for Randomization) and 9.5 (Data Review after each Cohort) have been changed accordingly.

Dosages of JNJ-40411813 in Cohort 2 will be CCI or placebo for CCI participants and CCI participants.

To also allow the evaluation of the Efficacy, Safety and Tolerability of JNJ-40411813 as Adjunctive Therapy in Subjects with Focal Onset Seizures with Suboptimal Response to Brivaracetam, from Cohort 2 onwards. Brivaracetam has the same Mechanism of Action as Levetiracetam and nonclinical models have shown a strong positive PD interaction of JNJ-40411813 with both levetiracetam and brivaracetam. Brivaracetam has been added in all relevant sections throughout the protocol.

To also add/clarify/correct:

Section number and Name	Description of Change	Brief Rationale
Section 1.1. Dosage and administration And Section 2.3.1: Risks for Study Participation And Section 4.2: Optional temporary dose reduction	Added: For participants receiving dosages of CCI, i.e. Cohort 2 and beyond, a temporary dosage reduction to CCI be permitted in case adverse events consisting of dizziness, incoordination, sedation, or fatigue (or similar descriptive terms) appear within the first 2 weeks of treatment and which, in the judgment of the investigator, potentially limit activities of daily living. This dosage reduction may last no longer than 2 weeks and may not be repeated. Following the return to the originally assigned dosage, recurrence of intolerable adverse events would require discontinuation of the study medication	To anticipate management of early onset AEs (dizziness incoordination, sedation, or fatigue)

Section number and Name	Description of Change	Brief Rationale
	Participants should be advised to call the site it they experience dizziness incoordination, sedation, or fatigue in the first 2 weeks of the double-blind phase.	
Section 1.1 Secondary objectives (and Section 3)	Changed: To evaluate the pharmacokinetics (PK) of JNJ-40411813 and selected metabolites and levetiracetam in participants with focal onset seizures who are receiving levetiracetam and up to 3 other AEDs. Into: To evaluate the pharmacokinetics (PK) of JNJ-40411813 and selected metabolites and levetiracetam or brivaracetam in participants with focal onset seizures who are receiving levetiracetam or brivaracetam and up to 3 other AEDs.	Due to fact that we now allow the use of brivaracetam as primary AED
Section 1.1 Exploratory objectives	Changed: To explore the exposure-response relationship using an estimate of individual participant exposures of JNJ-40411813, and levetiracetam if deemed warranted, from the population PK and/or physiologically based pharmacokinetic (PBPK) analyses, and the primary and secondary endpoints. Into: To explore the exposure-response relationship using an estimate of individual participant exposures of JNJ-40411813, and levetiracetam or brivaracetam if deemed warranted, from the population PK and/or physiologically based pharmacokinetic (PBPK) analyses, and the primary and secondary endpoints.	Due to fact that we now allow the use of brivaracetam as primary AED
Section 4.2 Duration of study period	Clarification: The double-blind study period will be followed by a follow-up period of 2 weeks. The dose will not be tapered after completion of the double-blind study period. Although there are no signals of a rebound effect after stopping the treatment with JNJ-40411813 from preclinical studies or previous clinical studies, the change of seizure count after stopping the treatment will be investigated in the follow-up period. Into: The double-blind study period will be followed by a follow-up period of 2 weeks if the participant does not take part in the OLE period. The dose will not be tapered after completion of the double-blind study period. Although there are no signals of a rebound effect after stopping the treatment with JNJ-40411813 from preclinical studies or previous clinical studies, the change of seizure count after stopping the treatment will be investigated in the follow-up period.	Participants entering the OLE will not have an interruption of dosing, therefore a followup visit after discontinuation of study drug does not apply

Section number and Name	Description of Change	Brief Rationale
Section 5.1: Exclusion 15	Added: does not apply for subjects using barbiturates as AED or rescue medication in Epilepsy	The urine drug screening test is to exclude patients abuse alcohol and/or drugs of abuse
Section 5.1. Inclusion 5	Clarification: Note: One-time changes in AED dosages do not represent a change in the daily AED regimen. For example, if the participant took an extra dose of an AED on one day, this would not represent a change in the daily AED regimen. Benzodiazepines received on a continuing basis at stable dosages for 1 month before screening should be considered as concomitant AEDs Into: Note: One-time changes in AED dosages do not represent a change in the daily AED regimen. For example, if the participant took an extra dose of an AED on one day, this would not represent a change in the daily AED regimen. Benzodiazepines and barbiturates received on a continuing basis at stable dosages for 1 month before screening should be considered as concomitant AEDs, except if they are taken to treat anxiety.	
Section 5.4	Added: Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time after discussion with the sponsor representative. Rescreened participants will be assigned a new participant number, undergo the informed consent process, and then start a new screening and baseline phases, Rescreened individuals must meet all criteria before entering the double blind phase.	In some cases, those factors that caused individuals to fail to meet criteria are judged as likely to remit (e.g., an unrelated intercurrent illness)
Sections 1.1, 9.3, 10.8.5, PK	Added: Addition of JNJ-40411813 metabolite [redacted]	
Section 10.10, SoA of the OLE period	Added: Electrocardiogram (single) at OLE1, OLE2 and OLE4	Omitted by error in Amendment 2

Amendment INT-2 (07-April-2022)

Overall Rationale for the Amendment: To add an open-label extension (OLE) treatment period after completion of the double-blind treatment period.

Section number and Name	Description of Change	Brief Rationale
Section 2.2.1	Added: Information about recently completed chronic rodent and non-rodent toxicology studies.	Chronic toxicology studies are required to support clinical trials of longer duration than 3 months.

Section number and Name	Description of Change	Brief Rationale
Sections, 2.3.2, 4.1, 4.4 and 6.7	Adding an OLE treatment period for subjects completing the double-blind treatment period.	Treatment resistant epilepsy has a severe impact on quality of life and risk of mortality. Continued use of JNJ-40411813 in combination with levetiracetam may result in a significant positive impact on this patient population.
Section 5.1, Inclusion criterion 3	Removed: "for at least 1 year"	In some regions, levetiracetam is started as first line therapy when diagnosis has been confirmed less than 1 year ago.
Section 5.1, Inclusion criterion 5	Changed: Current treatment with at least 1 and up to 4 AEDs (including levetiracetam), administered at stable dosage(s) for at least 1 month before screening, and no new AEDs added for the previous 2 months; these AEDs must remain unchanged throughout the pretreatment and double-blind treatment periods (with the exception of dosage reductions of concomitant AEDs because of suspected elevated AED levels or side effects). Into: Current treatment with at least 1 and up to 4 AEDs (including levetiracetam), administered at the appropriate dosage(s) and for a sufficient treatment period before screening. These AEDs must remain unchanged throughout the pretreatment and double-blind treatment periods (with the exception of dosage reductions of concomitant AEDs because of suspected elevated AED levels or side effects).	In some treatment strategies, the time window to add or change AEDs differs from the timelines described before. The new wording fits better in different treatment strategies.
Section 5.1, Inclusion criterion 6	This inclusion criterion "Currently showing inadequate response to levetiracetam, administered at the appropriate dosage(s) and for a sufficient treatment period, based on the judgment of the investigator" has been removed.	The term "inadequate" has not been defined in detail and clear criteria on seizure count for inclusion have been already described in inclusion criterion 3.
Section 5.1, Exclusion criterion 5	Changed: Current treatment with vagus nerve stimulation, deep brain and cortical stimulation for 1 year or less Into: Recently initiated vagus nerve stimulation, deep brain and cortical stimulation (i.e. in the last 12 months before screening).	Original text caused some confusion.
Section 7.3	Added: "promptly" to the referral for appropriate medical/psychiatric care.	Medical and ethical consideration.
Section 8.4.3	Remove the sentence "The mean values of ECG parameters will be calculated for entry into the eCRF."	The eCRF has been designed to enter the 3 individual ECGs of the triplicate ECG
Section 9.4	Added that the safety analysis will be done per cohort.	This detail was missing in the original text.
Section 10.4.2, Duration of the study	Added: Participants will participate in the open-label period for a period of up to 2 years. If they still benefit from treatment with JNJ-40411813, they will be transferred to a new central OLE study **when**	Due to unforeseen circumstances, the open label extension period may not be completed as planned.

Section number and Name	Description of Change	Brief Rationale
	available, in which also participants from other (late phase) studies with JNJ-40411813 will participate. and The OLE extension period may be stopped when the development of the compound is stopped by a decision of the sponsor or because of insufficient efficacy or safety concerns.	
Newly added Addendum (section 10)	Adding an OLE treatment period for subjects completing the double-blind treatment period.	To comply with the considerations for an OLE treatment as indicated in Sections 2.3.2 and 6.7 of the protocol.

Amendment INT-1 (18-January-2021)

Overall Rationale for the Amendment: To implement several different corrections as listed below.

Section number and Name	Description of Change	Brief Rationale
Synopsis, secondary objectives	Changed: ….and up to 4 other AEDs. Into: …and up to 3 other AEDs.	Correction of typo
Synopsis and Section 4.1	Change: a 12-week double-blind treatment period…. Into An up to 12-week double-blind treatment period….	The double-blind treatment period may be shorter if the participant reached the baseline seizure count
Synopsis, SoA and Sections 3, 4.1, and 9.2.1.	Changed: .. number of focal onset seizures… Into .. number of observable focal onset seizures…	To have a more precise definition of seizures to be reported.
SoA and Section 8.2.2	A telephone contact has been added to the baseline period. In the SoA footnotes and Section 8.2.2 the following text has been added: During the baseline period, the participant will be contacted by phone by the investigator or study nurse to confirm correct use of the e-diary. This contact should take place at least 4 weeks after the start of the baseline period, but multiple contacts are allowed when required.	A period of 8 weeks is too long to keep the participant motivated without support from the site team.
Section 5.1, inclusion criterion 4	Changed: Must have had a neuroimaging procedure within 5 years, including a computed tomography (CT) scan or magnetic resonance imaging (MRI), that excluded a progressive neurologic disorder; these procedures may be performed within the 8-week baseline period. When one was obtained earlier and the clinical situation is not changed, the participant may be allowed in the study	To be in line with current clinical practice.

Section number and Name	Description of Change	Brief Rationale
	after approval by the epilepsy consortium in the adjudication process. Into: Must have had a neuroimaging procedure within 10 years, including a computed tomography (CT) scan or magnetic resonance imaging (MRI), that excluded a progressive neurologic disorder; these procedures may be performed within the 8-week baseline period.	
Section 5.4. and Section 8.2.1	Added: If the adjudication process is not possible e.g., because of technical limitations of protected data transfer, the participant will not be a screen failure.	To prevent participants to be a screening failure, when the adjudication process should fail for technical reasons.
Section 5.1, inclusion criterion 3	Removed: The diagnosis will have to be confirmed by the Epilepsy Consortium's Review before randomization.	May conflict with the exception mentioned above.
Synopsis Section 3 Section 4.1 Section 5.1 Inclusion Criterion 7 Section 8.2.2 Section 8.3.1 Section 9.2.1	Original text: Seizures that will be counted during baseline and throughout the study include focal onset motor seizures with or without impaired consciousness, focal onset nonmotor seizures with impairment of consciousness and focal to secondarily generalized seizures. Focal onset nonmotor seizures without impairment of consciousness, myoclonic, or other generalized seizures will not be counted. Changed into: Participants must be compliant with the recording of information in the e-diary throughout the study. Observable seizures that will be entered during baseline and throughout the study include focal aware seizures with and without motor signs, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures. Myoclonic, or other generalized seizures will not be entered.	The terminology of seizures is incorrect in several places and does not exactly reflect the ILAE 2017 criteria.
Synopsis and Section 9.2.2, Secondary generalized seizures	Change: Separate analyses (including time to baseline count and % reduction of counts) for secondary generalized seizures only and complex focal and secondary generalized seizures, will be performed if a large enough number of events is observed. Into: Separate analyses (including time to baseline count and % reduction of counts) for focal to bilateral tonic-clonic seizures will be performed if a large enough number of events is observed.	To comply with ILAE 2017 criteria.
Section 9.2.1	Added: Although focal aware seizures with and without motor signs are entered in the e-diary, focal aware seizures without motor signs will not be counted in the analysis.	For participants it is not always clear how to differentiate between motor and non-motor seizures. So, therefore all seizures will be entered in the e-diary, but focal aware seizures without motor signs will not be counted.

Section number and Name	Description of Change	Brief Rationale
Section 9.3	Change: Population PK and/or PBPK analyses of JNJ-40411813, levetiracetam and AED CCI [redacted] Into: Population PK and/or PBPK analyses of JNJ-40411813 and levetiracetam …	Population PK and PBPK analysis of AEDs CCI [redacted]
Section 7.3	Added: A participant who shows signals of clinically meaningful acute suicidal ideation at any time during the study should be withdrawn from the study and referred for appropriate medical/psychiatric care.	A withdrawal criterion for response to the C-SSRS was missing.
Schedule of Activities Section 8.5	Changed Visits 3 and 5 from site visits into telephone contacts removing blood collection, C-SSRS and some safety assessments. Adverse events and concomitant medication will be followed up.	Because of the potentially ongoing COVID-19 pandemic and to limit the burden for the study participants in general, it has been decided to limit Visits 3 and 5 to a telephone contact. No blood for PK will be collected.
SoA Section 8.5 Section 6	Blood collections for PK have been removed from the screening visit but added to Visit 7. Table 3 and several sections have been updated for consistency.	Blood collection at screening should require pre-ICF activities. More information on steady state PK is required.
Section 8.1	Blood volume to be collected reduced from 83.5 to 75.5 mL. In text formulated as approximately 76 mL.	Change volume of blood to be collected due to changes in PK sampling plan.
Section 8.2.3	Original text: The participant will visit the study center after 2, 4, 6, 8 and 12 weeks. Changed into: The participant will visit the study center after 4, 8 and 12 weeks. After 2 and 6 weeks, the investigator will have a telephone call with the participant to discuss adverse events, use of the e-diary and concomitant medication.	Because of the potentially ongoing COVID-19 pandemic and to limit the burden for the study participants in general, it has been decided to limit Visits 3 and 5 to a telephone contact. No blood for PK will be collected.
Section 10.10. Appendix 10: Guidance on Study Conduct during the COVID-19 Pandemic	Original text: • According the protocol, visit 2 (Day 1) may be postponed for 1 week without inducing a protocol deviation. Participants must continue to record their (baseline) seizures in the e-diary. • Visits 3 to 7 may be delayed up to 2 days without inducing a protocol deviation. Participants must continue to record their seizures in the e-diary. Participants have spare intervention. • Visits 3 to 7 may be delayed up to 4 days. This will be recorded as a COVID-19 related minor protocol deviation. Participants must continue to record their seizures in the e-diary. Participants have spare intervention for up to 4 days. • Only when required in the context of COVID-19, the visits 3, 4, 5, 6 or 7 may be cancelled and	Because of the potentially ongoing COVID-19 pandemic and to limit the burden for the study participants in general, it has been decided to limit Visits 3 and 5 to a telephone contact

Section number and Name	Description of Change	Brief Rationale
	done by telephone instead. For Visits 3 to 6, this is only allowed when the study center can dispense the study intervention at home within 4 days after the planned visit and after temperature-controlled transport. This missing visit will be documented in the eCRF and recorded as a COVID-19 related major protocol deviation. Participants must continue to record their seizures in the e-diary. Changed into: • According the protocol, visit 2 (Day 1) may be postponed for 1 week without inducing a protocol deviation. Participants must continue to record their (baseline) seizures in the e-diary. • Visits 3 and 5 will be done by telephone limiting the number of site visits. • Visits 4, 6 and 7 may be delayed up to 2 days without inducing a protocol deviation. Participants must continue to record their seizures in the e-diary. Participants have spare intervention. • Visits 4, 6 and 7 may be delayed up to 4 days. This will be recorded as a COVID-19 related minor protocol deviation. Participants must continue to record their seizures in the e-diary. Participants have spare intervention for up to 4 days. • Only when required in the context of COVID-19, the visits 4, 6 or 7 may be cancelled and done by telephone instead. For Visits 4 and 6, this is only allowed when the study center can dispense the study intervention at home within 4 days after the planned visit and after temperature-controlled transport. This missing visit will be documented in the eCRF and recorded as a COVID-19 related major protocol deviation. Participants must continue to record their seizures in the e-diary.	
Multiple Sections	Removed: Sections 8.3.2.1. and 10.8. Text removed from synopsis, SoA and Sections 3, 4.2, 8.1, 8.2.3, 9.2.2 and references.	CCI [redacted]
Synopsis and Sections 4.1 and 9.5	Original text: If the assessment of efficacy favors JNJ-40411813, the second cohort will receive a lower dose. If the assessment of efficacy does not favor JNJ-40411813, the second cohort will be enrolled at a higher dosage if there are no safety concerns. In case of doubtful results, it may be decided to add sub-cohorts including a lower dose as well as a higher dose. Changed into: If the assessment of efficacy favors JNJ-40411813 but with concerns about tolerability, the second cohort will receive a lower dose. If the assessment of efficacy does not favor JNJ-40411813, the second	The procedure of decisions on the dose levels of following cohorts has been adapted to optimize the efficiency of study execution.

Section number and Name	Description of Change	Brief Rationale
	cohort will be enrolled at a higher dose if there are no safety concerns. If the assessment of efficacy favors JNJ-40411813 and there are no safety concerns, the following cohort may include both a lower dose and a higher dose. Such a cohort will randomize 100 subjects in a ratio 40:40:20 (high dose/low dose/placebo). Subjects and investigators will be blinded for treatment but not for dose level. Figure 1 in Section 4.1 has been adapted.	
Section 6.3	Added: description of the protocol numbering given the options described above.	See above.
Section 6.3	Added: Participants and investigators will be blinded for treatment (JNJ-40411813 or placebo) but not for dose.	Multiple dose levels may be possible in one cohort (e.g., due to enzyme induction or different dose levels in one cohort [see above]. Blinding for dose level is technically not possible in this study.
Section 6.1	Original text: The participants will take the study intervention and levetiracetam with them at each study visit. Changed into: The participants will bring the study intervention and all other AEDs currently taken with them at each study visit. Added: For Visit 7, ingest morning doses of study drug and AED medications at home, before going to the clinic.	To give more detailed instructions on drug intake and documentation around study visits.
Section 6.4	Added: For study visits 2, 4 and 6, participants are requested to record the time of last dosing of levetiracetam , their CCI [redacted] and the study drug on the day before the study visit. Participants will also record the time of last dosing of levetiracetam and study drug taken at home before visit 7. An appointment-card will be provided for documentation.	To give more detailed instructions on drug intake and documentation around study visits.
Section 6.5	Added: For study visits 2, 4, and 6 participants are requested to record the time of last dosing of levetiracetam on the day before the study visit. Participants will also record the time that levetiracetam is taken at home prior to visit 7. An appointment-card will be provided for documentation. Added: For the study visits 2, 4 and 6, participants are requested to record the date and time of last dosing of CCI [redacted] when applicable on the day before the study visit. An appointment-card will be provided for documentation.	To give more detailed instructions on drug intake and documentation around study visits.

Section number and Name	Description of Change	Brief Rationale
Section 6.6	A new Section 6.6, "Recording of drug intake; overview" has been added.	To instructions on drug intake recording were fragmented throughout the protocol. To clarify this better, a new section has been added.

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[a] This section has been amended by Amendment INT-1

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	17-Nov-2022 13:13:44 (GMT)	Document Approval