Janssen Research & Development

Statistical Analysis Plan

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

Protocol 40411813EPY2001; Phase 2a

JNJ-40411813

Status: Approved
Date: 12 March 2024
Prepared by: Janssen Research & Development, LLC
Document No.: EDMS-RIM-634383, 4.0

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	1 March 2022	Not Applicable	Initial release
2.0	22 November 2023	Brivaracetam has been added to all relevant sections throughout the SAP.	To align with Protocol Amendment 3
		Section 1.1: Table of endpoints and objectives included for the open label extension (OLE)	To align with Protocol Amendment 2
		Section 1.2: Study design section updated to include dosages for Cohort 2 CCI [redacted] and remove text describing how subsequent Cohort dosage will be decided as Cohort 2 dosage already specified.	To align with Protocol Amendment 3
		Section 1.2: Study design section updated to include details of OLE phase	To align with Protocol Amendment 2
		Section 4: Added analysis sets FASOLE and SAFOLE to summarize efficacy and safety in the open label phase. CAS analysis set definition changed by removing medication intake data from the e-diary as a data source. PK analysis set (PKAS) defined.	Additional analysis sets defined to align with Protocol Amendment 2, e-diary medication data removed from CAS definition as a data source due to poor data quality. PK analysis set define for analysis of PK concentration data.
		Section 5.1: OLE phase described including reference start and end dates	To align with Protocol Amendment 2
		Section 5.1.1: Visit windows updated to include OLE visits	To align with Protocol Amendment 2
		Section 5.2: Participant disposition categories updated to include OLE phase	To align with Protocol Amendment 2
		Section 5.3.1: The time to baseline monthly seizure count definition corrected and removed the incorrect text "using 4-week sliding window approach)"	Correction
		Section 5.3.3: Removed sensitivity analysis text comparing the two medication intake data sources (e-diary and drug accountability data)	Drug accountability data is more reliable and better quality than e-diary medication intake data
		Section 5.3.3: Additional sensitivity analysis included to assess the impact of the Ukraine and Russia conflict on the primary endpoint	To incorporate additional statistical sensitivity analyses

SAP Version	Approval Date	Change	Rationale
		Section 5.5: Added text to say efficacy data analysis in the OLE will use the FASOLE analysis set	To align with Protocol Amendment 2
		Section 5.5.2.1: Text added to clarify that participants who opt not to participate in the OLE will go not the follow-up phase	Clarification to align with Protocol Amendment 2
		Section 5.5.4: new section added to provide analysis details of the efficacy data in the OLE	Incorporate statistical methods to align with Protocol Amendment 2
		Section 5.6: Safety analyses text updated to include analysis of OLE safety data using the SAFOLE analysis set	To align with Protocol Amendment 2
		Section 5.6.1: Extent of exposure section text updated to include summary of OLE exposure data and OLE intervention compliance data. Additional listing included for all dose adjustments for each participant stating the reason	To align with Protocol Amendment 2 and to summarize dosage adjustment form data
		Section 5.6.2: Rescue medication analysis section removed	Rescue medication intake poorly/incorrectly reported by participants during study, thus making it unreliable data.
		Section 5.6.2: Additional text to describe assignment rules for AE's to each phase (DB, Follow-up and OLE)	To align with Protocol Amendment 2 and to give clarity to which phase AE's should be assigned
		Section 5.6.2.1: Clinical laboratory text updated to include summary of OLE data	To align with Protocol Amendment 2
		Section 5.6.2.2: Vital signs and physical examination section updated to include summary of OLE data	To align with Protocol Amendment 2
		Section 5.6.2.3: ECG section updated to include summary of OLE data	To align with Protocol Amendment 2
		Section 5.6.2.4.1: C-SSRS section updated to include summary of OLE data	To align with Protocol Amendment 2
		Section 5.7: PK/PD section updated to include descriptive statistics of PK data	To summarize available PK data
		Section 5.8: Purpose of IRC changed from "deciding dose in the following cohort" to "provide recommendation on study progression"	To re-define the purpose of the IRC since Cohort 2 dosage already specified
		Section 6.3: Appendix 3 updated to include summary of demographic and baseline data for OLE population using SAFOLE analysis set	To align with Protocol Amendment 2

SAP Version	Approval Date	Change	Rationale
		Section 6.4: Appendix 4 updated to include summary of protocol deviations during OLE phase using the SAFOLE analysis set	To align with Protocol Amendment 2
		Section 6.5: Appendix 5 updated to include summary of prior and concomitant medications during OLE phase using the SAFOLE analysis set	To align with Protocol Amendment 2
		Section 6.7.1: Appendix 7 updated to include summary of intervention compliance during OLE phase using drug accountability data	To align with Protocol Amendment 2
		Section 6.7.2: Appendix 7 seizure e-diary compliance definition updated	Definition updated to align with CAS analysis set definition in Section 4
3.0	16 January 2024	Section 5.3.1: Sentence included to define when seizure data on a given day is classed as being missing	To clarify/define when seizure data are classed as being missing
		Section 5.7.1: Additional text to clarify who will produce the PK results	To clarify that the Pharmacometrics group will produce the PK results
4.0	8 March 2024	Section 4.0 and 5.3.3: Compliance analysis set (CAS) definition and analysis methods text updated	Current CAS definition too stringent therefore the e-diary criteria was removed.
		Section 5.3.3: Descriptive summary statistics text updated so that only the 95% CI is shown for the median. The last paragraph introducing best-case and worst-case scenario sensitivity analysis removed	The 95% CI for quartiles not required and only needed for the median. Best/worst case scenario removed since the results of such sensitivity analyses deemed not appropriate/informative.
		Section 5.4.1.2: Description of best-case and worst-case scenario sensitivity analysis removed. Sensitivity analysis criteria for imputing 0% percent reduction for discontinued participants updated	Results of such best/worst case sensitivity analyses deemed not appropriate/informative. Imputation criteria updated to make it more conservative.
		Section 5.4.3.2: Details of best-case and worst-case scenario sensitivity analysis removed	Results of such sensitivity analyses deemed not appropriate/informative
		Section 5.4.4.1: The definition of the response ratio has been updated to add further clarity	To clarify/define the response ratio
		Section 5.5.4: Included the line to say box-plots will be presented if the nature of the outcome is nonparametric	If the nature of the outcome is nonparametric then a box-plot is a more appropriate graphical representation of the data
		Section 5.6.2.3: Criteria for Abnormal QTc Values table updated	Criteria updated to include QTc criteria for males and females

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the analysis of efficacy, safety and tolerability data for the 40411813EPY2001 Phase 2a study.

1.1. Objectives and Endpoints

Double-blind Treatment Phase

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 anti-epileptic drugs (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, CSSRS 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.
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	Plasma concentrations of JNJ-40411813 and levetiracetam or brivaracetam and metabolites

Objectives	Endpoints
with focal onset seizures who are receiving levetiracetam or brivaracetam and up to 3 other AEDs.	at baseline (Day 1) and on study weeks 4, 8, and 12
Exploratory	

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[redacted]

Open-Label Extension Phase

Objectives	Endpoints
Primary	
The primary objective of this open-label period is to evaluate the long-term efficacy and safety	Seizure count by using an (e-)diary, adverse events, significant changes in vital signs, and safety laboratory results.

Objectives	Endpoints
of adjunctive therapy with JNJ-40411813 in participants with epilepsy.	
Secondary	
To evaluate, during long-term treatment, the pharmacokinetics (PK) of JNJ-40411813, levetiracetam/brivaracetam, CCI [redacted]	Plasma concentrations of JNJ-40411813, levetiracetam/brivaracetam, and CCI [redacted]

1.2. 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 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 the 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 60 participants are randomly assigned in a 2:1 ratio to receive either JNJ-40411813 twice daily (bid) or placebo. For each following cohort, approximately 60 eligible participants will be initially enrolled to ensure that 50 participants are randomly assigned in a 4:1 ratio to receive either JNJ-40411813 bid or placebo.

In each cohort, participants will be CCI [redacted] At least 20% of the participants must be included in each of the two groups.

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/ XBL, where XBL is the number of days comprising the baseline.

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. Central randomization will be implemented in this study. Participants will be randomly assigned to one of two treatment groups (JNJ-40411813 or Placebo) 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 stratified by the prescribed baseline CCI [redacted]

Dosages of JNJ-40411813 in the first cohort will be CCI [redacted] or placebo for CCI [redacted], and CCI [redacted] or placebo for 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] for 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] for CCI [redacted]. The highest dose selected to be administered by induced participants will be expected not to exceed the 95th percentile of the plasma Cmax for JNJ-40411813, based on a population PK and/or PBPK model, after 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.

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 of the protocol) 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 phase will not have follow-up and will continue to record seizures by using an e-diary.

In general, randomization codes will be disclosed fully once the study is completed and the clinical database is closed. However, for the interim review in each cohort (see protocol Section 9.5) and for unblinded review by the data review committee (DRC, see protocol 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. After at least 55 participants in Cohort 1 and at least 45 participants in Cohor 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 whether there should be any

addition or modification to the dose(s) in the following cohorts and subsequent clinical studies. If the results after the last participant has completed the 4-week visit 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.

Figure 1: Study flow diagram

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2. STATISTICAL HYPOTHESES

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 (28 days) seizure count in participants with focal onset seizures who are receiving levetiracetam or brivaracetam and up to 3 other anti-epileptic drugs (AEDs). The null hypothesis that is to be tested to address the primary objective of the trial is that there is no difference between JNJ-40411813 doses and placebo in the time to baseline monthly seizure count

3. 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 over-dispersed 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% (30% in a scenario with less efficacy) for JNJ-40411813, a cohort with 40 participants randomized to JNJ-40411813 and 20 to placebo would achieve a power of 99% (83% for the less

efficacy scenario) 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.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

For purposes of analysis, participants will be classified into the following analysis sets. For each analysis set described below, participants will be analyzed according to the planned study intervention irrespective of what they actually received.

Analysis Sets	Description
Enrolled	All participants who sign the ICF.
Randomized	The randomized analysis set includes all participants who were randomized in the study.
Full Analysis Set (FAS)	The full analysis set (FAS) includes all randomized participants assigned to receive study intervention and have both baseline and postbaseline seizure data. This definition is the same as the ITT set.
Full Analysis Set: Open-Label Extension (FASOLE)	The FASOLE analysis set includes all FAS participants who received at least 1 dose of study intervention in the OLE phase.
Compliance Analysis Set (CAS)	The compliance analysis set (CAS) includes a subset of participants in the FAS who were in compliance with their medication intake. In other words, exclude those who with <80% compliance for medication intake. Medication intake data will come from the drug accountability data collected at monthly visits.
"Modified" FAS	The modified FAS includes a subset of participants in the FAS who remained in the treatment period beyond 4 weeks. In other words, participants who exit the study by 4 weeks having reached their pre-randomization baseline seizure count will not be included.
Safety (SAF)	The safety analysis set includes all randomized participants who received at least 1 dose of JNJ-40411813 or placebo in the double-blind phase.
Safety: Open-Label Extension (SAFOLE)	The SAFOLE analysis set includes all randomized participants who received at least 1 dose of study intervention in the OLE phase. This analysis set is the same as the FASOLE analysis set.
PK Analysis Set (PKAS)	The PK analysis set (PKAS) included all randomized participants who have received at least 1 dose of JNJ-40411813 and have at least 1 valid blood sample drawn for PK analysis.

5. STATISTICAL ANALYSES

5.1. General Considerations

Study Phases

There are five study phases defined in this study: Screening, Pre-treatment Baseline, Double-blind, Follow-up (post double-blind) and Open-Label Extension (OLE). Each analysis phase has its own analysis reference start date.

Screening Phase

Participants will have a screening visit immediately prior to the start of the pre-treatment baseline period, where the date of screening will be defined as the date written informed consent is obtained.

Pre-treatment Baseline Phase

After screening, participants will start the 8-week prospective pre-treatment baseline period pending the results of the central laboratory and, if applicable, the adjudication process. If the results suggest 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 pre-treatment baseline phase, participants will record seizure information in an e-diary. The pre-treatment baseline phase is defined as starting on the day of screening when the participant has initiated the e-diary and ends on the day of Visit 2 after the investigator enters the baseline period as completed in the diary dashboard.

Double-blind Phase

The analysis reference start date of the double-blind phase is the date of the first dose of the double-blind medication (i.e. Clinic Visit 2, Day 1). A participant will be considered to have completed the study if they complete the double-blind period up to Week 12, or have elected to exit after reaching the baseline monthly seizure count by Day 28 or after exceeding the monthly baseline seizure count during a moving 28-day interval after Day 28. In either case, participants should complete Visit 7 (Week 12/Early Withdrawal) and the reference end date of the double-blind phase is the Visit 7 date.

Follow-up Phase

Participants who continued treatment to the end of the double-blind period (Week 12) or have completed the study (as defined above) and have not elected to participate in the OLE will go into the follow-up phase. In the follow-up phase, participants will continue to record only the number of seizures using the e-diary until 2 weeks after the last dose and will have a telephone follow-up visit at 2 weeks ±2 days after the last dose. The analysis reference start date of the follow-up analysis phase is the day after the reference end date for the double-blind phase. The analysis reference end date of the follow-up analysis phase is the maximum of the telephone follow-up visit date or the e-diary follow-up date.

Open-Label Extension Phase

For participants electing to participate in the OLE, the reference start date of the OLE phase will be either the date of last study drug intake by the participant in the double-blind period for subjects who continue into the OLE without an interruption of ≤4 weeks from the double-blind period, or the date of the OLE baseline visit when there is an interruption of >4 weeks (i.e. the last visit of the double-blind period was more than 4 weeks ago). Participants participating in the OLE without an interruption of ≤4 weeks from the double-blind period will not have the follow-up visit (Visit 8), and those with an interruption of >4 weeks will complete the follow-up visit. The analysis reference start date for the OLE phase is the date of the last dose taken in the double-blind phase. The analysis reference end date of the OLE phase is either the date when the last dose of study drug is taken in the OLE phase (Visit OLE11), the date OLE is stopped by the sponsor or the date of early withdrawal from the OLE phase. The open-label efficacy data will be summarized by the double-blind treatment group in the form of an intervention sequence (PBO/JNJ and JNJ/JNJ).

5.1.1. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1. If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table 2) are the analysis visit windows and the target days for each visit defined in the protocol.

Table 2: Visit Windows

Parameter	Analysis Period	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
Hematology, Serum Chemistry and Urinalysis	Screening	1	Screening	<1	-57
	DB	2	Day 1	≤1	1
		4	Day 29	2 to 43	29
		6	Day 57	44 to 71	57
		7	Day 85	72 to end of DB	85
		DB last visit	EW	2 to EW	
	OLE[b]	OLE1	Baseline (OLE)	≤1	1
		OLE2	Month 1	2 to 47	31
		OLE3	Month 2	48 to 78	62
		OLE4	Month 3	79 to 138	93
		OLE5 to OLE11[a]	Month 3 + 3*i	[138+90*(i-1)+1] to [138+90*i]	93+90*i
		OLE12	EW (OLE)	2 to EW (OLE)	
CCI	DB	2	Day 1	≤1	1
		4	Day 29	2 to 43	29
		7	Day 85	44 to end of DB	85
		DB last visit	EW	2 to EW	
Physical examination, Neurologic examination, Body weight	Screening	1	Screening	< 1	-57
	DB	7	Day 85	72 to end of DB	85
		DB last visit	EW	2 to EW	
	OLE[b]	OLE1	Baseline (OLE)	≤1	1
		OLE2	Month 1	2 to 47	31
		OLE3	Month 2	48 to 78	62
		OLE4	Month 3	79 to 138	93
		OLE5 to OLE11[a]	Month 3 + 3*i	[138+90*(i-1)+1] to [138+90*i]	93+90*i
		OLE12	EW (OLE)	2 to EW (OLE)	
Brief neurological examination	DB	2	Day 1	≤1	1
		4	Day 29	2 to 43	29
		6	Day 57	44 to 85	57
	Screening	1	Screening	<1	-57

Parameter	Analysis Period	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
C-SSRS, Vital signs	DB	2	Day 1	≤1	1
		4	Day 29	2 to 43	29
		6	Day 57	44 to 71	57
		7	Day 85	72 to end of DB	85
		DB last visit	EW	2 to EW	
	OLE[b]	OLE1	Baseline (OLE)	≤1	1
		OLE2	Month 1	2 to 47	31
		OLE3	Month 2	48 to 78	62
		OLE4	Month 3	79 to 138	93
		OLE5 to OLE11[a]	Month 3 + 3*i	[138+90*(i-1)+1] to [138+90*i]	93+90*i
		OLE12	EW (OLE)	2 to EW (OLE)	
Electrocardiogram	Screening	1	Screening	<1	-57
	DB	4	Day 29	2 to 43	29
		7	Day 85	72 to end of DB	85
		DB last visit	EW	2 to EW	
	OLE[b]	OLE1	Baseline (OLE)	≤1	1
		OLE2	Month 1	2 to 47	31
		OLE4	Month 3	79 to 138	93
		OLE5 to OLE11[a]	Month 3 + 3*i	[138+90*(i-1)+1] to [138+90*i]	93+90*i
Seizure counts in e-diary	Baseline	Continuous collection	Baseline	<1	-56 to -1
	DB		DB Period	1 to end of DB	1 up to 85
	FU		FU Period	End of DB to End of FU	End of DB + 14
	OLE[b]		OLE Period	End of DB to End of OLE	End of DB + 730

*Relative to Study Day 1; DB=double-blind; EW=Early withdrawal; FU=Follow-up; OLE=Open-Label extension
Footnotes:

a) Visits occur every 3 months after visit OLE4. To note, the "i" term is the iterator for the 3 monthly visits that occur after OLE4 e.g., i=1 for OLE5

b) 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

5.2. Participant Dispositions

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants randomized
- Participants who received study intervention during each phase (double-blind and open-label)
- Participants who completed the study during each phase (double-blind and open-label)
- Participants who discontinued study intervention during each phase (double-blind and open-label)
- Reasons for discontinuation of study intervention during each phase (double-blind and open-label)

- Participants who terminated study prematurely during each phase
- Reasons for termination of study prematurely during each phase

Listings of participants will be provided for the following categories:

- Participants who discontinued double-blind study intervention
- Participants who discontinued open-label study intervention
- Participants who terminated study prematurely
- Participants who were randomized yet did not receive study intervention

The above summaries and listings will be provided for the randomized analysis set.

5.3. Primary Endpoint(s) Analysis

The primary efficacy endpoint will be evaluated at a 1-sided significance level of 0.05. For all other efficacy endpoints, no multiplicity adjustment will be done.

5.3.1. Definition of Endpoint(s)

The primary endpoint is the time to baseline monthly seizure count. The baseline monthly seizure count is an individualized measure and 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 participants baseline period. Seizure data on a given day are said to be missing if the participants report no seizures and also do not complete the reminder diary. For all participants, it will be assumed that no seizures occurred on the days where seizure data are missing in the e-diary because the majority of participants have more days where no seizures occcur, than days when a seizure occurred. 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 without motor signs and other seizures will not be counted towards baseline monthly seizure count. Cluster seizures will be counted as a single seizure. The endpoint time to baseline monthly seizure count is defined, for each participant, as the number of days until the cumulative seizure count for the participant is equal to the baseline monthly seizure count, up to the end of the 12-week double-blind treatment period. Participants have the option to continue with the protocol having reached their baseline monthly seizure count in the double-blind period, however the primary analysis itself will not include seizure data beyond this point. For all subsequent analyses, seizure data collected during the entire DB period will be included.

5.3.2. Estimand

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 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 participants who had the ICE as those participants from the same treatment group who did not have the ICE.

Population-level summary: the difference in estimated hazard ratio between the treatments.

The primary analysis will be based on the full analysis set.

5.3.3. Analysis Methods

The intent-to-treat population will be the primary efficacy population. For each cohort, Kaplan-Meier analyses will be conducted to describe the time to reaching baseline monthly seizure count for each treatment group (JNJ-813 or Placebo) pooled over CCI [redacted], and also treatment group by CCI [redacted] for all observable focal-onset seizures using the full analysis set. Descriptive summaries of the Kaplan-Meier estimates will be presented by treatment group (JNJ-813 or Placebo) pooled over CCI [redacted], and also treatment group by CCI [redacted] which will include the median with 95% CI and quartiles. Participants who have exceeded their pre-randomization monthly seizure count will be considered an 'Event' and the date of the seizure recorded in the e-diary that equals or exceeds the baseline monthly seizure count will be used in the time to event calculation. Participants who have not exceeded the baseline monthly seizure count and complete the double-blind treatment period through Week 12 will be censored at day 85. Participants who discontinue the study early during the double-blind treatment period will be censored at the date of discontinuation.

A formal comparison of time to monthly baseline seizure count will be made by estimating the hazard ratio and its 95% CI using a Cox proportional hazard regression model, including treatment and baseline CCI [redacted] CCI [redacted]. Primary endpoint data from participants on placebo in subsequent cohorts will be combined with those from the previous cohort(s) if the Kaplan-Meier curves of the participants treated with placebo are comparable between cohorts. Where placebo groups are comparable, Kaplan-Meier curves for each cohort will be presented together to demonstrate comparability prior to combining the placebo groups.

Provided there are sufficient participants within each arm, additional sensitivity analyses will be undertaken to assess the robustness of the primary analysis to compliance with the intervention during the double-blind phase. Here the same analysis as the primary efficacy endpoint will be performed using the compliance analysis set (CAS). In addition, e-diary seizure reporting compliance will be summarized descriptively as defined in Appendix 7.

During Cohort 1, all participants and sites in Ukraine were impacted by the Russian invasion of Ukraine. To assess the impact of these data on the study, a sensitivity analysis on the primary efficacy endpoint will be performed where all Ukraine participants in Cohort 1 who were active in the study on or after 24th February 2022 (date invasion began) will be excluded.

5.4. Secondary Endpoint(s) Analysis

All secondary efficacy analyses will be based on the full analysis set. Data from participants on placebo in subsequent cohorts will be combined with those from the previous cohort(s) only if the secondary endpoint of those treated with placebo are comparable between cohorts. Where placebo groups are comparable, descriptive statistics for the placebo groups within each cohort will be presented to demonstrate comparability prior to combining the placebo groups.

5.4.1. Percent reduction in the double-blind monthly seizure count

5.4.1.1. Definition

A secondary efficacy endpoint is the percent reduction in the double-blind monthly seizure count which is defined as 100*(Baseline monthly seizure count - Double-blind monthly seizure count)/(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 X_{DB} is the number of days comprising the double-blind period. A positive percentage change in the double-blind monthly seizure count indicates improvement. The number of seizures experienced by participants who exit the study at Week 4 (i.e. after reaching the baseline seizure count) will be either equal to or larger than their baseline monthly seizure count. Therefore, their observed % seizure rate reduction will either be zero, or negative (implying an increase). For participants who discontinue during the double-blind phase, the actual seizure frequency up to the day of discontinuation will be used.

5.4.1.2. Analysis Methods

Descriptive statistics (N, mean, SD, median, 25th percentile and 75th percentile) of the percent reduction in the double-blind monthly seizure rate will be summarized for each cohort by treatment group (JNJ-813 or Placebo) pooled over CCI [redacted], and also treatment CCI [redacted] The distribution of the percent reduction in the double-blind monthly seizure count will be categorized into the following levels: ≤ 0% to < 25%; ≥ 25% to < 50%; ≥ 50% to < 75%; ≥ 75% to < 100%; 100% (seizure freedom). A bar graph of the proportions of participants within each category will be presented by treatment group and stratum.

For each cohort, the percent reduction in the double-blind monthly seizure rate will be analyzed using an ANCOVA model containing treatment group and CCI [redacted] as factors. Treatment effect will be estimated based on the difference of the treatment group least-square (LS) means with 95% confidence interval. If the nature of the outcome is nonparametric, the percentage reduction will be analyzed using a Wilcoxon rank-sum test.

A sensitivity analysis will be performed where participants who discontinue the study during the double-blind phase and whose double-blind monthly seizure count does not exceed their baseline

monthly seizure count are assumed to have no change in seizure frequency (0% reduction in seizure frequency) even if they reported no seizures prior to discontinuing. The percent reduction will remain the same for those participants whose double-blind monthly seizure count was greater than their baseline monthly seizure count (i.e. increase in seizures) at the time of discontinuation.

5.4.2. Seizure Freedom

5.4.2.1. Definition

A secondary efficacy endpoint is the proportion of participants with seizure freedom where seizure freedom is defined as having no seizures over the complete double-blind period. Participants who record any seizures in the DB period, whether they complete or not, will be included in this analysis (i.e., they will be in the denominator).

5.4.2.2. Analysis Methods

The number and percentage of participants with seizure freedom at the end of the double-blind period will be summarized for each cohort by treatment group (JNJ-813 or Placebo) pooled over CCI, and also treatment group by CCI The treatment effect point estimate (odds ratio) and 2-sided 95% confidence interval will be provided using a logistic regression model containing treatment group and CCI as factors. Exact logistic regression will be used if the number with seizure freedom is small. If it is not possible to obtain estimates, then Fishers exact test will be used providing point estimate and 95% confidence interval for the percentages.

Sensitivity analyses will be performed where participants who discontinue the study during the double-blind phase are assumed not to be seizure-free, even if they reported no seizures prior to discontinuing.

5.4.3. Responder rate

5.4.3.1. Definition

A secondary efficacy endpoint is the responder rate which is defined as a participant having at least a 50% reduction of the monthly seizure rate during the double-blind period. The percent reduction in the double-blind monthly seizure count is defined in Section 5.4.1.1. A participant is defined a responder (yes=1) if the percent reduction in the double-blind monthly seizure count is ≥ 50%. Participants who do not meet such a criterion will be considered as non-responders and will be assigned a value of 0 (i.e. No). Participants who exit the study at Week 4 after reaching the baseline seizure count will be treated as non-responders in this analysis.

5.4.3.2. Analysis Methods

For each cohort, the number and percentage of participants who achieve a response during the double-blind period will be summarized by treatment group (JNJ-813 or Placebo) pooled over CCI, and also treatment group by CCI The treatment effect point estimate (odds ratio) and 2-sided 95% confidence interval will be provided using a logistic regression model containing treatment group and CCI as factors.

Exact logistic regression will be used if the number with seizure freedom is small. If it is not possible to obtain estimates, then Fishers exact test will be used providing point estimate and 95% confidence interval for the percentages.

5.4.4. Secondary generalized seizures

5.4.4.1. Definition

Provided a large enough number of events are observed, separate analyses for focal to bilateral tonic-clonic seizures will be performed; namely, the same analysis as that of the primary endpoint and the analysis of the percent reduction.

There may be a number of participants with no focal to bilateral tonic-clonic seizures reported in the baseline period but reported some during the double-blind period. This would have an impact on the aforementioned analyses by reducing the analysis sample or resulting in undefined outcome for these participants. If this is the case, the time-to-event analysis and percent reduction analyses will not be undertaken and instead the response ratio will be calculated and analyzed. The response ratio will range from -1 to 1 and is defined as (T - B)/(T + B), where T is the double-blind monthly seizure count and B is the baseline monthly seizure count, where a negative ratio indicates improvement.

5.4.4.2. Analysis Methods

For each cohort, the time to baseline seizure count will be analyzed for focal to bilateral tonic-clonic seizures in the same way as described in Section 5.3.3 for the primary efficacy endpoint. Kaplan-Meier analyses will be presented for the time to reaching baseline monthly seizure count (with 95% CI) for each group (JNJ-813 or Placebo) pooled over CCI, and also treatment group by CCI for all focal to bilateral tonic-clonic seizures. Descriptive summaries of the Kaplan-Meier estimates will be presented by treatment group (JNJ-813 or Placebo) pooled over CCI and also treatment group by CCI CCI, which will include the median with 95% CI and quartiles. The hazard ratio and its 95% CI will be estimated using a Cox proportional hazard regression model, including treatment and baseline CCI CCI. Primary endpoint data from participants on placebo in subsequent cohorts will be combined with those from the previous cohort(s) if the Kaplan-Meier curves of the participants treated with placebo are comparable between cohorts. Where placebo groups are comparable, Kaplan-Meier curves for each cohort will be presented together to demonstrate comparability prior to combining the placebo groups.

In addition, the percent reduction in the double-blind monthly seizure count will be analyzed as described in Section 5.4.1.2 for focal to bilateral tonic-clonic seizures by treatment group and stratum.

Descriptive statistics (N, mean, SD, median, 25th percentile and 75th percentile) will be summarized for each cohort by treatment group (JNJ-813 or Placebo) pooled over CCI,

and also treatment group by CCI) where the response ratio approach is utilized.

5.5. Exploratory Endpoint(s) Analysis

All exploratory analyses will be based on the full analysis set apart from Section 5.5.3 (i.e. Seizure freedom and responder rate after the first 4 weeks) which will be based on the modified full analysis set and Section 5.5.4 (Efficacy data in the Open-Label Extension) which will be based on the FASOLE analysis set.

5.5.1. CCI

5.5.1.1. Definition

CCI .

5.5.1.2. Analysis Methods

For each cohort, descriptive statistics for actual values and changes from baseline for the seizure-related CCI at each time point (4 and 12 weeks) of the double-blind treatment period will be provided by treatment group (JNJ-813) pooled over CCI , and also treatment group by CCI Mean (±SE) plot for total CCI will be provided for each time point by treatment group and CCI

5.5.2. CCI

5.5.2.1. Definition

Participants who continue treatment to the end of the double-blind treatment period (Week 12) or have completed the study early i.e. reached their baseline seizure count before Week 12, and who decide not to participate in the open-label phase w CCI diary until 2 weeks after the last dose of study medication.

5.5.2.2. Analysis Methods

To evaluate the CCI , descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) for actual values for the weekly seizure count during each study period (baseline, double-blind and follow-up) will be provided by treatment group (JNJ-813) pooled over CCI , and also treatment group by CCI

CCI for all observable focal-onset seizures. Mean (±SE) plot for the weekly seizure count will be provided for each week by treatment group and by stratum.

Furthermore, the following additional safety findings will be reported:

- for each cohort the number and percentage of participants with cluster seizures will be summarized by treatment group (JNJ-813) pooled over CCI CCI, and also treatment group by CCI within each study period (baseline, double-blind and follow-up).
- for each cohort the number and percentage of participants in the follow-up period with focal to bilateral tonic-clonic seizures who had none reported in the baseline or double-blind period will be summarized by treatment group (JNJ-813) pooled over CCI CCI, and also treatment group by CCI
- for each cohort the number and percentage of participants in the follow-up period with a seizure rate that is more than twice that of the baseline monthly seizure count will be summarized by treatment group (JNJ-813) pooled over CCI and also treatment group by CCI The follow-up monthly seizure count is defined as the total number of observable focal onset seizures occurring during the follow-up period, multiplied by $28/X_{FU}$, where X_{FU} is the number of days comprising the follow-up period.

5.5.3. CCI

5.5.3.1. Definition

The proportion of participants with CCI (as defined in Section 5.4.3.1) will be assessed in the treatment period after the first 4 weeks to explore if the compound needs some time to develop effect. Only the subset of participants who remained in the treatment period beyond 4 weeks will be included. In other words, participants who exit the study by 4 weeks having reached their pre-randomization baseline seizure count will not be included.

5.5.3.2. Analysis Methods

For each cohort, the number and percentage of participants with CCI and, CCI rate during the double-blind period after the first 4 weeks will be summarized by treatment group (JNJ-813 or Placebo) pooled over CCI and also treatment group CCI CCI.

5.5.4. Analysis of Efficacy data in the Open-Label Extension

Efficacy assessments during the open-label extension phase include percent reduction in seizure frequency, the percent of participants with seizure freedom and the participant responder rate.

The percent reduction in the OLE monthly seizure count is defined as 100*(Baseline monthly seizure count - OLE monthly seizure count)/(Baseline monthly seizure count). The OLE monthly seizure count is defined as the total number of observable focal onset seizures occurring during the OLE period, multiplied by $28/X_{OLE}$, where X_{OLE} is the number of days comprising the OLE.

Descriptive statistics (N, mean, SD, median, 25th percentile and 75th percentile) of the percent reduction in the OLE monthly seizure rate will be presented. The number and percentage of participants with seizure freedom at the end of the OLE period will be summarized. The number and percentage of participants who achieve a response during the OLE period will be presented.

The analyses will be performed for the FASOLE analysis set for the open-label phase.

The open-label efficacy data will be summarized for each cohort intervention sequence by treatment group (JNJ-813) pooled over CCI treatment group by CCI nd overall.

Plots of the mean (±SE) percent reduction in seizure count over time spanning the double-blind and open-label phase will also be presented for the observed cases by the double-blind treatment group (in the form of an intervention sequence) pooled over CCI and also treatment group by CCI If the nature of the outcome is nonparametric then box-plots for the percent reduction in seizure count will be presented instead.

5.6. (Other) Safety Analyses

All safety analyses will be based on the safety (SAF and SAFOLE) analysis sets based on actual intervention received, unless otherwise specified.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

Analysis of safety data in the open-label phase: All open-label safety data will be summarized by the intervention received in the double-blind phase (in the form of an intervention sequence), and overall.

5.6.1. Extent of Exposure

The number and percentage of participants who receive study intervention will be summarized.

Descriptive statistics for duration of study intervention (N, mean, SD, median, range, minimum, maximum) will be summarized.

Duration of intervention during the double-blind phase will be summarized in the following duration categories: <2 week, 2-<4 weeks, 4-<6 weeks…10-<12 weeks for each study agent within a study intervention and presented graphically in a histogram. Cumulative duration of intervention [>=2 week, >=4 weeks, …] will also be summarized. Frequency distribution of duration of intervention during the open-label phase (week 1-4, week 5-8,….,week 101-104, or >week 104) will also be summarized.

Total duration of intervention for the double-blind phase and open-label phase is defined as (date of last dose of study intervention – date of first dose of study intervention) +1. If the date of last dose of study intervention is missing, it will be imputed as the day prior to the double-blind or

open-label disposition date for calculating exposure duration. Descriptive statistics (N, mean, SD, median, range, minimum, maximum) of total duration of intervention will be summarized for each study drug within a study intervention.

Total dose days of intervention is defined as the total number of days that study intervention was administered to the participant (excluding days off study intervention). Descriptive statistics (N, mean, SD, median, range, minimum, maximum) of total dose days of intervention will be summarized for the double-blind phase and open-label phase for each study agent within a study intervention.

A listing to show all dose adjustments for each participant including the reason for dose adjustment will be provided.

Study intervention compliance during DB and OLE will be summarized descriptively. See Appendix 7 for further details.

The analysis will be performed on SAF and SAFOLE analysis sets.

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 5 days is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Assignment of adverse events to double-blind or open-label analysis phase, or the follow-up phase will be made based on the following rules:

Double-blind analysis phase:

All AEs that are assigned to the double-blind analysis phase as detailed below will be considered as treatment-emergent.

- For participants who did not continue to open-label treatment phase: double-blind phase start date ≤ AE onset date ≤ date of the last dose of study intervention in the double-blind phase plus 5 days.

- For participants who continued to open-label treatment phase: double-blind phase start date ≤ AE onset date ≤ earlier of (date of the last dose of study intervention in the double-blind phase + 5, open-label study intervention start date)
    - AEs that occur more than 5 days after the last dose of double-blind study intervention but prior to open-label dosing will not be considered as treatment-emergent for either the double-blind or the open-label phase. These AEs will be flagged as 'Pre-open label';

Open-label analysis phase:

All AEs that are assigned to the open-label analysis phase as detailed below will be considered as treatment-emergent.

- For participants who entered open-label treatment phase < 6 days from the last dose double-blind study intervention: open-label phase start date < AE onset date ≤ date of the last dose of study intervention in the open-label phase plus 5 days.
- For participants who entered open-label treatment phase ≥ 6 days from last dose of double-blind study intervention: open-label phase start date ≤ AE onset date ≤ date of the last dose of study intervention in the open-label phase plus 5 days.

Follow-up phase:

AEs that are assigned to the follow-up phase are not considered as treatment-emergent. AEs with onset date > date of last dose of double-blind study intervention plus 5 days will be assigned to this phase.

Summary tables will be provided for treatment-emergent adverse events:

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of each study drug within a study intervention/termination of study participation
- AEs by relationship to study intervention
- AEs leading to dose interruption of each study agent within a study intervention.

In addition to the summary tables, listings will be provided for participants who:

- Had SAEs
- Had AEs leading to discontinuation of study intervention/termination of study participation

A listing of participants who died will be provided.

5.6.2.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Descriptive statistics will be presented for all chemistry, hematology, and urinalysis (pH and specific gravity) laboratory tests at scheduled time points in the double-blind and open-label phases.

Change from their respective baselines to each scheduled time point in the double-blind and open-label phases will be summarized for chemistry, hematology, and urinalysis (pH, and specific gravity) tests and displayed by treatment group.

Abnormality criteria based on normal ranges will be applied to baseline and postbaseline values.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- For abnormalities based on normal range and/or criteria: If the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low), then the postbaseline abnormality will be considered TE. The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

Number and percentage of participants with markedly abnormal postbaseline values in the double-blind and open-label phases will be presented by treatment group over time. A listing of TE laboratory values will be provided.

Shift tables will be provided for the double-blind and open-label phases summarizing the shift in laboratory values from baseline over time with respect to abnormality criteria (low, normal, high).

5.6.2.2. Vital Signs and Physical Examination Findings

Vital sign parameters including temperature (oral or tympanic), pulse and blood pressure (systolic and diastolic) will be summarized at each assessment timepoint for the double-blind and open-label phases. Body Mass Index will be calculated as weight (kg)/(height (m))^2, at each time point that body weight is measured. The height measurement collected at screening will be used in the calculation. Descriptive statistics (N, mean, standard deviation, median, minimum and maximum) and change from the respective baselines will be summarized for the double-blind and open-label phases by treatment group at each scheduled visit.

Abnormality criteria (based on criteria defined below) will be applied to baseline and postbaseline values in the double-blind and open-label phases. For baseline values, increase or decrease criteria are not applied.

Postbaseline values will be considered TE if they meet both value and change criteria in the table below.

For criteria that do not include an increase or decrease from baseline for both double-blind and open-label phases:

- TE will be concluded if the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

Incidence of treatment-emergent clinically important abnormalities in vital signs during the double-blind phase, as defined in Table 3, will be summarized for participants who had a baseline assessment and at least 1 postbaseline assessment for that vital sign.

Table 3: Clinically Important Abnormalities in Vital Signs

Vital Sign	Criteria
Pulse	>100 bpm and with >30 bpm increase from baseline
	<50 bpm and with >20 bpm decrease from baseline
Systolic blood pressure	>140 mm Hg and with >40 mm Hg increase from baseline
	<90 mm Hg and with >30 mm Hg decrease from baseline
Diastolic blood pressure	>90 mm Hg and with >30 mm Hg increase from baseline
	<50 mm Hg and with >20 mm Hg decrease from baseline
Temperature	>38ºC and with >=1ºC increase from baseline

A listing of participants with treatment-emergent clinically important abnormalities in vital signs will be presented, along with a listing of all vital sign measurements.

In addition, a by-subject listing of the physical examination data, neurological examination data and Brief neurological data will be presented.

5.6.2.3. Electrocardiogram

At screening a triplicate ECG is required where the mean values of ECG parameters will be used for entry into the eCRF. At all other visits, single twelve-lead ECG will be recorded. The screening ECG values are the last available ECG measurements before dosing and will therefore be used as the baseline values. The ECG parameters that will be analyzed are heart rate, PR interval, RR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: Bazett's formula (QTcB), Fridericia's formula (QTcF).

Bazett's formula: QTcB (msec) = QT (msec) / (RR (msec)/1000)$^{1/2}$; if RR is missing, use QT (msec) * (HR(bpm)/60)$^{1/2}$;

Fridericia's formula: QTcF (msec) = QT (msec) / (RR (msec)/1000)$^{1/3}$; if RR is missing, use QT (msec) * (HR(bpm)/60)$^{1/3}$;

The number and percentage of participants with QTc interval will be summarized at each scheduled time point for each treatment phase (double-blind and open-label) by treatment group. The number and percentage of participants with QTc interval increases from baseline to the maximum postbaseline value will be summarized for double-blind and open-label phases by treatment group. Refer to the following table for summary categories.

Criteria for Abnormal QTc Values and Changes From Baseline		
Clinically Significant QTc Value	No	≤500
	Yes	>500
QTc change from baseline (msec)	No concern	≤30
	Concern	>30 to ≤60
	Clear concern	> 60
QTc value (msec)	Normal QTc	≤450 for male, ≤470 for female
		>450 to ≤480 for male, >470 to ≤480 for female
		>480 to ≤500
		>500
These criteria are based on the ICH E14 Guideline		

A shift table will be provided summarizing the shift from baseline to maximum QTc interval classification through the double-blind phase.

Descriptive statistics of ECG parameters and change from baseline will be summarized by treatment group at each scheduled visit for double-blind and open-label phases

If ECG measurements are repeated at a visit, they will be averaged. The averaged value will be considered the 'Visit' ECG result.

Abnormality criteria (based on criteria defined below) will be applied to baseline and postbaseline values.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- TE will be concluded if the postbaseline value is above the upper limit and the baseline value is below the upper limit (e.g., Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

The number and percentage of participants with treatment-emergent ECG values and abnormal postbaseline values (relative to baseline) will be presented by treatment group over time for each phase of the study:

- Heart rate (bpm): <45 and >100
- PR interval (msec): <120 and >200
- QRS interval (msec): >120
- QTc (msec): >470 in women and >450 in men

The interpretation of the ECGs will be displayed by the number and percentage of participants meeting the normality criteria. The interpretation will be summarized over time by the two intervention phases.

A listing of clinically relevant ECG abnormalities will also be provided.

5.6.2.4. Other Safety Parameters

5.6.2.4.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed to assess severity and track suicidal events through any intervention (Posner 2007). It is a clinical interview providing a summary of both suicidal ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS has been used frequently in clinical studies, and is a validated, standard measure for suicidal ideation assessment. Using the C-SSRS, the outcomes will be categorized using the scoring for the 11 categories:

Suicidal Ideation (1-5)	
1	Wish to be dead
2	Non-specific active suicidal thoughts
3	Active suicidal ideation with any methods (not plan) without intent to act
4	Active suicidal ideation with some intent to act, without specific plan
5	Active suicidal ideation with specific plan and intent
Suicidal Behavior (6-10)	
6	Preparatory acts or behavior
7	Aborted attempt
8	Interrupted attempt
9	Actual attempt
10	Suicide
Non-suicidal self-injurious behavior (11)	
11	Non-suicidal self-injurious behavior

If no events qualify for a score of 1 to 10, a score of 0 will be assigned (0="no suicidal ideation or behavior that can be assessed on the basis of C-SSRS"). A participant with a score of 11 will be considered as not having suicidal ideation or behavior.

Shifts from baseline to the maximum postbaseline score pertaining to suicidal ideation or suicidal behavior (i.e., scores 0 to 10) will be summarized by intervention for each cohort for the double-blind phase and open-label phase.

The maximum score (of scores 0 to 10) assigned to each participant will be grouped into one of three broad categories: No suicidal ideation or behavior (0), Suicidal ideation (1-5), Suicidal behavior (6-10). Shifts from the baseline to the maximum postbaseline category will be summarized by intervention for each cohort for the double-blind phase and open-label phase.

A frequency distribution of the scores for the 11 categories will be provided at each time point within each phase for each cohort.

Listings will be provided for participants with suicidal ideation/behavior at screening (lifetime recall and past 12 months recall) and also for participants with post-baseline non-suicidal self-injurious behavior during the study conduct.

5.7. Other Analyses

5.7.1. Pharmacokinetics/Pharmacodynamic

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.

PK analyses will be performed by the pharmacometrics group in clinical pharmacology on the PK analysis set (PKAS), defined as participants who have received at least 1 dose of JNJ-40411813 and have at least 1 valid blood sample drawn for PK analysis.

Descriptive statistics will be calculated for the plasma concentrations of JNJ-40411813 and CCI [redacted]. Descriptive statistics will be calculated for the plasma concentrations of JNJ-40411813 metabolites including CCI [redacted], and levetiracetam at each applicable time point. If warranted and feasible, summary statistics will be provided for brivaracetam and additional CCI [redacted]. Statistics include number of participants (N), number of observations (n), mean, standard deviation, coefficient of variation (CV), geometric mean, median, minimum, and maximum. PK data may also be displayed graphically, plotting boxplots of PK concentrations over time by treatment group.

Population PK analysis of JNJ-40411813 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. If conducted, the results of the population analyses will be reported separately from the clinical study report.

5.7.2. Pharmacokinetics/Pharmacodynamic Relationships

If deemed feasible, exploratory PK-PD analyses, including graphical exploration of PK-PD data, may be explored. If conducted, results of such analyses will be reported separately.

5.7.3. Biomarkers

During the study, blood will be collected at Visit 2 (baseline), Visit 4 and Visit 7/EW for the potential assessment of the biomarkers CCI [redacted] Biomarkers may be added or deleted based on scientific information or technical innovations. Details of the exploratory biomarker analysis, if conducted, will be provided in a separate document.

5.8. Interim Analyses

This study has an Interim Review Committee (IRC) who will conduct interim reviews unblinded at the individual level. In Cohorts 1 and 2, after all participants in a cohort have completed 4 weeks of treatment, the IRC will review all cumulative safety, PK and efficacy data of JNJ-40411813 available to that date to provide recommendation on study progression. If the results after the last participant has completed the 4-week visit 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.

5.8.1. Data Monitoring Committee (DMC) or Other Review Board

Continuous or periodic blinded safety reviews will be done by the SRP. If there are safety concerns from these reviews, a Data Review Committee (DRC) will be called upon to conduct an unblinded review of the data at the individual participant level. The DRC will consist of at least one medical expert from the relevant therapeutic area and at least one statistician.

A separate short SAP detailing the deliverables and the decision criteria will be written for the DRC and IRC respectively, and will be completed before the first interim review.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

ADA	anti-drug antibody
AE	adverse event
AED	Anti-epileptic drug
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
AUC	area under the curve
BMI	body mass index
BSA	body surface area
CAS	Compliance analysis set
CI	confidence interval
CL	total systemic clearance
Cmax	maximum concentration
CRF	case report form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DB	Double-Blinded
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
DRC	Data Review Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
CCI C	[redacted]
EW C	Early Withdrawal
F (%)	absolute SC bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IQ	interquartile
IRC	Interim Review Committee
IVRS	interactive voice response system
IWRS	interactive web response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimum required dilution
NAb	neutralizing antibodies
OLE	Open Label Extension
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMQs	standardised MedDRA queries
SRP	Senior research physician
TEAE	treatment-emergent adverse event
Tmax	time to maximum concentration
US NCI	United States National Cancer Institute
V	volume distribution

Vz	volume of distribution based on terminal phase
Vz/F	apparent volume of distribution based on terminal phase after extravascular administration
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

ADA	anti-drug antibody
AE	adverse event
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
AUC	area under the curve
BMI	body mass index
BSA	body surface area
CI	confidence interval
CL	total systemic clearance
Cmax	maximum concentration
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
ECG	electrocardiogram
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Vz	volume of distribution based on terminal phase
Vz/F	apparent volume of distribution based on terminal phase after extravascular administration
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

There have been no changes to protocol-planned analyses.

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by treatment group, and overall. In addition, the distribution of participants by country and site ID will be presented unless otherwise noted.

Table 4 and Table 5 present a list of the demographic variables and baseline characteristics respectively, that will be summarized by treatment group and overall for the safety analysis sets (SAF and SAFOLE). Demographics will also be summarized by CCI [redacted] within treatment group using the safety analysis set.

Table 4: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum])
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age (18-25 years, 26-50 years, 51-64 years, and >=65 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, undifferentiated)	
Region[a] (America, Asia, Eastern Europe, Western Europe)	
Race[b] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI (underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese >=30 kg/m^2)	

[a] America includes Canada, USA; Asia includes Australia, Japan, South Korea; Eastern Europe includes Russia, Turkey, Ukraine; Western Europe includes Belgium, France, Germany, Greece, Italy, Netherlands, Portugal, Spain, UK

[b] If multiple race categories are indicated, the Race is recorded as 'Multiple'

Table 5: Baseline Characteristics

Continuous Variables:	**Summary Type**
CCI [redacted] Baseline monthly seizure count	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Categorical Variables	
CCI [redacted]	Frequency distribution with the number and percentage of participants in each category.
Seizure type (focal aware seizures with and without motor signs, focal impaired awareness seizures, focal to bilateral tonic-clonic seizures, other)	
Cluster seizures (proportion of participants who report cluster seizures)	
AED use (Levetiracetam etc)	
Number of baseline AED's used (1,2,3,4)	

6.4. Appendix 4 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants whose major protocol deviations are determined to meet the above criteria (have the potential to impact participants' rights, safety or well-being, or the integrity and/or the primary endpoint of the clinical study) will be identified by medical and statistical review prior to database lock and will be summarized by the following categories for the SAF and SAFOLE analysis sets:

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention.

Summaries of concomitant medications will be presented by ATC term, cohort and treatment group for the double-blind and open-label phases for the SAF and SAFOLE analysis sets. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

Prior medications will be summarized by treatment group, cohort and ATC term.

6.6. Appendix 6 Medical History

A listing for participant medical history will be provided.

6.7. Appendix 7 Compliance

6.7.1. Intervention Compliance

Intervention compliance data comes from the drug accountability data collected at study visits during the DB and OLE phase. Intervention compliance will be summarized descriptively by phase (DB and OLE) for each study drug within a study intervention.

The intervention compliance calculation is detailed below.

Study visit intervention compliance data

Compliance (%) = (actual number of tablets taken/total number of tablets supposed to be taken) x100

In instances where a participant's drug accountability is not completed for a dispensed kit at a study visit, the average study visit compliance value during that phase (DB or OLE) will be assigned for that participant.

6.7.2. Seizure e-diary Compliance

For each participant, e-diary compliance (%) in the study (i.e. baseline period plus double-blind period) will be defined as 100 x (Number of days with non-missing seizure data / number of days comprising the baseline period and double-blind period). Seizure data on a given day are said to be missing if the participants report no seizures and also do not complete the reminder diary. If, however, seizures that occurred on the days that the reminder diary was not completed are entered at a later date e.g. data correction form, then these days will be not be classed as days with missing seizure data. Descriptive statistics (N, mean, SD, median, 25^{th} percentile and 75^{th} percentile) of e-diary compliance (%) will be summarized for each cohort by treatment group (JNJ-813 or Placebo).

6.8. Appendix 8 Adverse Events of Special Interest

There are no adverse events of special interest.

6.9. Appendix 9 Medications of Special Interest

There are no concomitant medications of special interest.

7. REFERENCES

CCI [redacted]

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164(7):1035-1043.