A Multicenter, Single-Arm, Open-Label, Post-Marketing Safety Study to Evaluate the Risk of Seizure Among Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated with Enzalutamide Who Are at Potential Increased Risk of Seizure (UPWARD)

ISN/Protocol 9785-CL-0403

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Sponsor: Astellas Pharma Global Development, Inc. (APGD)

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STATISTICAL ANALYSIS PLAN

Final Version 1.00, dated 25-Mar 2014

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Table of Contents

I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
APGD	Astellas Pharma Global Development
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Intervals
CRF	Case Report Form
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EOS	End of Study
H	High
ICH	International Conference on Harmonization
L	Low
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
N	Normal
PT	Preferred Term
QTc	Corrected Q-T Interval
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings and Figures
ULN	Upper Limit of Normal

List of Key Terms

Terms	Definition of terms
Endpoint	A variable that pertains to the trial objectives
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

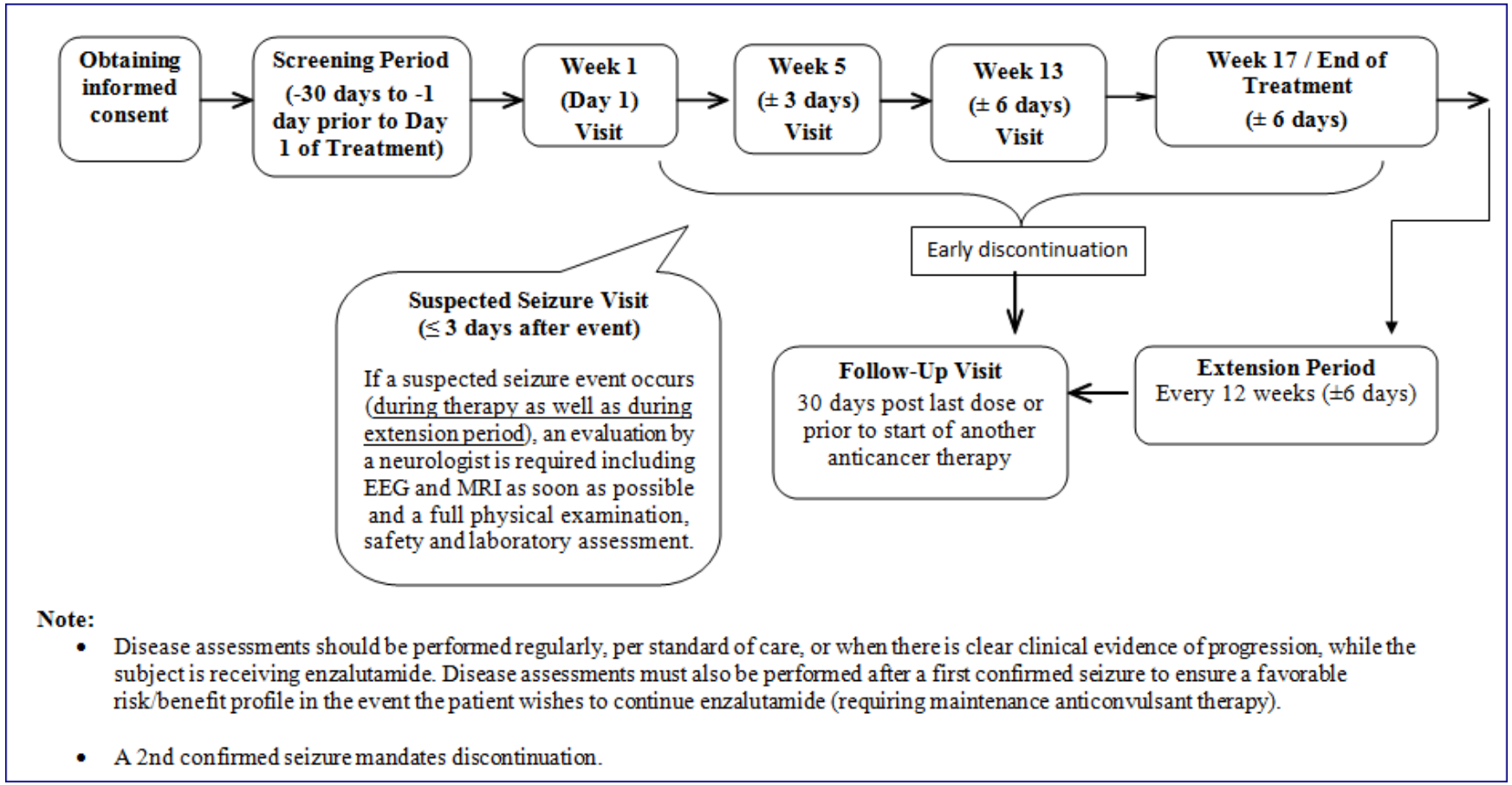
The SAP is finalized and signed prior to database hard lock to ensure lack of bias. For operational efficiency an earlier time is usually targeted. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

This statistical analysis is coordinated by the responsible biostatistician of APGD-US. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review of data and TLFs meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database hard lock.

2 FLOW CHART AND VISIT SCHEDULE

Flow Chart



Note:

- Disease assessments should be performed regularly, per standard of care, or when there is clear clinical evidence of progression, while the subject is receiving enzalutamide. Disease assessments must also be performed after a first confirmed seizure to ensure a favorable risk/benefit profile in the event the patient wishes to continue enzalutamide (requiring maintenance anticonvulsant therapy).
- A 2nd confirmed seizure mandates discontinuation.

Table 1: Schedule of Assessments

Assessments	Screening Period (-30 days to – 1 day prior to Day 1 of Treatment)	Treatment Period					Extension Period i	Follow-up Visit [b]
		Week 1 Day 1 (n/a)	Week 5 (± 3 days)	Week 13 (± 6 days)	Week 17/End of Treatment (±6 days)	Suspected Seizure Visit [c] (≤ 3 days after event)	Every 12 weeks (±6 days)	30 days post last dose or prior to start of another anticancer therapy
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Upon occurrence	--	--
Informed Consent [a]	X							
Verify Inclusion/Exclusion	X							
Medical History	X							
Prostate Cancer History	X							
Demographics	X							
ECOG Performance Status	X							
Vital Signs (Blood Pressure, Heart Rate and Temperature)	X	X	X	X	X		X	X
Physical Examination [d]	X	X	X	X	X		X	X
Neurologist Examination [e]	X							
Weight and Height	X							
Clinical Labs [f]	X	X	X	X	X	X	X	X
12-Lead ECG	X			X	X	X		X
Blood Sample Collection for PGx Analysis	X							
Evaluation by a Neurologist, MRI, EEG						X		
Seizure Event Questionnaire						X		
Disease Assessments [g]	X			X	X	X	X	X
Adverse Events	X[h]	X	X	X	X	X	X	X
Concomitant Medications	←							→
Enzalutamide Dispensing		X	X		X[j]		X	

See footnotes on following page

a. Informed consent form must be obtained prior to any study-specific procedures being performed.
b. A Follow-up Visit will be performed 30 days after the last dose of enzalutamide, or prior to the initiation of another anticancer therapy, whichever occurs first.
c. Suspected seizure visit occurring any time during the 4 month therapy as well as during extension period.
d. Full physical exams will be performed including neurological exam. The physical examination performed at the Screening Visit does not need to be repeated on Day 1, if the Day 1 visit occurs within 72 hours of Screening.
e. At Screening, a thorough neurological history and examination will be performed by a local neurologist to obtain complete medical history relating to seizure risk, to confirm that a subject has met seizure risk entry criteria and to complete neurological baseline examination.
f. The laboratory assessments performed at the Screening visit do not need to be repeated on Day 1, if the Day 1 visit occurs within 72 hours of Screening.
g. Disease assessments will be performed regularly, per standard of care, or when there is clear clinical evidence of progression, while the subject is receiving enzalutamide. Disease assessments will also be performed after a first confirmed seizure to ensure favorable risk/benefit profile to continue enzalutamide. Disease assessments may include clinical, radiographic and/or PSA assessments.
h. Serious adverse events (SAEs) including death will be collected from the time the subject signs the consent form until 30 days after last dose of enzalutamide. Non-serious adverse events will be collected from time of study drug administration on Day 1 until 30 days after last dose of enzalutamide.
i. Extension period will begin for subjects who are assessed as deriving benefit from enzalutamide treatment after completion of the 4-month treatment. Data will be collected in the extension period for each subject for a period of 1 year after the 4-month treatment visit or 30 days post discontinuation during the one year timeframe. For any subject who continues on treatment after his 12-month extension period, data collection will be limited to dosing information, SAE, AEs Grade 3 or higher that are drug related and AEs of special interest or that lead to discontinuation.
j. For only subjects continuing in the extension period.

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objective(s)

The study objective is to evaluate the seizure rate and monitor the safety of enzalutamide treatment in subjects with metastatic castration-resistant prostate cancer known to have risk factor(s) for seizure.

3.2 Study Design

This is a multicenter, single-arm, open-label, post-marketing safety study to evaluate the risk of seizure among subjects with metastatic castration-resistant prostate cancer (mCRPC) treated with enzalutamide who are at potential increased risk of seizure.

Subjects will be enrolled into the study and participate in a 4-month treatment period of enzalutamide (160 mg/day). At the end of the 4-month treatment visit, subjects who are assessed as deriving benefit from enzalutamide treatment may continue in the extension period. Data will be collected in the extension period for each subject per the Schedule of Assessments for a period of one year after the 4-month treatment visit or 30 days post discontinuation during the one year timeframe.

When any subject who continues on treatment after his 12-month extension period, data collection will be limited to dosing information, serious adverse events (SAEs), AEs Grade 3 or higher that are drug related, and AEs of special interest or that lead to discontinuation.

Each subject will be given a patient card with the following information; a list of signs and symptoms of a suspected seizure (Seizure Description Subject Information) and a Suspected Seizure Event Questionnaire list as well as instructions regarding what to do in the event of a suspected seizure for awareness.

3.3 Randomization

This is a single-arm study and no randomization is considered.

4 SAMPLE SIZE

Approximately four hundred (400) subjects will be enrolled to target approximately 350 evaluable subjects, assuming a drop-out rate of approximately 13% for this population and based on the recommendation from the FDA, respectively. Assuming the true incidence of seizure as 1% and the sample size of 350, the chance of observing 5 or less subjects with seizure events is 85.9%. Given 5 out of 350 subjects, i.e., point estimate of 1.43%, the upper limit 95% exact confidence interval will be 3.31% and the width of the exact confidence interval will be 2.84%.

5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

Detailed criteria for analysis sets will be laid out in Classification Specifications (CS) and the allocation of subjects to analysis sets will be determined prior to database hard lock.

5.1 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) consists of all randomized subjects who received at least one dose of study drug and for whom any data is reported after first dose of study drug.

The SAF will be used for summaries of demographic and baseline characteristics and all safety and tolerability related variables.

5.2 Seizure Risk Evaluation Set (SRES)

For the statistical summary and analysis of seizure events, seizure risk evaluation set (SRES) will be used by including all evaluable subjects. An evaluable subject is defined as a subject with a confirmed seizure during the 4-month treatment period of the study or who completed at least 3 months (75%) of the planned treatment.

6 ANALYSIS VARIABLES

6.1 Efficacy Variables

Efficacy variables include clinical, radio-graphic and/or PSA assessments.

6.2 Safety Variables

6.2.1 Primary Endpoint

The proportion of subjects in SRES with at least one confirmed seizure as adjudicated by the Independent Adjudication Committee (IAC) during the 4-month treatment duration.

An evaluable subject is defined as a subject with a confirmed seizure during the 4-month treatment period of the study or who completed at least 3 months (75%) of the planned treatment. Only an enrolled subject who discontinues the study before completing 3 months on treatment may be replaced at the discretion of the Sponsor, however, an enrolled subject who is discontinued due to a confirmed seizure event will not be replaced.

A cumulative summary to include all seizure events, including those occurring beyond the 4 month treatment period will be included.

In case the drop-out rate is higher than expected, appropriate method such as Kaplan-Meier estimations may be considered.

6.2.2 Other Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug).
- Clinical laboratory variables (hematology, biochemistry including liver function tests, and urinalysis)
- Vital signs (systolic and diastolic blood pressure and pulse rate)
- 12-lead electrocardiogram (ECG)

TEAE is defined as an adverse event observed after starting administration of the test drug/comparative drug. If the adverse event occurs on Day 1 and the onset check box is marked "Onset after first dose of study drug" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked "Onset before first dose of study drug", then the adverse event will not be considered treatment emergent. If a subject experiences an event both during the pre-investigational period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity (i.e. it is reported with a new start date). All adverse events collected that begin within 30 days after taking the last dose of study drug will also be counted as TEAE.

A drug-related TEAE is defined as any TEAE with at least possible relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

6.3 Other Variables

- <u>The duration of exposure</u>
  For each subject, the Length of Time on study drug will be calculated in days, using the following formula:

  ('Date last dose of study drug'[#] - 'Date first dose[*]) + 1

  # = [End of study (EOS)-page of the Case Report Form (CRF)]
  * = 'date first study drug taken since last visit' [Visit 3-page of the CRF]

- <u>Previous and concomitant medication</u>

Previous medication is defined as medication with at least one dose taken before the date of the first dose of study drug.

Concomitant medication is defined as medication with at least one dose taken between the date of first dose (inclusive) and the date of last dose (inclusive) of study drug.

7 STATISTICAL METHODOLOGY

7.1 General Considerations

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. When needed, the use of other percentiles (e.g.10%, 25%, 75% and 90%) will be mentioned in the relevant section. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing data, i.e. will add up to 100%.

All data processing, summarization, and analyses will be performed using SAS® Version 9.1.3 or higher on Unix. Specifications for table, figures, and data listing formats can be found in the TLF specifications for this study.

For the definition of subgroups of interest please refer to section 7.8.

7.2 Study Population

7.2.1 Disposition of Subjects

The following subject data will be presented:

- Number and percentage of subjects in each analysis set;
- Number and percentage of subjects completed and discontinued 4 month treatment period, by primary reason for treatment discontinuation;
- Number and percentage of subjects completed and discontinued the 1 year extension period, by primary reason for discontinuation; and

7.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 8.1.6 Protocol Deviations) will be assessed for all enrolled subjects. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by total as well as by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by descriptive statistics.

Number and percentage of subjects enrolled in each country and site will be presented for the SAF.

Medical history is coded in MedDRA, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone for the SAF.

Baseline tumor burden will be summarized by body system.

Prostate cancer diagnosis and the categories of seizure risk will be summarized using frequencies.

7.2.4 Previous and Concomitant Medications

Previous medications are coded with WHO-DD, and will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF.

As with previous medication, concomitant medication will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

Prostate cancer treatment history will be summarized.

7.3 Study Drugs

7.3.1 Exposure

The following information on drug exposure will be presented for the SAF:

- Descriptive statistics for average daily dose; and
- Number and percent of subject with dose increases, decreases or interruptions

Duration of exposure will be summarized in two ways.

- Descriptive statistics will be presented.
- Exposure time will be categorized according to the following categories:
  - less than 3 months
  - at least 3 month, less than 6 months
  - at least 6 month, less than 9 months
  - at least 9 month, less than 12 months
  - at least 12 month, less than 15 months
  - 15 months or more

- Unknown.

Counts and percentages of subjects in each of these categories will be summarized for the SAF.

7.3.2 Treatment Compliance

Overall compliance will be examined for subjects in the SAF whose total study drug count and first and last days of treatment are known. The drug dispense records will be collected as a part of IVRS data.

Percent overall compliance will be summarized in two ways for the SAF:

- Descriptive statistics will be presented
- Percent compliance will be categorized according to the following categories:
  - less than 50%
  - at least 50%, less or equal to 75%
  - greater than 75%
  - Unknown.

The summaries described above will be provided for 4 month treatment period and entire study period separately.

7.4 Analysis of Efficacy

Efficacy data will be collected at baseline and at the time of seizure event for this study. No statistical analysis will be conducted. Instead, disease assessments including clinical, radiographic and/or PSA assessments collected will be listed.

7.5 Analysis of Safety

All analysis of safety will be presented for SAF, unless specified otherwise.

7.5.1 Analysis of Primary Endpoint

7.5.1.1 Primary Analysis

Primary endpoint, the proportion of evaluable subjects with at least one confirmed seizure as adjudicated by the IAC during the 4-month treatment duration, will be estimated using point estimate and its 95% exact confidence interval using all SRES.

7.5.1.2 Secondary Analysis

The same analysis of the primary endpoint as described in 7.5.1.1 will be conducted for a cumulative proportion to include all seizure events, including those occurring beyond the 4 month-treatment period using all SRES. Incidence of seizure events, including only the first seizure event, per patient-time exposure will be summarized for SAF. Any subsequent seizure event(s) will be listed.

In addition, seizure event free rate at 4 months, 12 months, and 16 months will be calculated using Kaplan-Meier estimation if data permit in SAF.

7.5.2 Adverse Events

The coding dictionary for this study will be MedDRA. It will be used to summarize AEs by SOC and PT.

An overview table will include the following details:

- Number of TEAEs,
- Number and percentage of subjects with TEAEs,
- Number of drug related TEAEs,
- Number and percentage of subjects with causally drug related TEAEs,
- Number of serious TEAEs,
- Number and percentage of subjects with serious TEAEs,
- Number of serious drug related TEAEs,
- Number and percentage of subjects with serious drug related TEAEs,
- Number of TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug, and
- Number of deaths.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized. Summaries will be provided for:

- TEAEs
- drug related TEAEs,
- serious TEAEs,
- drug related serious TEAEs,
- TEAEs leading to permanent discontinuation of study drug,
- drug related TEAEs leading to permanent discontinuation of study drug,
- TEAEs excluding serious adverse events that equal to or exceed a threshold of 3.0%, and
- common TEAEs that equal to or exceed a threshold of 5.0%

The number and percentage of subjects with TEAEs, as classified by PT only, will be summarized.

TEAEs and the number and percentage of subjects with TEAEs, as classified by SOC and PT will also be summarized by CTC Grade. If an adverse event changes in CTC Grade, then the subject will be counted only once with the worst grade. The adverse event however will be presented in each category they were classified to. If a subject has an event more than once with missing grade and with non-missing grade, then the subject will be counted as missing.

7.5.3 Clinical Laboratory Evaluation

The baseline visit is the last measurement taken prior to initial study drug administration.

Quantitative clinical laboratory variables, i.e. hematology, biochemistry, and urinalysis will be summarized using mean, standard deviation, minimum, maximum and median at each visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way. Each

laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges.

The number and percentage of subjects below and above reference range will be summarized at each visit.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented at each visit.

For hematology and biochemistry two types of shift tables will be presented:

- Shift tables of reference range changes from baseline to worst finding during the treatment period (low, normal, high), and
- Shift tables of NCI CTC Grade changes from baseline to worst grade during the treatment period.

7.5.3.1 Liver function tests

The following potentially clinically significant criteria in liver function tests for Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The subject's highest value during the investigational period will be used.

Parameter	Criteria
ALT	> 3xULN
	> 5xULN
	> 10xULN
	> 20xULN
AST	> 3xULN
	> 5xULN
	> 10xULN
	> 20xULN
ALT or AST	> 3xULN
Total Bilirubin	> 2xULN
ALP	> 1.5xULN
ALT and/or AST AND Total Bilirubin(*)	(ALT and/or AST > 3xULN) and total bilirubin > 2xULN

(*) Combination of values measured within same sample

The number and percentage of subjects with potentially clinically significant values in liver function tests during the investigational period will be presented.

7.5.4 Vital Signs and physical exam

The baseline visit is the last measurement taken prior to initial study drug administration.

Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be summarized using mean, standard deviation, minimum, maximum and median by visit.

Additionally, a within-subject change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by visit.

7.5.5 Electrocardiograms (ECGs)

ECG variables will be summarized using mean, standard deviation, minimum, maximum and median at each treatment visit and time point, including changes from baseline.

Number and percent of subjects with normal, not clinically significant abnormal, and clinically significant abnormal results as assessed by investigator for the 12 lead ECG will be tabulated at each treatment visit and time point.

The QTc interval will be summarized using frequency tables for each treatment visit and time point for values of clinical importance using the range criteria below.

	QTc Interval Criteria Value (msec)
Normal	≤ 450
Borderline	> 450 to ≤ 480
Prolonged	> 480 to ≤ 500
Clinically significant	> 500

The QTc interval will also be summarized by the frequencies of subjects with a change from baseline of clinical importance using the criteria identified below. These summaries will be provided for each treatment visit and time point.

Variable	**Change from Baseline**
QTc Interval (msec)	<0 ≥ 0 to <30 ≥ 30 to < 60 ≥ 60

Number and percent of subjects with 12 lead ECG abnormalities as well as number and percent of subjects whose 12 lead ECG reading changed from normal at baseline to abnormal will be tabulated at each treatment visit and time point.

7.5.6 Pregnancies

Not applicable.

7.5.7 Brain Imaging and Electroencephalogram

Brain imaging and electroencephalogram results collected from suspected seizure visit will be listed.

7.6 Analysis of PK

No analysis of PK is planned.

7.7 Analysis of PD

No analysis of PD is planned.

7.8 Subgroups of Interest

In case subgroups which may have association with the risk of seizure are identified during the study, the incidence of seizure events, will be summarized using a proportion estimate and its 95% exact confidence interval for the subgroups of the SRES.

7.9 Interim Analysis (and Early Discontinuation of the Clinical Study)

No formal interim analysis is planned for a specific timepoint.

The study design considers early stopping criteria that can be applied to a study as a whole or a specific risk factor group, if any, based on the statistical boundary calculated from Maximized Sequential Probability Ratio Test [Kulldorff, 2011].

The DSMB will examine safety data and be informed of seizure events as expediently as possible. Statistical boundaries for continuously monitoring of the seizure event will be provided in the DSMB charter as guidance for early stopping criteria. The DSMB will use them to appropriately recommend either stop the enrollment of specific subgroup(s) identified during the DSMB review period or in extreme circumstance DSMB may ask sponsor to stop the study.

7.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information

Refer to the data specification document in which more details are provided.

7.10.1 Missing Data

As a general principle, no imputation of missing data for other variables will be done. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to allocate the concomitant medication and AEs, in addition to determining whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

7.10.2 Outliers

All values will be included in the analyses.

7.10.3 Visit Windows

The study protocol gives the overall study schedule and the permissible intervals for the study visits. Analyses will not exclude subject data due to the subject's failure to comply with the visit schedule.

8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.00	DD-MMM-YYYY	NA	Document finalized

9 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

10 APPENDICES

<The handwritten signature page should be the last appendix of the document, if necessary.>

10.1 Appendix 1: Signatures

Prepared by: _____ Date: _____
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Global Data Science
Date (DD MMM YYYY)

Approved by: _____ Date: _____
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